Molecular Technologies in Gynecologic Oncology

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Abstract: In recent years, the application of molecular biological techniques to the diagnosis and treatment of cancer has proved successful. In this kind of pathologies, molecular diagnosis is of fundamental importance as it allows identification at a pre-symptomatic stage, and then in the early phase, of the subjects in which cancer disease is developing. Molecular diagnosis of tumors by deoxy-ribonucleic acid (DNA) analysis is conducted on biological samples such as urine, feces, sputum, vaginal swab, and blood, searching and identifying in the various samples for the presence of cell carriers of an altered genetic information. The sensitivity of this kind of analysis is so high as to be very reliable even in the presence in the sample of a few tumor cells, level not reachable through the traditional "tumor markers". The achievement of a facilitated early diagnosis of the tumor and, consequently, through the organization of specific therapeutic interventions, the prevention of the invasiveness of the pathology, allow to insert this kind of analysis among the most important investigations in the field of cancer prevention. Molecular oncology examinations have targeted the mutational study of the most involved genes in the onset of hereditary and/or family cancers such as breast, ovary, colon, melanoma, stomach, thyroid, etc. In addition, given the growing focus on the molecular mechanisms underlying the individual response to conventional chemotherapeutic drugs and molecular targeted agents responsible for drug resistance, pharmacogenetics exams have been added to those of molecular oncology.

Some genes, when altered and/or mutated, can cause the development of tumors. In some types of cancer, the mutation may affect only somatic cells: in this case, the development will manifest itself only in the subject carrier of the mutation. Otherwise, if the mutation affects germ cells genes, it may occur the possibility to convey to children a susceptibility to the development of tumors. In fact, a significant proportion of cancers are hereditary. For example, it is estimated that about 7% of breast cancers, 10% of ovarian cancers, and about 5-10% of colorectal cancers, are caused by recurrent mutations at specific genes level. The early detection of cancer, with the ability to identify individuals at risk of developing the disease, is now the best way to reduce mortality from it. Determining whether a person has a mutation in a gene involved in neoplastic transformation that predisposes to the development of cancer (susceptibility or genetic predisposition) can significantly decrease its incidence and mortality. For example, as a result of in-depth studies of families at risk, it has been estimated that women who have inherited mutations in breast cancer genes (BRCA1 or BRCA2) are likely to develop breast cancer in 87% of cases, compared with 10% of non-bearers. This probability falls to 44-60% in the case of ovarian cancer, compared with 1% probability of not carriers. In this area, basic research has been developed with the aim of contributing to the study of the molecular mechanisms of oncogenesis, which generally has multistage character, with an initial immortalization and cell transformation and subsequent tumor progression. In this regard, studies at the molecular and functional level have been focused on models of different types of cancer, e.g. melanoma. In parallel, it has been studied the possible oncogenetic role of certain families of genes that have a functional role in embryogenesis, and in general in cell proliferation/differentiation, e.g. homeotic (HOX) genes. The gene expression profiles of purified cancer cells can be evaluated by microarray technique, comparing them with those of normal cells: comparative analysis, based on specific software, allows the identification of genes selectively modulated in the genetic program of tumor cells, in particular of genes specifically involved in the onset and progression of tumors.

The modern goal of cancer therapy is to eliminate the disease by minimizing trauma and paying attention to the quality of life (QOL). With the passing of time, there has been a change of therapeutic paradigms and we have gone from the objective of maximum tolerable treatment to that of minimum effective treatment. This clinical imperative has its foundation in the quick transfer of biological knowledges to the care, integrating molecular informations with the development of new treatment methods. Especially for a delicate operation, even psychologically, such as that for breast cancer. In this setting, we have focused particularly on the technique of sentinel lymph node, demonstrating the possibility to avoid the treatment of the axilla in patients at low risk of recurrence. The term "molecular targeted therapy" is used to refer to agents that target specific pathways activated in the processes of growth, survival, invasion, and metastasis of cancer cells and in tumor neo-angiogenesis. The large and perhaps excessive optimism, caused by the gradual deepening of the knowledges of these mechanisms, has received a further boost by the arrival on the therapeutic scene of imatinib and other drugs belonging to the class of targeted biomolecular agents, including some monoclonal antibodies (McAb) such as trastuzumab, rituximab, cetuximab, and bevacizumab, and some small molecules, already entered clinical practice. But the question we must ask is whether that enthusiasm is justified and supported by scientifically strong and clinically proven data. The difficulties encountered in the research and development of new truly effective molecules and the disappointing results obtained in the early life of some of these agents and, not least, the high costs of treatments must lead to greater caution. The medical oncologist has the inescapable duty to possess sufficient culture to be able to properly use these new therapies in his diagnosis and treatment decision-making.

Keywords: Gynecologic malignancies, diagnosis, treatment, prevention, molecular biology, genetics.

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INTRODUCTION

Gynecologic malignancies, representing 13% of all cancers affecting women, have a major impact on women's health. Cervical, endometrial, and ovarian cancers comprise the majority of these tumors and contribute significant morbidity and mortality to the female population. While cervical and endometrial cancers can be detected early in their development, sadly, many patients present with advanced disease, as do the majority of patients with ovarian cancer. Unfortunately, advanced cases of these malignancies are usually lethal despite modern therapeutic modalities. In order to affect upon these grim statistics, gynecologic researchers have turned to molecular biology in an attempt to elucidate the etiology of these cancers. Recent research describing dominant oncogene and tumor suppressor gene mutations common to these malignancies is providing a basis for the molecular genesis of these cancers. This information should offer new avenues for the development of early detection and chemoprevention, as well as novel treatment strategies [1]. The pioneers in the field of gynecologic oncology set out to establish an evidence-based approach to the care of women with gynecologic cancer, combining the modalities of surgery, chemotherapy, and radiation. Quality of life (QOL) has become the cornerstone of care for these patients, in addition to advancing survival through surgical technology, collaborative research trials, and molecular approaches to early diagnosis and management [2].

OVERVIEW

Cancer is a genetic disease, and inherited or acquired genetic defects contribute to the initiation and progression of cancer. Improved molecular techniques have led to the identification of many of these genetic mutations in gynecologic malignancies. The molecular characterization of cancer has provided a better understanding of tumor formation and the clinical behavior of different tumor types, with important implications for developing screening tests and prognostic markers. Applications of these findings have led to novel targeted gene therapies that correct the critical genetic defects seen in gynecologic cancers [3]. Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant cancer susceptibility syndrome associated with inherited defects in the deoxy-ribonucleic acid (DNA) mismatch repair (MMR) system. HNPCC family members are at high risk for developing colorectal, endometrial, and ovarian cancers. Studies of HNPCC families have helped define the important role that MMR genes play in the molecular pathogenesis of endometrial and ovarian cancers. In fact, genetic susceptibility can be identified in patients with sporadic endometrial and ovarian cancers. It is important to identify patients with HNPCC, as families of mutation carriers may benefit from genetic counseling, testing, and intensified cancer surveillance [4]. Recent studies have estimated that the lifetime risk of endometrial cancer in women with Lynch syndrome/HNPCC is 40-60%. This risk equals or exceeds their risk for colon cancer. While much research has been done to define the natural history and molecular features of Lynch syndrome/HNPCC associated colon cancer, there has been considerably less research defining Lynch syndrome/HNPCC associated endometrial cancer. Given the increased risk of multiple cancers, changing the name of this syndrome from HNPCC syndrome to Lynch syndrome may benefit both patients and clinicians. Clinicians caring for women with Lynch syndrome/HNPCC may stress colon cancer screening and prevention without reviewing endometrial cancer risks and symptoms or screening and prevention options. Perhaps more importantly, women with Lynch syndrome/HNPCC may focus on colon cancer risks and lack understanding of endometrial cancer risks. With increasing evidence that women with Lynch syndrome/HNPCC have significant risks for both colon and endometrial cancers, a multi-disciplinary approach to the management of these individuals is crucial [5].

Gynecologic oncology is a rapidly growing field due to constant advances in immune-histochemistry (IHC) and molecular biology. Currently, molecular pathology plays a limited role in improving patient outcome in gynecologic oncology. However, molecular investigation is providing important insights into the epidemiology, pathogenesis, and progression of female genital cancers. Future roles should include prediction of poor outcome in low-risk cases, more accurate staging of multifocal tumors, identification of new precursor lesions, and prediction of response to specific therapeutic regimens. Gene therapy of some malignant tumors may become important in the near future. In the present time, however, the most significant role of molecular pathology is in the screening and triage of putative cervical cancer precursors and in the possible prophylaxis of these lesions by means of vaccines against Human Papillomaviruses (HPV) [6]. The presence of certain oncogenes within gynecologic tumors indicates that

transformation may be associated with genetic alteration of normal regulatory processes. Several oncogenes have been implicated in the transformation of gynecologic tissues [7]. Mutation of the tumor protein p53 (TP53) suppressor gene, often accompanied by overexpression of mutant TP53, is the most frequent molecular genetic event described thus far in human cancers. In adenocarcinomas of the ovary and endometrium, TP53 overexpression is seen in approximately 10-15% of early and 40-50% of advanced cancers. Similar to many other types of human cancers, ovarian and endometrial cancers that overexpress TP53 contain mutations in conserved regions of the TP53 gene. These mutations are predominantly transitions, which suggest that they arise spontaneously rather than being caused by carcinogen exposure. Alteration of the TP53 gene does not appear to be a feature of endometrial hyperplasias or benign or borderline ovarian tumors (BOT). Although mutation and overexpression of TP53 rarely occur in cancers of the cervix, vulva, and vagina, it has been shown that HPV "early" E6 oncoproteins bind to and inactivate TP53 [8]. The retinoblastoma family members (pRb, pRb2/TP130, and TP107) are tumor suppressor genes involved in controlling four major cellular processes: growth arrest, apoptosis, differentiation, and angiogenesis. Molecular genetic studies have identified abnormalities of these tumor suppressor genes in a large proportion of human cancers. These genetic alterations have emerged as significant factors in the pathogenesis and progression of many types of tumors and are therefore likely to provide relevant information to assess risk in cancer patients. There is a pressing clinical need to identify prognostic and predictive factors for patients with cancer, because there is an undeniable importance in being able to determine which patients will have a favorable outcome without further therapy (prognostic factor) and which will need some additional treatment (predictive factor) [9].

Slow but steady progress has been made in the earlier diagnosis and better treatment of gynecologic cancers, particularly over the last 60 years. Cervical cytology screening programs, where implemented, have led to a remarkable reduction in both the incidence and mortality from clinically invasive cervical cancer. This relatively simple technology has been truly one of the major success stories of modern medicine, but unfortunately this technique has not been uniformly applied to all women in the world, particularly to women in developing countries. New research into cervical cancer etiology, the role of HPV, and the development of vaccines against this virus offer a great hope particularly for developing countries. In addition, the combination of radiotherapy and chemotherapy has resulted in a marked improvement in outcome results for women with advanced cervical cancer. Ovarian cancer has seen the development of effective chemotherapy strategies for this disease. Currently, this disease remains one of the major scourges in industrialized countries, but the continued evolution of knowledge with regard to optimum sequencing of chemotherapeutic agents and surgery offers the prospect for better outcomes, less morbidity, and a better QOL. Ongoing research into the development of newer chemotherapeutic agents and a better understanding of the actual mechanisms regarding the efficacy of chemotherapy and drug resistance offers great promise for the future. Endoscopic surgery for staging and for therapy shows promise for improved QOL as well as outcomes for patients in the future, and offers the challenge of trying to make this technology readily available to all women in the world. As we gain a better understanding of the molecular basis of disease and health, we will truly be able to intervene in a preventive mode [10]. Screening for cervical cancer with the Papanicolaou (Pap) cervical smear has resulted in a decline in incidence and mortality from cervical cancer. Targeting the unscreened population is the next challenge to reduce the incidence of this disease further. Currently, there are no available screening modalities for endometrial or ovarian cancer. Breakthroughs in molecular genetics may result in screening tests for ovarian cancer [11]. The development of biochemical tumor markers has increased the use of antibody-dependent tumor marker assays in gynecologic oncology. Several monoclonal antibodies (McAb) directed against novel epitopes on tumor-associated antigens (TAA) have allowed the development of sensitive assays for serum markers. Assays for human chorionic gonadotrophin (hCG) and TA-4 antigen have been improved. Cancer antigen 125 (CA 125) has provided a useful first-generation marker. Ovarian cystadenocarcinoma-associated antigen (OCAA) and lipid-associated sialic acid (LASA) have been developed for ovarian cancer, transforming growth factor (TGF) for squamous cancer, and placenta protein 4 (PP4) for endometrial and cervical cancer. The most widely applied procedures to identify these markers are immune-fluorescent (IF) microscopy and immune-cytochemical (ICC) staining. Multiple markers and modalities may be required to increase the sensitivity of tumor detection. CA 15-3 and gross cystic disease fluid protein 15 (*GCDFP-15*) markers

have been useful in detecting breast cancer. The application of radionuclide imaging has provided a new field for the diagnosis of gynecologic malignancies [12]. The majority of new studies promoting the use of tumor markers and molecular biological prognostic factors in malignancies affecting women focus on either endometrial or ovarian carcinoma. Other gynecologic malignancies (cervical, vulvar, and vaginal carcinoma) have a much smaller representation in the world literature. Multiple new markers were examined over the last years. Although some markers show promise as potential new consensus prognostic indicators, more work is needed to confirm results and clarify any existing discrepancies [13].

Epigenetic modifications, including DNA methylation, are critically important mediators of normal cell function over the course of our lives. These modifications, therefore, also can play prominent roles in the development of disorders and diseases, including cancer. Genome-wide studies are now beginning to comprehensively decipher the methylome in normal and diseased tissues and cells, providing new insights into the distribution, specificity, and magnitude of modifications that occur and raising questions about these changes at specific loci. Further study of these alterations in specific tissues usually involves targeted approaches, of which there are a number available, all with distinct advantages and disadvantages [14]. Bisulfite sequencing of cloned alleles is a widely used method for capturing the methylation profiles of single alleles. This method combines polymerase chain reaction (PCR) amplification of the bisulfite-modified DNA with the subcloning of the amplicons into plasmids followed by transformation into bacteria and plating on selective media. The resulting colony forming units (CFU) are each comprised of bacterial clones containing the same plasmid reflecting a single allele in the original PCR reaction. Following whole cell PCR and sequencing, the results provide highly detailed information about the status of each cytosine-guanine (CG) site within an allele. Sequencing of a large number of individual clones can provide quantitative information, assuming unbiased PCR, subcloning, and clone selection. The proportion of methylated cytosine at a particular position within the sequenced alleles can be determined by counting the number of alleles showing methylation at the position of interest and dividing this by the total number of clones sequenced [15].

The treatment of gynecologic cancer has evolved over the years, with greater emphasis on tailored surgery and reducing morbidity and mortality related to surgery, particularly in the management of vulvar and cervical cancer. The addition of concurrent chemotherapy to radiation regimens has improved survival of patients with cervical cancer in developed countries. However, most women with cancer in developing countries have advanced untreatable disease and minimal access to anticancer therapies. In the past 15 years, there has been intense research into alternatives to cervical cytologic testing, particularly in low-resourced regions but also in an attempt to improve on cytologic testing in developed countries. Surgical staging in endometrial cancer has enabled the use of adjuvant radiation to be individualized to the patient's particular risk factors for recurrence. The management of ovarian cancer, long stagnant since the introduction of platinum and paclitaxel as chemotherapeutic agents, is set to change with the onset of molecular and genetic profiling and the introduction of novel therapies [16, 17]. Cytotoxic therapy and surgery have improved outcomes for patients with gynecologic malignancies over the last 20 years, but women's cancers still account for over 10% of cancer related deaths annually. Insights into the pathogenesis of cancer have led to the development of drugs that target molecular pathways essential to tumor survival including angiogenesis, DNA repair, and apoptosis [18]. With the rapid development of high-throughput techniques for identifying novel specific molecular targets in human cancer over the past few years, attention to targeted cancer therapy has dramatically increased. The term "targeted cancer therapy" refers to a new generation of drugs designed to interfere with a specific molecular target that is believed to play a critical role in tumor growth or progression, is not expressed significantly in normal cells, and is correlated with clinical outcome. There has been a rapid increase in the identification of targets that have potential therapeutic application. The clinical success of the small-molecule kinase inhibitor imatinib mesylate in chronic myeloid leukemia (CML) and gastrointestinal stromal tumors has accelerated the development of a new era of molecular targeted cancer therapy. The number of agents under preclinical and clinical investigation has grown accordingly. This emphasis on molecular biology and genetics has also resulted in significant changes in the treatment of gynecologic cancers. The most promising signaling pathways to be targeted for therapies in these tumors are the tyrosine kinases (TK) such as epidermal growth factor receptors (EGFR), human EGFR 2 neural (Her-2/Neu), and tyrosine-protein kinase Kit (c-KIT),

mammalian target of rapamycin (mTOR), mitogen-activated protein kinases (MAPK), proteasome, and histone deacetylases, as well as drugs affecting apoptosis and mitosis are under development for clinical application. However, some clinical trials of TP53 gene therapies and farnesyl transferase inhibitors (FTI) have had limited success [19-23].

Gene therapy has rapidly evolved into a field that is treating not only inborn errors of metabolism, but other diseases associated with poor outcomes such as malignancy, where transient gene expression can be therapeutic. Cancer gene therapy is a novel form of treatment that exploits differences at the molecular level between normal and malignant cells. Current gene therapy approaches that are being evaluated include the use of replication competent viruses, mutation compensation strategies, improved targeting with tumor specific promoters, and the utilization of enhanced infectivity viruses. An additional aspect of gene therapy that has gained increased interest in the last several years is the utilization of single-chain antibodies (SCAb). Specifically, SCAb have been utilized to target molecular processes associated with carcinogenesis, as well as to improve gene transfer efficiency [24]. In the era of targeted therapies, patients with gynecologic malignancies have not yet been major beneficiaries of this new class of agents. This may reflect the fact that the main tumor types (ovarian, uterine, and cervical) are a highly heterogeneous group of cancers with variable response to standard chemotherapies and the lack of models in which to study the diversity of these cancers. Cancer-derived cell lines fail to adequately recapitulate molecular hallmarks of specific cancer subsets and complex microenvironments, which may be critical for sensitivity to targeted therapies. Patient-derived xenografts (PDX) generated from fresh human tumor without prior *in vitro* culture, combined with whole genome expression, gene copy number, and sequencing analyses, could dramatically aid the development of novel therapies for gynecologic malignancies. Gynecologic tumors can be engrafted in immune-deficient mice with a high rate of success and within a reasonable period. The resulting PDX accurately recapitulates the patient's tumor with respect to histologic, molecular, and *in vivo* treatment response characteristics. Orthotopic PDX develop complications relevant to the clinic, such as ascites and bowel obstruction, providing opportunities to understand the biology of these clinical problems. Thus, PDX have great promise for improved understanding of gynecologic malignancies, serve as better models for designing novel therapies and clinical trials, and could underpin individualized, directed therapy for patients from whom such models have been established [25].

Neo-vascularization is an early and critical step in tumor development and progression. Tumor vessels are distinct from their normal counterparts morphologically as well as at a molecular level. Recent studies on factors involved in tumor vascular development have identified new therapeutic targets for inhibiting tumor neo-vascularization and thus tumor progression. However, the process of tumor blood vessel formation is complex, and each tumor exhibits unique features in its vasculature. An understanding of the relative contribution of various pathways in the development of tumor vasculature is critical for developing effective and selective therapeutic approaches [26]. Angiogenesis has long been considered an important target for cancer therapy. Initial efforts have primarily focused on targeting of endothelial and tumor-derived vascular endothelial growth factor (VEGF) signaling. As evidence emerges that angiogenesis has significant mechanistic complexity, therapeutic resistance and escape have become practical limitations to drug development. Dynamic changes occur in the tumor microenvironment in response to anti-angiogenic therapy, leading to drug resistance. These mechanisms include direct selection of clonal cell populations with the capacity to rapidly upregulate alternative pro-angiogenic pathways, increased invasive capacity, and intrinsic resistance to hypoxia. A better understanding of the biology of hypoxia and reoxygenation, as well as the depth and breadth of systems invested in angiogenesis, may offer putative biomarkers and novel therapeutic targets. Insights gained through this work may offer solutions for personalizing anti-angiogenesis approaches and improving the outcome of patients with cancer [27]. More recently, the identification of several non-VEGF factors such as ***platelet-derived growth factor*** **(**PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), angiopoietins, a receptor-like kinase 1 (ALK1)/endoglin, endothelins, and ephrins involved in tumor angiogenesis have emphasized the need to develop agents targeting multiple pro-angiogenic pathways. So, besides the successful development of drugs providing a specific VEGF blockade, novel agents targeting alternative angiogenesis-related pathways are being tested. Although it seems that the potential clinical usefulness of these novel compounds have been not yet fully

investigated, sunitinib, sorafenib, pazopanib, and other multikinase inhibitors have certainly displayed encouraging results. A more in-depth clarification of anti-angiogenic agents is still needed, in order to design the best clinical setting and schedule for target-based agents and possibly anticipate potential tools to overcome the emerging issue of anti-angiogenic drug resistance [28].

The family of EGFR is overexpressed in many gynecologic malignancies. Extensive preclinical studies of these receptors demonstrate that they play an important role in supporting the growth of a wide variety of malignancies and that interruption of receptor function or signaling from these receptors leads to inhibition of tumor growth or in certain cases tumor regression. Recently, many therapeutic agents targeting this receptor have demonstrated activity in lung cancer, colon cancer, and head and neck malignancies. Both small molecule inhibitors of EGFR and antibody-based inhibitors in both cervical and ovarian cancer suggest that their activity in unselected women with advanced gynecologic malignancies is very modest. Recently, molecular analysis of lung cancers has identified that the response to small molecule inhibitors of EGFR is highly correlated with activating mutations within the EGFR. It is possible that these agents will be highly effective in a small subset of patients with gynecologic malignancies whose tumors are dependent on EGFR signaling, perhaps through an activating mutation in EGFR or its downstream pathway [29]. Focal adhesion kinase (FAK) is a non-receptor TK, which plays a pivotal role in many aspects of malignant growth including cancer cell survival, migration, invasion, angiogenesis, and metastasis. Various human cancer tissues have demonstrated high expression of FAK or activated FAK, which has been correlated with survival of cancer patients. Among gynecologic cancers, reports have emerged demonstrating that FAK is involved in the pathogenesis of ovarian, endometrial, and cervical cancers. In addition, the polycomb group protein enhancer of Zeste homologue 2 (EZH2), δ-like ligand 4 (Dll4)/notch, and ephrin type-A receptor 2 (EphA2) have also emerged as important regulators of endothelial cell biology and angiogenesis [30, 31]. In ovarian cancer, the best-established anti-angiogenic drug, bevacizumab, has demonstrated only modest prolonged progression-free survival (PFS) and no increased overall survival (OS). The unanswered question is in which clinical situation bevacizumab might benefit ovarian cancer patients most. The cost-benefit analysis in the primary treatment was found not to be favorable but the use in the recurrent ovarian cancer setting might be more compelling. Multi-targeted anti-angiogenic TK inhibitors (TKI) such as cediranib and pazopanib have shown some therapeutic benefits with improvements of PFS and OS in patients with platinum-sensitive as well as resistant ovarian cancers, in whom there is a major need for novel therapies. Very promising is also the observed improvement of PFS in recurrent ovarian cancer in patients when combining cediranib with the poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitor olaparib without giving additional chemotherapy. The anti-angiogenic agent trebananib has achieved similar results like TKI, but has a favorable toxicity profile that does not overlap with those of VEGF inhibitors. In cervical cancer, the addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic chemotherapy-naïve disease results in a significant increase in OS. Considering the lack of therapeutic options in this difficult clinical setting, the inclusion of bevacizumab most likely will become a new standard for recurrent cervical cancer. In uterine sarcomas, as very aggressive malignancies with a substantial need for better therapies, the observed improved PFS with sorafenib warrants further investigation. No data showing a convincing improvement of survival in endometrial cancer have been presented yet. In view of the limited PFS and OS benefit observed with anti-angiogenics in gynecologic oncology, increased morbidity due to side effects of this treatment resulting in loss of QOL and substantial costs, have to be taken into consideration. Thorough case selection based on molecular subgrouping of gynecologic cancers will therefore be a prerequisite for future anti-angiogenic therapy. This will require the integration of molecular diagnostics which still have to be developed and standardized [32].

BREAST CANCER

Breast cancer is one of the most common and leading causes of cancer death in women. Early diagnosis, selection of appropriate therapeutic strategies, and efficient follow-up play an important role in reducing mortality. Dysregulation of apoptosis plays a major role in breast cancer etiology. Cancer cells often contain genetic abnormalities that allow the cells to survive under conditions that normally would trigger their demise. The identification of these mutations has changed the models of cancer progression from a disease of excessive proliferation to one of unbalanced cell death and cell growth. During the last decade,

fundamental knowledge delineating the molecular mechanisms of apoptosis has emerged and now can be exploited to identify novel apoptotic modulators for the treatment of cancer [33]. Taxane-based cytotoxic therapy is commonly prescribed for breast and ovarian cancers. Although these cancers are often sensitive to such therapy, clinical benefit and OS are limited owing to the development of chemoresistance and recurrence. Biologic agents that specifically target proteins of growth factor signaling pathways, which are hyperactivated in cancers, offer attractive targets for cancer therapeutics and may work synergistically with standard taxane-based chemotherapy to improve patient outcomes. Many clinical trials of biologic agents (angiogenic, TK, and antibody inhibitors) in combination with taxane-based therapy for ovarian and breast cancers have shown promising results [34]. Recently, HER-2/neu in breast cancer has been routinely used to guide treatment of using trastuzumab in <25-30% of patients. More new biomarkers will be still expected in the future to tailor treatments. However, there are still many obstacles in developing clinically useful biomarker tests for clinical practice. A lack of specificity of tumor markers and lack of sensitivity of testing systems have been noticed, which limit their clinical use. Finding biomarkers for breast cancer could allow physicians to identify individuals who are susceptible to certain types and stages of cancer to tailor preventive and therapeutic modalities based on the genotype and phenotype information. These biomarkers should be cancer-specific, and sensitively detectable in a wide range of specimens containing cancer-derived materials, including body fluids (plasma, serum, urine, saliva, etc.), tissues, and cell lines. The new trends and approaches in breast cancer biomarker discovery could be potentially used for early diagnosis, development of new therapeutic approaches, and follow-up of patients [35]. However, some biologic agents still need larger trials to assess safety and efficacy. As research into the heterogeneity and complexity of ovarian and breast cancers improves our understanding of the molecular pathways involved, there is no question that targeted therapies with biologic agents will expand the future array of available cancer therapeutics.

CERVICAL CANCER

Cervical cancer is the second most common malignancy and the second leading cause of cancer death and remains an important health problem for women worldwide, especially minority and underserved women, despite its decline in countries where organized screening programs are in place. Each year, an estimated 500,000 cases are newly diagnosed. Among populations, there are large differences in incidence rates of invasive cervical cancer: these reflect the influence of environmental factors, screening Pap tests, and treatment of pre-invasive lesions. The morbidity of treatment and the mortality for advanced lesions are high, OS remains 40%, despite an understanding of the epidemiologic risks, and morbid and costly treatment, a frustrating situation because the cervix is accessible and a good screening test, the Pap smear, exists. HPV is an important risk factor, and the molecular evidence for its role is overwhelming. HPV infection is the most common sexually transmitted disease (STD), with >80% of the population infected at some time in their life. In rare cases, this infection may lead to cervical cancer. Virtually all squamous cell carcinomas (SCC) and the overwhelming majority of adenocarcinomas of the cervix are HPV positive. HPV integration in the genome will lead to inactivation of the TP53 and the Rb pathways. Integration is essential for the onset of cervical carcinogenesis, but is probably not sufficient for progression to invasive cervical cancers. It is likely that several cofactors, such as environmental, viral, and host-related factors, are necessary for the development of cervical cancer.

The high-risk HPV subtypes 16, 18, 31, 33, and 51 have been recovered from >95% of cervical cancers. New strategies, based on the clinical and molecular aspects of cervical carcinogenesis, are desperately needed. Molecular markers may help us decide which lesions are at highest risk of progression to invasion and which invasive lesions are likely to recur. The HPV vaccine could be effective in eradicating this cancer. Chemoprevention of precursor lesions is promising [36, 37]. Chemoprevention refers to the use of chemical agents to prevent or delay the development of cancer in healthy populations. Chemoprevention studies have several unique features that distinguish them from classic chemotherapeutic trials: these features touch on several disciplines and weave knowledge of the biology of carcinogenesis into the trial design. In the design of chemoprevention trials, four factors are important:

1) high-risk cohorts must be identified;

2) suitable medications must be selected;

3) study designs should include phases I, II, and III; and

4) studies should include the use of surrogate endpoint biomarkers (SEB).

SEB are sought because cancer develops over a long period, and studies of chemopreventives would require a huge number of subjects followed for many years. SEB serve as alternative endpoints for examination of the efficacy of chemopreventives in tissue. High-risk cohorts include women with cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL). Nutritional studies have helped define micronutrients of interest (folate, carotenoids, vitamin C, and vitamin E). Other medications of interest include retinoids (4-hydroxyphenylretinamide [4-HPR], retinyl acetate gel, topical all-trans-retinoic acid), polyamine synthesis inhibitors (α-difluoromethylornithine [DFMO]), and nonsteroidal anti-inflammatory drugs (NSAID) such as ibuprofen. Chemoprevention studies of the cervix have tested retinyl acetate gel and all-trans-retinoic acid. Trials of all-trans-retinoic acid, β-carotene, and folic acid have been carried out, whereas phase III trials of all-trans-retinoic acid have been completed and have shown significant regression of CIN 2 but not CIN 3. SEB under study include:

1) quantitative cytology and histopathology;

2) HPV type testing;

3) biologic measures of proliferation, regulation, differentiation, and genomic instability; and

4) fluorescence spectroscopic emission [38].

We have made great strides in understanding the molecular mechanism of oncogenesis of HPV, focusing on the action of the E6 and E7 viral oncoproteins. These oncoproteins function by inactivating cell cycle regulators TP53 and pRb, thus providing the initial event in progression to malignancy. Cervical cancers develop from precursor lesions, which are termed SIL and are graded as high or low, depending on the degree of disruption of epithelial differentiation. Viral production occurs in low-grade lesions and is restricted to basal cells. In carcinomas, viral DNA is found integrated into the host genome, but no viral production is seen. The well-defined pre-invasive stages, as well as the viral factors involved at the molecular level, make cervical carcinoma a good model for investigating immune therapeutic alternatives or adjuvants to standard treatments [39]. Although a complete paradigm of the development of cervical cancer from normal cervical epithelium is not yet known, continued study in this area will hopefully lead to a defined progression of molecular and immunologic abnormalities that cause the disease. The goal would be to use this information to help prevent and/or treat cervical cancer in the future [40]. HPV prophylactic vaccines are expected to eradicate ~70% of cervical cancers. An HPV test was demonstrated to improve the sensitivity of cytology and prolong the screening interval safely. Type-specific HPV testing will play an important role in the detection and follow-up of cervical neoplastic lesions, as well as monitoring the efficacy of HPV vaccines. The combined use of cell proliferation markers with cytology can improve sensitivity, and some molecular markers seem to be related to the degree of dysplasia [41-43].

Several lines of evidence suggest the importance of the host's immune response, especially cellular immune response, in the pathogenesis of HPV-associated cervical lesions. These observations formed a compelling rationale for the development of vaccine therapy to combat HPV infection. Because there is no effective culturing system to propagate HPV, traditional approaches for studying HPV and developing vaccines have been hampered. However, studies using recombinant subunit preparations in animals have yielded promising results and encouraged their investigation in human trials. Strategies focused on the induction of effective humoral immune responses for prophylaxis against subsequent HPV infection [44]. Both prophylactic and therapeutic HPV vaccine strategies have been developed. Prophylactic strategies focus on the induction of effective humoral immune responses against subsequent HPV infection. In this respect, impressive immune-prophylactic effects have been demonstrated in animals using virus-like particles (VLP). VLP are antigenic and protective, but are devoid of any viral DNA that may be carcinogenic to the host. For treatment of existing HPV infection, techniques to improve cellular immunity by enhancing viral antigen recognition are being studied. For this purpose, the oncogenic proteins E6 and E7 of HPV-16 and -18 are the focus of current clinical trials for cervical cancer patients. The development of successful HPV-specific vaccines offers an attractive alternative to existing screening and treatment programs for cervical cancer and may result in a substantial reduction in the worldwide morbidity from this disease [45].

Although current cytomorphology-based cervical cancer screening has reduced the incidence of cervical cancer, Pap smears are associated with high false positive and false negative rates. This has spurred the search for new technologies to improve current

screening. New methodologies are automation of Pap smear analysis, addition of new biological or molecular markers to traditional cytology, or using these new markers to replace the current screening method. New screening approaches, such as quantitative cytochemistry, detection of loss of heterozygosity (LOH), and hypermethylation analysis have the potential to replace or augment current screening. In short, HPV DNA detection stands closest to implementation in nation-wide screening programs of all markers reviewed. However, specificity is low in women aged <35 years and the psychological effects of knowledge of HPV positivity in absence of cervical pre-malignant disease are important drawbacks. New technologies based on molecular changes associated with cervical carcinogenesis might result in comparable sensitivity, but improved specificity. Hypermethylation analysis is likely to be more objective to identify patients with high-grade SIL (H-SIL) or invasive cancer with a higher specificity than current cytomorphology-based screening [46]. Since the introduction of molecular biology into the HPV field, there have been rapid advances and improvements in HPV diagnosis. The various molecular diagnostic methods for detection of HPV DNA (dot blot hybridization, Southern blot hybridization, in situ hybridization [ISH], Hybrid Capture [HC] Test, and PCR) can be selected by taking into consideration some factors such as characteristics of sample, sensitivity of HPV test, and expenses. HPV DNA testing is a clinically useful diagnostic method, when used in conjunction with the Pap smear in population screening or in conjunction with cytology and colposcopy to identify women infected with high-risk HPV or women who had equivocal cervical lesions. Despite the confusion, a multitude of reports demonstrate that HPV DNA testing has clinical utility [47, 48].

Cervical cancer is a preventable disease that is curable when detected early. For advanced-stage cancer, the prognosis is worse. Current therapy for early-stage disease is surgical, with adjuvant therapy being administered according to histopathologic findings. Cisplatin, in combination with external beam irradiation for locally advanced disease, or as monotherapy for recurrent/metastatic disease, has been the cornerstone of treatment for more than two decades. Other investigated cytotoxic therapies include paclitaxel, ifosfamide, and topotecan, as single agents or in combination, revealing unsatisfactory results. Pelvic radiation with concomitant platinum-based chemotherapy is used to treat locally advanced disease, whereas metastatic and recurrent lesions continue to be difficult to effectively treat and cure. Clinical trials in this latter scenario have suggested that clinical benefit may be associated with biologic therapies [49]. Until recently, the role of pharmacotherapy in cervical cancer was restricted to palliation of advanced/metastatic or recurrent disease. During the past two decades, this reluctant attitude towards chemotherapy has been modified after a series of randomized controlled trials (RCT) demonstrated its beneficial contribution as an adjunct to radiotherapy or surgery in early and locally advanced cervical cancer. Moreover, new combinations of cytotoxics, together with novel molecular target agents, open new perspectives in the treatment of primary and recurrent cervical cancer [50]. Over the years, much progress has been made in radiation therapy and in chemotherapy, but it took three decades for the arrival of concurrent chemoradiation therapy, which significantly improved survival among women with advanced cervical cancer. This fact underscores the need and the importance for continuing efforts in clinical research. While current standards of therapy are being fine-tuned as more information is being gathered, great strides are being made in the areas of molecular and cancer biology [51]. Effective cytotoxic treatment options for advanced cervical cancer are exceedingly limited. Cisplatin-based combination chemotherapy, the most commonly used cytotoxic therapy, has produced response rates ranging from 20% to 30% and OS <10 months. Because of the minimal degree of success with cytotoxic therapies and the poor prognosis of patients with this disease, interest has increased in targeted therapeutics for the treatment of cervical cancer. In recent years, significant improvements in our understanding of the altered molecular events in tumor cells have led to the discovery of new targets and agents for clinical testing. Among the most investigated molecular targets are EGFR and VEGF signaling pathways, both playing a critical role in cervical cancer development. Studies with anti-angiogenetic agents showed encouraging clinical efficacy and acceptable toxicity. A great number of other molecular agents targeting critical pathways in cervical malignant transformation are being evaluated in preclinical and clinical trials, reporting preliminary promising data. Other interesting results have been obtained by immune-therapeutic strategies. Since biological characteristics of cervical cancer, especially in recurrent disease, are still partially unknown, future studies are necessary to understand mechanisms involved in cervical cancer carcinogenesis, in order to

give to patients the most tailored and efficient treatments [52-57].

ENDOMETRIAL CANCER

Among female-specific cancers worldwide, carcinoma of the endometrium is the third most common after breast cancer and cervical cancer. In addition, it is the most common gynecologic cancer in the United States (USA) and Europe. The incidence of this disease appears to be increasing. The cause of this increase is multifactorial, but a few possible factors involved are increasing obesity, an aging population leading to more post-menopausal women, and greater tamoxifen use. Most endometrial cancers, in fact, occur in post-menopausal women and produce abnormal uterine bleeding (AUB). Some women exhibit the pre-malignant changes of atypical endometrial hyperplasia before developing an overt carcinoma. Identified epidemiologic risk factors include obesity, diabetes mellitus, use of unopposed exogenous estrogens, estrogen-secreting tumors, and a reproductive history characterized by prolonged estrogenic predominance. Diagnosis can be readily established by outpatient endometrial biopsy. Because clinical estimates of disease extent and spread are subject to substantial error, endometrial cancer is now a surgically staged neoplasm. A well-defined set of surgico-pathologic risk factors have been incorporated into the staging scheme. Women with extra-uterine disease comprise about 20% of cases and are at greatest risk for tumor recurrence and death from disease. Within the much larger group of women whose tumors are limited to the uterus, recurrence risk can be stratified by cytologic grade, cell type, depth of myometrial invasion, and extension to the cervix. About 2/3 of women have low-risk disease confined to the uterus when these criteria are employed, while the remaining 1/3 have high-risk subtypes. Recent areas of investigation have focused on molecular and genetic markers. Two clinical observations currently being examined are the poorer survival of black women with uterine cancer and the apparent association of endometrial lesions with chronic tamoxifen suppression in women with breast carcinomas [58]. The etiology of the racial and ethnic disparities that exist in endometrial cancer incidence and outcome is multifactorial and complex. Potential explanations include cancer biology, differences in access to care, socio-demographic characteristics, response to treatment, and comorbid factors. Strategies and recommendations to reduce or eliminate differences in endometrial cancer outcome include advocacy for more research to clarify the underlying causes of cancer disparities at all levels, including the molecular basis of disparate outcomes, improving access to quality healthcare services, establishing culturally competent models of healthcare delivery, and developing novel cost-effective screening and early prevention methods [59].

Endometrial cancer fortunately has low mortality, which is due largely to its presentation with AUB and its subsequent early diagnosis. The morbidity associated with therapy for early lesions is moderate. Hyperplasia with atypia should be treated as early cancers. Many molecular markers are currently under study. Markers may soon help us identify invasive lesions at higher risk of recurring and thus more suitable for adjunct therapy. Screening in the general population is not recommended, but a high-risk group that is more suitable for screening could be identified, including obese and nulliparous women, those treated with unopposed estrogen or tamoxifen, or those with family or past histories of breast or colon cancer. Development of chemoprevention with an oral contraceptive (OC) during the reproductive years is under way, and there may be a role for chemoprevention in the reversal of hyperplasias [60, 61]. From the dualistic classification that divides endometrial cancer into two types with distinct underlying molecular profiling, histopathology, and clinical behavior, arises a deeper understanding of the carcinogenesis pathways. Controversies are still seen in the histological differential diagnosis of hyperplasia and well-differentiated endometrial carcinoma. Prediction of endometrial cancer in patients with hyperplasia with atypia, with the available markers has not been reliable yet. Hence, these patients require more attention in the clinical management. Endometrial hyperplasia is proliferation of endometrial glands resulting in a higher gland/stroma ratio. Cytological atypia, which may progress to or co-exist with endometrial cancer and other pathological changes, results from estrogen stimulation unopposed by progesterone. Biomarkers whose expression is altered in cases of endometrial hyperplasia or cancer such as progesterone receptor (PR), insulin-like growth factor 1 (IGF-1), retinaldehyde dehydrogenase type 2 (RALDH2), and secreted frizzled-related protein 4 (SFRP4), seem to be promising to use as early-stage tumor markers. Mutation of phosphatase and tensin homolog (PTEN) is present in 83% of endometrial adenocarcinoma cases, making it the most frequent early molecular genetic alteration in type I endometrial tumors, which are generally associated with

hyperplasia. Cyclooxygenase-2 (COX-2) is important in tumorogenic transformation of hyperplasia. Expression of COX-2 decreases apoptosis, increases angiogenesis, and is related to invasiveness. COX-2 expression increases significantly in cases of well-differentiated endometrial adenocarcinoma. Prostaglandin E2 (PGE2) is known to regulate aromatase gene expression and is the product of COX-2. The data about aromatase inhibitors (AI) are promising: in breast cancer patients, treatment with tamoxifen induces uterine abnormalities as early as 3 months after the initiation of therapy. In contrast, these abnormalities are not seen in patients who receive AI and switched therapy after tamoxifen withdrawal may reverse tamoxifen-associated endometrial thickening [62].

The clinical and pathologic prognostic factors for endometrial cancer are well known and instrumental in determining the need for adjuvant therapy. Recently, research has been focused on the identification of molecular changes leading to different histologic subtypes to improve classification of endometrial cancer. The identification of novel mutations and molecular profiles should enhance our ability to personalize adjuvant treatment with genome-guided targeted therapy [63]. Most human cancers are thought to arise from alterations in oncogenes and tumor suppressor genes. Molecular techniques have been used to identify specific genetic alterations in endometrial cancers. Overexpression of the HER-2/neu oncogene occurs in 10% of endometrial cancers and correlates with poor survival. Alterations in other receptor TK such as macrophage colony-stimulating factor receptor (M-CSFR) and EGFR also occur in some cases. The myelocytomatosis (c-myc) oncogene, which encodes a nuclear transcription factor, also may be overexpressed in some invasive cancers. Mutations in the Kirsten rat sarcoma (K-ras) oncogene occur in 10% and in 20-30% of American and Japanese endometrial cancers, respectively. K-ras mutations also have been observed in endometrial hyperplasias, and this may represent an early event in the development of some cancers. Mutation of the TP53 gene, with resultant overexpression of mutant TP53, occurs in 20% of endometrial adenocarcinomas and in 90% of cases of serous endometrial tumors. Overexpression of TP53 is associated with advanced stage and poor survival. Because TP53 mutations do not occur frequently in endometrial hyperplasias, this may be a relatively late event in endometrial carcinogenesis. Recent studies have shown that mutations occur in microsatellite sequences in some endometrial cancers. Because microsatellite instability in HNPCC has been found to be caused by mutations in DNA repair genes, similar mutations are being sought in endometrial cancers. Although several molecular alterations have been identified, the molecular pathogenesis of endometrial cancer remains poorly understood [64]. Aberrant DNA methylation is an important molecular alteration commonly detected in various malignancies. Hypermethylation and expression silencing have been frequently found in multiple genes including those for steroid receptors, tumor suppressors, and DNA repair factors. Differential DNA methylation patterns are detected in type I and type II endometrial cancers, suggesting divergent epigenetic backgrounds and unique tumorigenic pathways. DNA methylation-based assays may be explored as a useful adjunct diagnostic tool. Epigenetic modification reagents, including DNA methyltransferase and histone deacetylase inhibitors, when used alone or in combination with conventional chemotherapy, may be beneficial for endometrial cancer patients. Recent studies on epigenetic reactivation of the PR provide a novel approach for re-sensitization of advanced, PR-negative endometrial cancers to progestational therapy [65]. The most frequent genetic alteration of endometrioid endometrial cancer is PTEN. Phosphatidylinositol-3 kinase catalytic subunit α (PI3CA) and K-ras mutations are less common but are often associated with PTEN. Alterations in MutL homolog 1 (MLH1) and Mut6 homolog 6 (MSH6) are documented with microsatellite instability. β-catenin has a minor but significant association. Epidemiological as well as clinical and experimental data identified the IGF (IGF-1, IGF-2) as important players in gynecologic cancers in general and endometrial tumors in particular. The IGF-1 receptor (IGF1R), which mediates the proliferative and anti-apoptotic activities of both ligands, emerged in recent years as a promising therapeutic target in oncology. However, most clinical trials conducted so far led to mixed results, emphasizing the need to identify biomarkers that can predict responsiveness to anti-IGF1R-targeted therapies. Anti-oncogenes TP53 and breast cancer susceptibility gene-1 (BRCA1) play a key role in the etiology of gynecologic cancers and, therefore, their interaction with IGF1R is of high relevance in translational terms [66]. Conversely, TP53 mutation is more often associated with non-endometrioid cancer, others being inactivation of TP16 and/or overexpression of HER-2/neu. Absence of E-cadherin is more often than not present in non-endometrioid cancers and is associated with poor

prognosis. Novel agents that target the v-akt murine thymoma viral oncogene (AKT)-phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-mTOR pathway and those that inhibit EGFR, VEGF, FGF receptor 2 (FGFR2), and folate receptors (FR) are currently being investigated. Novel targeted agents, either alone or in combination with cytotoxic agents, may result in superior treatment for patients [67]. Understanding and identifying molecular biology and genetics of endometrial cancer are central to the development of novel therapies. More recently, with the introduction of personalized cancer treatment, several biologic agents have been developed that target specific pathways critical to tumor initiation and growth. Molecular studies have found that many endometrial cancers are driven by some of these tumorigenic pathways, which has led to early clinical studies evaluating the role of these targeted agents in patients with advanced or recurrent endometrial cancer [68]. Hence, targeted molecular therapies are emerging as possible treatment candidates [69, 70].

The median survival of women with advanced or recurrent endometrial cancer is <1 year. Only half the women with early stage endometrial cancer and poor prognostic factors such as high grade or deep myometrial invasion will survive for 5 years. The treatment of endometrial cancer is rapidly evolving. The cornerstone of curative therapy for patients with endometrial cancer is surgical treatment. Surgical therapy of early-stage endometrial cancer includes full staging, including pelvic and para-aortic lymphadenectomy. While most women with early-stage endometrial cancer can anticipate tumor recurrence, studies have demonstrated no improvement on survival. With surgery alone, a significant minority of women with deeply invasive or high-grade tumors will experience local, regional, or distant recurrences of their disease. Therefore, adjuvant therapies have been proposed for these women. While radiotherapy is effective at reducing the risk of local and regional recurrences, systemic adjuvant chemotherapy in this high-risk, early-stage patient population is currently the focus of several RCT. In addition, for women with early-stage tumors with atypical histology, such as papillary serous and clear cell malignancies, the role of adjuvant therapy remains uncertain. Optimizing management of women with early-stage disease requires a careful assessment of the risk of recurrent disease, the potential benefit of various adjuvant strategies, and the risk associated with adjuvant therapy [71]. Cytotoxic chemotherapy is the mainstay of therapy for metastatic and advanced endometrial cancer. However, survival rates remain poor. The most active chemotherapy agents are anthracyclines, platinum compounds, and taxanes. Single-agent chemotherapy with the most activity includes ifosfamide, cisplatin/carboplatin, doxorubicin, and paclitaxel. Combination chemotherapy provides a response rate of 40-60%: however, median survival is still <1 year. Combination chemotherapy has produced higher response rates than single agent therapy. Cisplatin and doxorubicin combination chemotherapy has served as the control arm in many trials. Three-drug combination regimen has shown the highest response rate but with increased toxicity. Despite the lack of published data supporting the superiority of the paclitaxel plus carboplatin combination over doxorubicin and cisplatin, many centers prefer this regimen as a standard of care. Hormonal therapy should be considered in patients with low-grade tumors and in those with a poor performance status. Progestin therapy offers a 10-20% response rate and survival of <1 year. Progestins are most effective in women with well-differentiated tumors and a long disease-free interval. There is no role for adjuvant progestin therapy in early-stage disease [72-74]. Hormone therapy has been palliative for advanced/recurrent endometrial cancer. High remission rates are seen in well-selected stage I, grade 1 endometrial cancer of young women using hormone therapy (usually progestins) as fertility-preserving treatment. Many other hormones, such as gonadotrophin-releasing hormone analogs (GnRHa), selective estrogen receptor (ER) modulators (SERM), AI, intrauterine progestins, and others are potential modalities. GnRHa has been used adjunctively as second-line hormone therapy for fertility sparing after progestin failed. AI have shown their potential in treating endometrial cancer and endometrial hyperplasia as single agent or in combination with progestins. Intrauterine progestins seem efficacious in treating endometrial hyperplasia: their applications on endometrial cancer patients, however, have been limited to post-menopausal women with poor surgical risk. Translational research based on molecular mechanisms is mandatory to a more appropriate utilization of hormone therapy [75]. New areas of research include the identification and evaluation of new active endocrine therapies (i.e. arzoxifene hydrochloride [LY353381.HCl] and letrozole), chemotherapeutics (i.e. herceptin), evaluating chemotherapeutic agents in combination (i.e. paclitaxel, doxorubicin, and platinum), in addition to radiation or instead of radiation. Further significant

advances in radiotherapy, hormonal therapy, and chemotherapy are unlikely. New avenues under development involve the specific molecules and pathways responsible for the initiation and growth of endometrial carcinoma, including tumor suppressor genes, DNA MMR genes, oncogenes, and molecules involved in adhesion, invasion, and angiogenesis. Exciting developments in understanding the molecules involved in tumor development and metastasis will allow the development of specific and selective inhibitors. Among targeted therapies, the more promising ones are mTOR inhibitors and anti-angiogenic agents. Clinical trials are ongoing to further explore how to best incorporate novel agents into the current treatment algorithm with the aim to improve outcome for women with endometrial adenocarcinomas [72, 74].

Since the outcome of primary advanced or recurrent endometrial cancer is still poor, there is a need to improve our knowledge on molecular markers in order to personalize treatment. In addition, we need to continue the search for new treatment strategies with a better balance between efficacy and toxicity. Among molecular and histological markers, blood vessel space involvement and chemotherapy induced regressive changes are new prognostic markers in endometrial cancer. The tumor biology changes during its evolution. The optimal moment to decide on tumor biology is therefore the recurrent setting. A biopsy of the recurrent tumor is the best guarantee to characterize it correctly. Furthermore, neo-adjuvant chemotherapy followed by interval debulking is a valuable treatment option for endometrial cancer with transperitoneal spread since optimal cytoreduction was achieved in 78% with a low morbidity [76]. However, progress in the treatment of advanced and recurrent endometrial cancer has been limited. This has led to a shift from the use of traditional chemotherapeutic agents and radiotherapy regimens to the promising area of targeted therapy, given the large number of druggable molecular alterations found in endometrial cancer. To maximize the effects of directed targeted therapy, careful molecular characterization of the endometrial tumor is necessary. This represents an important difference in the use of targeted therapy vs. traditional chemotherapy or radiation treatment [77, 78]. Molecular therapies are potential therapeutic candidates for more effective and specific treatments. In the genomic era, a deeper knowledge about molecular characteristics of cancer provides the hope for the development of better therapeutic approaches. Targeting both genetic and epigenetic alterations, attacking tumor cells using cell-surface markers overexpressed in tumor tissue, reactivating anti-tumor immune responses, and identifying predictive biomarkers represent the emerging strategies and the major challenges [79, 80].

OVARIAN CANCER

Ovarian cancer accounts for approximately 4% of cancer deaths in women worldwide, with around 225,000 estimated new cases diagnosed each year and 140,000 related deaths. Prompt diagnosis is challenging because of the non-specific symptoms exhibited during the early stages of the disease: consequently, 50% of cases present with advanced metastatic cancer, and 5-year survival rates are limited to 10-30%. Furthermore, disease recurrence occurs in a high proportion of cases, and the survival rate is only 30% even in patients who are sensitive to platinum-based chemotherapy. The increased characterization of the molecular mechanisms involved in the development and progression of ovarian cancer has resulted in improved therapeutic strategies with molecular-targeted agents. These include targeting BRCA mutations to affect DNA repair, inhibition of the mTOR and MAPK pathways, and anti-angiogenesis therapies. Ultimately, personalized therapy using novel biomarkers in parallel with improved early detection techniques could significantly enhance the prognosis of ovarian cancer patients [81]. Nevertheless, the molecular events leading to the development of epithelial ovarian cancer and the molecular factors that may predict response to treatment are not well established. Such knowledge would not only improve the understanding of the biology of epithelial ovarian cancer, but may help in the identification of new tumor markers and the design of molecular therapies for epithelial ovarian cancer. The accumulation of data derived from new technologies, as well as that obtained from well-established methods, has provided new insights into gene expression profiles in epithelial ovarian cancer. The utilization of novel technologies that allow high throughput analysis of thousands of genes may lead to the development of new biomarkers or novel therapies that are urgently needed in this deadly disease [82]. In recent years, the development of knowledge in molecular biology of ovarian cancer coupled with the new technologies offers enormous opportunity to learn about etiology of ovarian cancer, and give us a powerful tool for early diagnosis, prognosis, and treatment of this disease. In particular, small cancer specimens from patients have become

extremely informative thanks to techniques such as laser capture microdissection (LCM), tissue lysate arrays (TLA), reverse trascriptase PCR (RT-PCR), and mass spectrometry. All of this, coupled with advancements in bioinformatics, have allowed the explosion of genomics, transcriptomics, and proteomics [83].

Ovarian cancer is a complex disease composed of different histological grades and types. Epidemiological studies identified multiple exogenous and endogenous risk factors for ovarian cancer development. Among them, an inflammatory stromal microenvironment seems to play a critical role in the initiation of the disease. The interaction between such a microenvironment, genetic polymorphisms, and different epithelial components such as endosalpingiosis, endometriosis, and ovarian inclusion cysts in the ovarian cortex may induce different genetic changes identified in the epithelial component of different histological types of ovarian tumors. Genetic studies on different histological grades and types provide insight into the pathogenetic pathways for the development of different disease phenotypes. However, the link between all these genetic changes and the etiological factors remains to be established [84]. In fact, despite numerous studies that have carefully scrutinized the ovaries for precursor lesions, none have been found. This has led to the proposal that ovarian cancer develops de novo. Studies have shown that epithelial ovarian cancer is not a single disease, but is composed of a diverse group of tumors that can be classified based on distinctive morphologic and molecular genetic features. One group of tumors, designated type I, is composed of low-grade serous, low-grade endometrioid, clear cell, mucinous, and transitional (Brenner) carcinomas. These tumors generally behave in an indolent fashion, are confined to the ovary at presentation, and, as a group, are relatively genetically stable. They lack mutations of TP53, but each histologic type exhibits a distinctive molecular genetic profile. Moreover, carcinomas exhibit a shared lineage with the corresponding benign cystic neoplasm, often through an intermediate step (BOT), supporting the morphologic continuum of tumor progression. In contrast, another group of tumors, designated type II, is highly aggressive, evolves rapidly, and usually presents in advanced stage. Type II tumors include conventional high-grade serous carcinoma, undifferentiated carcinoma, and malignant mixed mesodermal tumors (carcinosarcoma). They display TP53 mutations in over 80% of cases and rarely harbor the mutations that are found in type I tumors. Recent studies have also provided cogent evidence that what have been traditionally thought to be primary ovarian tumors actually originate in other pelvic organs and involve the ovary secondarily. Thus, it has been proposed that serous tumors arise from the implantation of epithelium (benign or malignant) from the Fallopian tube. Endometrioid and clear cell tumors have been associated with endometriosis, which is regarded as the precursor of these tumors. As it is generally accepted that endometriosis develops from endometrial tissue by retrograde menstruation, it is reasonable to assume that the endometrium is the source of these ovarian neoplasms. Finally, preliminary data suggest that mucinous and transitional (Brenner) tumors arise from transitional-type epithelial nests at the tubal-mesothelial junction by a process of metaplasia. Appreciation of these new concepts will allow for a more rationale approach to screening, treatment, and prevention that potentially can have a significant impact on reducing the mortality of this devastating disease [85]. Thus, although ovarian carcinomas have been thought to arise from the ovarian surface mesothelial layer for a long time, the possibility that they develop from Müllerian remnants within para-ovarian tissues merits further consideration. Molecular genetic studies suggest that ovarian cystadenomas, low-malignant potential tumors, and carcinomas are not part of a disease continuum but do represent separate disease entities. Recent advances in our understanding of the molecular genetic changes associated with ovarian epithelial tumor development can be summarized in a working genetic model for ovarian tumorigenesis, which can provide a framework for further studies. Certain molecular changes, such as telomerase expression and alterations at DNA methylation levels, are associated with both tumors of low-malignant potential and carcinomas but not with cystadenomas. Mutations in the TP53 gene and the development of multiple LOH are specific for the malignant phenotype. The nature of the specific chromosomes affected by the latter losses in a given tumor dictates its biologic aggressiveness [86-88].

In this way, the study of ovarian embryogenesis can provide important clues about the etiology and development of the different subtypes of ovarian neoplasms. The celomic epithelium, also called germinal epithelium, was once thought to represent the site of origin of most cellular elements present in the adult ovary. However, recent observations at the morphological, functional, and molecular biological

levels strongly suggest that this epithelium plays little or no role in ovarian development. The same observations provide strong support for an important role of the components of the fetal excretory system. These conclusions weaken the hypothesis that the celomic epithelium is the site of origin of ovarian epithelial tumors. Knowledge of the origin and maturation of germ cells can shed light on several clinico-pathological characteristics of germ cells tumors, including their occasional extra-gonadal origin and differences in the biological behavior of ovarian versus testicular lesions. Knowledge of the mechanisms of regulation of mitotic and meiotic activity during ovarian germ cell maturation can provide insights into the molecular genetic determinants of germ cell neoplasms. The elucidation of molecular pathways actively involved in controlling gonadal differentiation may shed further light into our understanding of the relationship between aberrant differentiation and predisposition to gonadal cancers [89]. Ovarian carcinogenesis, as in most cancers, involves multiple genetic alterations. A great deal has been learned about proteins and pathways important in the early stages of malignant transformation and metastasis, as derived from studies of individual tumors, microarray data, animal models, and inherited disorders that confer susceptibility. However, a full understanding of the earliest recognizable events in epithelial ovarian carcinogenesis is limited by the lack of a well-defined pre-malignant state common to all ovarian subtypes and by the paucity of data from early-stage cancers. Evidence suggests that ovarian cancers can progress both through a stepwise mutation process (low-grade pathway) and through greater genetic instability that leads to rapid metastasis without an identifiable precursor lesion (high-grade pathway) [90-94].

Preferential involvement of peritoneal structures contributes to the overall poor outcome in epithelial ovarian cancer patients. Advances in biotechnology, such as DNA microarray, are a product of the Human Genome Project (HGP) and are beginning to provide fresh opportunities to understand the biology of epithelial ovarian cancer. In particular, it is now possible to examine in depth, at the molecular level, the complex relationship between the tumor itself and its surrounding microenvironment. Changes in both the inflammatory and non-inflammatory cell compartments, as well as alterations to the extracellular matrix, appear to be signal events that contribute to the remodeling effects of the peritoneal stroma and surface epithelial cells on tumor growth and spread. These alterations may involve a number of proteins, including cytokines, chemokines, growth factors, either membrane or non-membrane bound, and integrins. Interactions between these molecules and molecular structures within the extracellular matrix, such as collagens and the proteoglycans, may contribute to a peritoneal mesothelial surface and stromal environment that is conductive to tumor cell proliferation and invasion. These alterations need to be examined and defined as possible prognosticators and as therapeutic or diagnostic targets [95]. Immune cells in the ovarian stromal microenvironment play an important role in ovarian tumorigenesis. Up-regulation of immune cell-derived mediators during ovulation may generate a pro-inflammatory niche, which may subsequently induce transformation of normal ovarian epithelial cells or endometriotic cells in the ovary. Once transformed ovarian epithelial cells develop, an immune-editing process occurs in which immune cells and their mediators dictate the development and progression of ovarian tumors. Tumor cells also develop several mechanisms to evade anti-tumor immunity by developing an immune-suppressive microenvironment. The differences in the population of immune cells infiltrating into ovarian tumor tissues are associated with differences in clinical outcomes. The underlying molecular mechanisms of the association begin to unravel with the development of microdissection techniques, high throughput technologies, *in vitro* functional assays, and *in vivo* mouse modeling. A better understanding of the complex relationship between ovarian tumor cells and the associated immune cells will allow us to develop novel immunologic strategies for ovarian cancer prevention and treatment [96]. Therefore, a search for biomarkers holds great promise not only for early detection of ovarian cancer at a pre-symptomatic stage and for monitoring the course of the disease during first-line chemotherapy treatment, but also for identifying those women whose disease is likely to recur. Research efforts have sought to unravel the complexity of the tumor specific proteome by profiling immune responses generated against TAA using multianalyte-based analytical discovery platforms readily adaptable to clinical diagnostic screening tests. The occurrence of tumor-specific autoantibodies directed to respective TAA can be observed before the development of clinical symptoms. Evaluation of the level of tumor autoantibodies during the time of tumor debulking followed by first-line chemotherapy for the prediction of early recurrence, as well as their correlation with other

clinical parameters to evaluate their prognostic value, has been conducted in various clinical studies. The anti-tumor immune response against ovarian cancer is the ultimate key to the development of multiple immune-based therapeutic strategies that have been proposed and tested in different clinical trials that may have beneficial impact on the disease outcome in ovarian cancer patients [97].

Epidemiologic studies have shown that the risk of cancer in the ovarian surface epithelium is decreased by factors that suppress ovulation, whereas uninterrupted ovulation has been associated with increased risk. This suggests that ovulation may play a critical role in ovarian carcinogenesis. More recently, molecular studies have demonstrated alterations in specific oncogenes and tumor suppressor genes in ovarian cancers. Regulatory mechanisms of the cell cycle are mainly composed of cyclins, cyclin-dependent kinases (CDK), and CDK inhibitors. Alteration of these mechanisms results in uncontrolled cell proliferation, which is a distinctive feature of human cancers. Recent evidence suggests that ovarian cancer is a heterogenous group of neoplasms with several different histologic types, each with its own underlying molecular genetic mechanism. Therefore, expression of cell cycle regulatory proteins should be tested separately according to each histologic type. In serous ovarian carcinoma, high expression of TP16, TP53, and TP27 and low expression of TP21 and cyclin E were shown. However, it is difficult to compare the results from different groups due to diverse methodologies and interpretations. Accordingly, researchers should establish standardized criteria for the interpretation of IHC results [98]. Overexpression of the HER-2/neu oncogene occurs in approximately 30% of ovarian cancers and correlates with poor survival. Although mutation of the K-ras oncogene has been found in some mucinous ovarian cancers, mutations in this gene appear to be more common in BOT. Amplification of c-myc occurs in approximately 30% of ovarian cancers and is more frequently seen in serous cancers. Mutation of the TP53 gene, with resultant overexpression of mutant TP53, occurs in 50% of stage III/IV and 15% of stage I/II ovarian cancers. Most TP53 mutations in ovarian cancers are transitions, which suggests that they arise spontaneously rather than due to exogenous carcinogens. In contrast to the acquired genetic alterations described above that are a feature of sporadic ovarian cancers, 5-10% of ovarian cancers probably arise due to inherited genetic defects. Recently, the BRCA1 tumor suppressor gene has been identified and shown to be responsible for most cases of hereditary ovarian cancer [99].

Ovarian cancer is caused by genetic alterations that disrupt proliferation, apoptosis, senescence, and DNA repair. The discovery of cancer-causing genes has provided us with the exciting opportunity to begin to understand the molecular pathology of ovarian cancer. Activation of several of these genes including HER-2/neu, myc, ras, and TP53 has been described in some ovarian cancers. In addition, some proto-oncogenes such as the EGFR (erythroblastic leukemia [erbB]) and the M-CSFR (fms) are expressed along with their respective ligands in some ovarian cancers. Finally, for every oncogene that has been studied in ovarian cancer, at least a half-dozen remain unexplored [100]. The ability to perform genetic testing allows identification of women at increased risk who can be offered prophylactic oophorectomy or other interventions aimed at preventing ovarian cancer. The vast majority of ovarian cancers are sporadic, resulting from the accumulation of genetic damage over a lifetime. Several specific genes involved in ovarian carcinogenesis have been identified, including the TP53 gene and HER2/ neu and PIC3KA oncogenes. The recent availability of expression microarrays has facilitated the simultaneous examination of thousands of genes, and this promises to extend further our understanding of the molecular events involved in the development of ovarian cancers [101, 102]. Epidemiologic data support the existence of two discrete manifestations of hereditary ovarian carcinoma: the breast and ovarian cancer syndrome and the HNPCC syndrome. Genetic linkage analyses reveal that the majority of breast and ovarian cancer families are linked to the BRCA1 gene, while some cases of hereditary ovarian cancer are also apparent in breast cancer families linked to the BRCA2 gene. The majority of HNPCC families are linked to one of four genes encoding a family of DNA MMR proteins. BRCA1 and BRCA2 germline mutations account for the majority of hereditary ovarian cancers and comprise 10% of total cases. Ovarian cancers arising from these mutations exhibit both overlapping and distinct clinical and molecular features. The expression profiles of sporadic ovarian cancers show similarities to those of BRCA1 and BRCA2-related tumors, suggesting that BRCA-related pathways may be involved in their development as well [103, 104]. Molecular analyses demonstrate that genetic screening for germline transmission of a defective allele of one or another of these genes is now possible for high-risk individuals.

The ethical, legal, and social implications of this type of analysis are multiple and complex and genetic counseling requires a thorough understanding of these issues and a cautious approach to most effectively meet the special needs of this patient population. Increased medical surveillance and prophylactic oophorectomy are among the management options that may be appropriate for some genetically predisposed, asymptomatic women [105, 106].

Because survival depends on stage of diagnosis, early detection is critical in improving clinical outcome. However, existing screening techniques (CA 125, transvaginal ultrasound [TV-US]) have not been shown to reduce morbidity or mortality. Moreover, with the exception of OC, there are no available chemopreventive agents. Bilateral salpingo-oophorectomy also has been shown to reduce incidence, but this procedure has several drawbacks in terms of a woman's reproductive, cardiovascular, skeletal, and mental health. Better methods to prevent, detect, and screen for ovarian cancer in all women, but particularly in high-risk women carrying mutations in BRCA1/2, are urgently needed [107]. CA 125 is an antigenic determinant on a high molecular weight glycoprotein. A McAb has been produced which recognizes this, and allows us to measure the expression of CA 125 in serum. Tissue distribution of the CA 125 determinant is most commonly seen in serous tumors of the ovary, with highest levels in borderline and frankly malignant serous cystadenocarcinomas. Occasionally, cancers of the breast, gastrointestinal tract, and kidney will show elevated levels of CA 125. Normal tissues that show varying levels of CA 125 include decidual tissue and structures derived from celomic epithelium. CA 125 is clearly tumor-associated, but not tumor-specific. Quantitative correlation of CA 125 levels with tumor volume has not been demonstrated. This observation limits the clinical usefulness of CA 125 as a screening tool, particularly in pre-menopausal patients who do not have a diagnosis of ovarian cancer. An undetectable level of CA 125 antigen does not rule out the presence of an early ovarian cancer. When CA 125 is used to monitor disease state in patients with known ovarian cancers (whose tumors express CA 125), changes in levels of CA 125 correlate with gross changes in tumor volume. Good prognostic significance is attributed to a rapid decline in CA 125 levels following induction chemotherapy in patients with advanced ovarian cancer. However, an undetectable serum level of CA 125 does not predict clinical cure for a patient with ovarian cancer. Further clinical studies continue in the use of CA 125 as a screening tool and as a means to monitor treatment responses of known ovarian cancer [108]. Advances in high throughput screening are making it possible to evaluate the development of ovarian cancer in ways never before imagined. Data in the form of human "-omes" including the proteome, genome, metabolome, and transcriptome are now available in various packaged forms. With the correct pooling of resources including prospective collection of patient specimens, integration of high throughput screening, and use of molecular heterogeneity in biomarker discovery, we are poised to make progress in ovarian cancer screening [109-113]. High-throughput genomic analyses have the potential to change the detection and the treatment of ovarian neoplasms. They can help diagnose subtypes of disease and predict patient survival. New diagnostic and prognostic markers for ovarian cancer are emerging. One day, profiling may influence treatment decisions, informing both which patients should receive chemotherapy and what type of chemotherapeutic agents should be employed. As greater numbers of tumor samples are analyzed, the power of these profiling studies will increase, raising the possibility that novel molecular targets and less toxic therapies will be identified. These powerful techniques hold the potential to unravel the genetic origins of ovarian cancer. We hope that this will translate into earlier diagnosis and better patient outcome from disease [114, 115].

"Omic" technologies promise to define genetically driven aberrant signaling pathways in malignant cells, if bioinformatic expertise can be focused on a cancer that is neither common nor rare. Molecular therapeutics must be linked to molecular diagnostics to permit individualized therapy. Not only epithelial cancer cells but also stroma, vasculature, and the immune response must be targeted. Closer collaboration between academic institutions, biotech, and pharma will be required to facilitate this process and to interest the private sector in an orphan disease. New pre-clinical models may permit more efficient development of drugs and small interfering RNA (*siRNA*) that can target dormant drug resistant stem cells. Strategies must be developed to deal with the heterogeneity of different grades and histotypes. Identification of women at increased risk will facilitate prevention and early detection in subsets of patients. BRCA1/2 might be sequenced in all ovarian cancer patients to identify new kindreds. Epidemiologic algorithms are being developed and validated. Awareness must be raised

that OC can reduce risk of developing ovarian cancer by 50%. Early detection is likely to require panels of complementary biomarkers, analyzed by sophisticated statistical techniques, to improve sensitivity while maintaining extremely high specificity. As ovarian cancer becomes a chronic disease, greater emphasis will be placed on the challenges facing survivors [116, 117]. In the last decade, several studies have been published using proteomics to unravel molecular pathways and to find biomarkers that can be used for diagnosis and/or prognostication in ovarian cancer. Most studies have focused on finding biomarkers for early diagnosis of ovarian cancer using blood samples though proteins identified until now are mainly acute phase reactants. Studies regarding platinum sensitivity have only been performed on cell culture models and need confirmation in tissue samples. Proteomic studies using ovarian cancer tissue are sparse and mostly contain a low number of samples. To date, no biomarkers for early diagnosis or prognostication in ovarian cancer have been found using proteomics. It would be interesting to investigate the tissue proteome in an attempt to overcome acute phase reactants and to facilitate the discovery of real tumor-specific biomarkers instead of the identification of secondary protein changes [118]. As recent scientific findings using whole-genome mutational scanning technologies have concluded, cancer is a protein pathway disease, which is often diagnosed too late, when the success of therapeutic modalities is very limited. Proteomics has been proposed as the field that can help overcome this limitation and usher in a new era of molecular investigation for early diagnosis and classification of tumors. Proteomics applications in cancer research encompass two general aspects:

1) the study and characterization of protein production; and

2) the definition of protein function.

The first aims to identify qualitative or quantitative differences in the proteome that can help differentiate between healthy and diseased states or achieve a better clinical classification of diseases. The second studies the complexity of protein interactions and their activation states, mapping the network of signaling pathways within and outside the cells. The challenges in translating the findings of proteomics research into clinical practice are numerous. Lack of reproducibility, variable availability of samples, and the bias associated with their selection and handling, the need for large, prospective validation trials, and finally the strict requirement for a very high level of clinical sensitivity and specificity are some of the hurdles that need to be overcome to achieve early detection and treatment. Nevertheless, proteomics is a field in rapid progression that has already developed beyond initial criticism and is making its way toward important applications and discoveries. Specifically, there has been an increasing number of reports on the potential clinical application of proteomics for early detection as well as risk assessment and management of ovarian cancer. In the future, serum proteomics applications in the gynecologic oncology field could identify blood-based biomarkers that are predictors of disease presence or progression, and tissue proteomics could help define the optimal targeted agent and effective dose for each patient's disease. These advances will allow improved monitoring of therapy response and disease relapse, and aid in the engineering of new drugs and strategies to circumvent resistance mechanisms while avoiding the adverse effects of traditional chemotherapy [119].

The standard initial management of epithelial ovarian cancer consists of surgical staging, operative tumor debulking including total abdominal hysterectomy and bilateral salpingo-oophorectomy, and administration of six cycles of intravenous chemotherapy with carboplatin and paclitaxel. Extensive and largely retrospective experience has shown that optimum surgical debulking to leave residual tumor deposits that are <1 cm in size is associated with improved patient outcomes. However, 75% of patients present with advanced (stage III or IV) disease and, although >80% of these women benefit from first-line therapy, tumor recurrence occurs in almost all these patients at a median of 15 months from diagnosis. Second-line treatments can improve survival and QOL but are not curative. Advances in screening and understanding of molecular pathogenesis of ovarian cancer and development of novel targeted therapies (e.g. bevacizumab) and practical intraperitoneal techniques for drug delivery are most likely to improve patient outcomes [120]. Advanced epithelial ovarian cancer is a highly chemosensitive solid tumor with response rates of 70-80% to first-line chemotherapy, including a high proportion of complete responses. The majorities of patients, however, eventually relapse and ultimately die of chemoresistant disease. Response rates to salvage agents are modest, and duration of response is relatively short. Important new agents have been identified in the salvage setting, however, and all patients with ovarian cancer recurring or persisting after front-line therapy should be encouraged to enroll in clinical trials.

Retreatment with a platinum-containing compound is appropriate in patients with platinum-sensitive disease. Trials of high-dose chemotherapy with hematologic support may be most appropriate for patients with minimal disease following first-line therapy, but are unlikely to benefit patients with platinum-resistant or bulky disease. Paclitaxel should figure prominently in consideration of salvage therapy for patients with platinum-resistant disease. Responses to other single agents or combination chemotherapy have been modest and generally of short duration. Efforts at hormonal therapy have been disappointing. Promising new agents introduced in the last 20 years include topoisomerase I inhibitors, such as topotecan, 9-aminocamptothecin, irinotecan (CPT-11), and pyrazoloacridine [121]. Vintafolide (EC145) is a novel folate-conjugated vinca alkaloid (desacetylvinblastine hydrazide [DAVBLH]) that binds with high affinity to the FR, expressed in a majority of epithelial ovarian cancers. In preclinical studies, vintafolide had significant anti-proliferative activity and tolerability. Phase I studies demonstrated an acceptable safety profile, with constipation being the dose-limiting toxicity. A phase II study of vintafolide plus pegylated liposomal doxorubicin (PLD) versus PLD alone in patients with platinum-resistant ovarian cancer showed a statistically significant improvement in PFS with combination therapy. (99m) technetium (Tc)-etarfolatide, a diagnostic radiopharmaceutical, determines FR status, which allows determination of those patients most likely to benefit from treatment with vintafolide. A phase III study evaluating vintafolide plus PLD versus PLD alone in patients with platinum-resistant ovarian cancer is currently underway [122]. Therapies focusing on novel molecular targets include anti-angiogenesis agents, anti-metastatic agents, and signal transduction inhibitors. Immune-therapy, including radioimmune-therapy, immune-toxins, and direct anti-tumor effects of McAb, may be useful. Greater understanding of the molecular pathology of ovarian cancer may help us develop more rational and effective treatment [121]. In fact, cisplatin or paclitaxel chemotherapy induces arrest of the cell cycle or apoptosis in ovarian cancer cells. Tumor suppressor genes such as TP53 play a paramount role in mediating this response and p21wAF1/CDK inhibitor 1 or CDK-interacting protein 1 (CIP1) is a major mediator of TP53-induced arrest of the cell cycle. Molecular alterations involving these tumor suppressor genes are related to the development of resistance to chemotherapy and represent possible targets for gene therapy in ovarian cancer [123].

New treatment approaches for patients with advanced ovarian cancer include consolidation and maintenance therapy, intraperitoneal administration of cytotoxic agents, new combination chemotherapy regimens, the development of new cytotoxic agents, and molecular-targeted therapies [124]. In particular, several nonplatinum agents have demonstrated activity among patients with recurrent platinum-resistant epithelial ovarian cancer. These agents include gemcitabine, topotecan, liposomal doxorubicin, and prolonged oral etoposide. Preclinical models have indicated a biologic basis for combinations of these agents with platinum, which has been attributed to inhibition of pathways involved in DNA repair. However, efforts to develop multidrug combinations with platinum and paclitaxel have encountered substantial bone marrow toxic effects, necessitating significant dose reductions and prompting exploration of alternative schedules and sequences of drug administration [125]. New developments in the treatment of platinum-resistant ovarian cancer patients are proteomic advances, including the HER kinases, the 26S proteasome, and the angiogenesis pathway [126]. These recent advances in the molecular understanding of ovarian cancer point to molecular differences between paclitaxel and carboplatin sensitivity that link to the status of BRCA genes, so called familial and sporadic “BRCAness”. It may be that the change in the way we use paclitaxel allows us to more effectively target the heterogeneity of such intrinsic sensitivity/resistance to these agents in the adjuvant therapy of ovarian cancer, leading to significant improvement in the management of the disease [127, 128]. Apart from varying the dosages, schedules, mode of delivery, and combinations of existing drugs, efforts must continue to identify signaling pathways in tumor cells sufficiently different from normal cells that can be a target for maximizing tumor kill and minimizing toxicity. It is only with a strong commitment, cooperation, and collaboration from the international ovarian cancer community that significant improvement in patient outcomes can be attained beyond the marginal gains achieved so far [129]. Small molecular-weight inhibitors, McAb, antisense therapy, and gene therapy have been evaluated alone and in combination with cytotoxic chemotherapy. Ultimately, the success of ovarian cancer therapy lies not just in the availability of new agents but in the ability to identify patients with biomarkers that may predict their response to these agents [130].

The most promising treatment strategies are those that target the drivers of tumorigenesis and enhance

the activity of cytotoxic agents. Receptor TK, non-receptor TK, serine/TK, transferases, proteases, and deacetylases are among the relevant molecular markers and targets for ovarian cancer. Collaboration, coordination, creativity, and aggressive outreach to patients and their advocates are essential for success in running the concurrent trials with multiple clinical ends and embedded translational research that are needed to evaluate the array of promising targeted therapeutics and combinations. Validated biomarkers, surrogate specimens and end points, and additional clinically relevant *in vitro* and *in vivo* models for ovarian cancer are needed to facilitate the drug development and evaluation process, and ultimately to make meaningful improvements in the diagnosis, prevention, and management of ovarian cancer [131]. Matrix metalloproteinases (MMP) are frequently expressed in ovarian cancer, and play an important role in the metastatic process. MMP mediate degradation of the basement membrane as a crucial step in epithelial transformation, ovarian tumorigenesis, and intraperitoneal metastasis. Various preclinical and clinical studies have demonstrated that MMP might provide a suitable therapeutic target [132]. Novel therapies directed at major pathways implicated in ovarian tumorigenesis include angiogenesis, PARP inhibition, signal transduction, antifolate therapies, death receptor-mediated therapies, histone deacetylase inhibition, immune-therapeutics, and oncolytics [133-135].

Angiogenesis is a complex and highly regulated process that is crucial for tumor growth and metastasis. Angiogenesis is a hallmark of malignant transformation and plays a role in recurrence, metastasis, and ascites in epithelial ovarian cancer. Insights into the molecular mechanisms of tumor angiogenesis have led to the identification of potential angiogenic targets and the development of novel anti-vascular agents. Many of these agents have been evaluated in clinical trials and have shown promising antitumor activity [136]. Angiogenesis inhibitors under evaluation in phase II and III trials for epithelial ovarian cancer (anti-angiogenesis agents) include aflibercept, bevacizumab, cediranib, fosbretabulin, imatinib, nintedanib, pazopanib, saracatinib, sorafenib, sunitinib, and trebananib. These agents have particular rationale for potential use in epithelial ovarian cancer due to the molecular changes associated with epithelial ovarian cancer tumorigenesis, namely a significant increase in angiogenic activity. Due to the costs and toxicities associated with anti-angiogenics, biomarker or molecular signature selection strategy for patients who will most benefit would be ideal but no such strategy has been validated to date [137, 138]. There have been a number of agents developed that target VEGF signaling. These targeted agents can affect downstream VEGF signal transduction *via* unique mechanisms at different cellular and extracellular locations [139, 140]. A statistically significant association between serum VEGF levels in ovarian cancer and International Federation of Gynecology and Obstetrics (FIGO) stage, tumor grade, residual tumor size, lymph node involvement, and presence of ascites was found in at least one study. Serum VEGF, in comparison with the established prognostic factors, appears to be the best prognostic marker for OS, since it stands out as an independent prognostic factor in most of the studies considered. Moreover, serum VEGF levels were shown to be independent prognostic factors by two out of the three studies that considered disease-free survival (DFS) as an end-point. High levels of serum VEGF identify a subgroup of patients with higher risk of death and/or recurrence. These patients should be eligible for individually tailored therapeutic interventions [141, 142]. The most studied of angiogenesis inhibitors has been the anti-VEGF McAb bevacizumab [143, 144]. Bevacizumab is the first molecular-targeted agent to be used for the treatment of ovarian cancer. Two randomized phase III trials evaluated the combination of bevacizumab plus standard cytotoxic chemotherapy for first-line treatment of advanced ovarian cancer. Additional phase III trials evaluated bevacizumab combined with cytotoxic chemotherapy in platinum-sensitive and platinum-resistant recurrent ovarian cancer. All these trials reported a statistically significant improvement in PFS but not in OS. Furthermore, bevacizumab effectively improved the QOL with regard to abdominal symptoms in recurrent ovarian cancer patients. Bevacizumab is associated with adverse events not commonly observed with cytotoxic agents used to treat gynecologic cancers, such as hypertension, bleeding, thromboembolism, proteinuria, delayed wound healing, and gastrointestinal events. However, gynecologists can adequately manage most of these events. The clinical trial results with bevacizumab have supported its recent approval in Europe and the USA as a treatment for ovarian cancer [145]. Novel biologic agents have demonstrated promising anti-tumor activity. AMG 386, a novel investigational angiopoietin antagonist peptide-Fc fusion protein (peptibody) potently and selectively inhibits angiopoietin-1 and angiopoietin-2 binding to the Tie2 TK receptor. AMG

386 has clinical activity and an acceptable safety profile both as monotherapy and in combination with chemotherapy. Of note, as the toxicity profiles of AMG 386 and inhibitors of the VEGF axis do not substantially overlap, AMG 386 could potentially be combined with other anti-angiogenic compounds to maximize disruption of malignant vascularization in ovarian cancer and other solid tumors [146, 147].

A number of molecular aberrations that drive tumor progression have been identified in ovarian cancer cells and intensive efforts have focused on developing therapeutic agents that target these aberrations. However, increasing evidence indicates that reciprocal interactions between tumor cells and various types of stromal cells also play important roles in driving ovarian tumor progression and that these stromal cells represent attractive therapeutic targets. Unlike tumor cells, stromal cells within the tumor microenvironment are in general genetically stable and are therefore less likely to become resistant to therapy [148, 149]. Given the above, an emphasis has been placed on exploring alternate therapeutics. With the discovery of BRCA1 and BRCA2 gene mutations and a more comprehensive assessment of heredity ovarian cancer syndrome, targeted interventions exploiting this biologic susceptibility have emerged. To date, the most studied of these have been PARP inhibitors [150]. PARP inhibitors exploit synthetic lethality to target DNA repair defects in hereditary breast and ovarian cancer. In recent clinical trials, epithelial ovarian cancer patients with BRCA mutations exhibited favorable responses to the PARP inhibitor olaparib compared with patients without BRCA mutations. Additionally, olaparib has been reported to augment the effects of cisplatin and carboplatin on recurrence-free survival (RFS) and OS in mice bearing BRCA1/2-deficient tumors. Given that hereditary epithelial ovarian cancers with deleterious BRCA1/2 mutations and BRCAness sporadic epithelial ovarian cancers are profoundly susceptible to synthetic lethality with PARP inhibition, it is imperative to identify a population of epithelial ovarian cancer patients that is likely to respond to PARP inhibitors. Recent studies have identified the gene expression profiles of DNA repair defects and BRCAness that predict clinical outcomes and response to platinum-based chemotherapy in epithelial ovarian cancer patients. Clinical development of PARP inhibitors that target DNA repair defects in cancer is a novel and imperative stride in individualized identification of molecular characteristics in management of ovarian cancer [151]. The BRCA1/2 proteins are important in homologous recombination (HR) repair of DNA. Patients with BRCA1/2 mutations have been reported to have improved chemosensitivity to platinum agents, longer disease-free intervals, and longer survivals than non-hereditary counterparts. Recent interest in PARP proteins that are key components of base excision repair, has led to the development of PARP inhibitors: tumors arising in BRCA1/2 mutation carriers and/or with HR deficiency (HRD) are particularly sensitive to the action of these drugs. As 60-80% of all advanced ovarian cancers are high-grade serous type, exhibiting HRD in at least 50% (referred as BRCAness), future anti-tumor strategies may depend on identifying these defects through molecular testing. Once HRD becomes amenable to routine testing, a larger group of ovarian cancer patients than are currently considered for PARP inhibitor trials may benefit from such targeted therapy [152, 153].

The major molecular and histologic subgroups of ovarian cancer include hormonal pathways, TP53 and adenine-thymine (AT) rich interactive domain 1A (SWI-like; ARID1A) mutation, and the BRCA1/2 early onset mutation/PARP1, PI3K catalytic subunit α (PI3KCA)/AKT homolog 1 (AKT1)/mTOR, and mitogen-activated protein kinase 1 and 2 (MAP2K1/2) pathways. This molecular characterization only very recently has affected clinical research efforts to develop targeted therapies for both common and rare ovarian cancer subtypes. This targeted strategy is illustrated by ongoing low-grade serous, clear-cell, and mucinous subtype exclusive clinical trials evaluating agents based on common molecular abnormalities among patients (i.e. PARP1 inhibitors for BRCA1/2 mutation-positive ovarian cancers). The efficacy of investigational therapies agents (e.g. temsirolimus, sunitinib, TP53 immune-therapy, olaparib, iniparib, veliparib) are being evaluated in clinical trials. Available data suggest that histologic profiles and molecular tumor markers are valuable resources for identifying patients who may benefit from these specific agents, and future research should focus on targeting molecules and signaling pathways that are most commonly altered in each subtype [154-156].

Epidemiologic studies indicate that steroid hormones play roles in ovarian carcinogenesis. Gonadotrophins, estrogen, and androgen may be causative factors, while GnRH and progesterone may be protective factors in ovarian cancer pathogenesis. Experimental studies have shown that hormonal receptors are expressed in ovarian cancer cells and mediate the growth-stimulatory or growth-inhibitory

effects of the hormones on these cells. Molecular mechanisms involved in ovarian carcinogenesis are still unclear, but there is growing evidence that estrogens promote tumor progression in an epithelial ovarian cancer subgroup. Experimentally, estrogen stimulates the growth of ovarian tumor cell lines expressing ER. Differential expression of ERα or β during ovarian carcinogenesis, with overexpression of ERα as compared to ERβ in cancer has been demonstrated. This differential expression in ER suggests that estrogen-induced proteins may act as ovarian tumor-promoting agents. Among these proteins, c-myc, fibulin-1, cathepsin-D, or several kallikreins may play a role, since high expression levels have been found in epithelial ovarian cancer. Consistently, recent prospective epidemiological studies have indicated that estrogen replacement therapy (ERT) in post-menopausal women may increase ovarian cancer incidence and mortality [157]. "Triple negative" epithelial ovarian cancer is characterized by lack of expression of ER, PR, and HER-2. "Triple negative" phenotype is traditionally referred to as a specific subtype of breast cancer negative for ER, PR, and HER-2 expression. Recent studies have shown that such "triple negative" phenotype also exists in ovarian and endometrial cancer. "Triple negative" epithelial ovarian cancer accounts for about 15% of epithelial ovarian carcinomas. This specific subtype tends to exhibit more aggressive characteristics and a worse prognosis. The molecular features of "triple negative" epithelial ovarian cancer are similar to those of "triple negative" breast cancer, a widely studied histological subtype. Recently, a panel of specific pathologic biomarkers has been identified in "triple negative" breast cancer. Currently, phase I and phase II trials to examine the safety and efficacy of a PARP inhibitor (olaparib) and angiogenesis inhibitors (sunitinib and bevacizumab) in "triple negative" breast cancer are ongoing. These "triple negative" breast cancer-associated pathologic markers could be used to screen for novel prognostic factors and therapeutic targets in "triple negative" epithelial ovarian cancer. "Triple negative" phenotype has important implications for clinical management of patients with ovarian cancer [158]. Hormonal therapeutic agents have been evaluated in several clinical trials. Most of these trials were conducted in patients with recurrent or refractory ovarian cancer, with modest efficacy and few side effects. Better understanding of the mechanisms through which hormones affect cell growth may improve the efficacy of hormonal therapy. Molecular markers that can reliably predict major clinical outcomes should be investigated further in well-designed trials [159].

To potentially circumvent chemo-resistance in recurrent ovarian cancer, immune-therapy is being explored as a novel treatment option. Laboratory findings demonstrate that immune effector cells from healthy donors elicit a significant cytotoxic response in the presence of interleukin-2 (IL-2) and interferon (IFN) α-2b against ovarian cancer *in vitro*. However, peripheral blood mononuclear cells (PBMC) isolated from ovarian cancer patients fail to elicit a similar response. A major obstacle to immune-therapy is the immune-suppressive environment supported by tumors, which limits the immune system's ability to fight the tumor. Myeloid-derived suppressor cells are an immature population of myeloid cells, which have recently been implicated to play a major role in immune-suppression and tumor evasion. In addition to novel immune-therapies, new diagnostic and prognostic markers are being identified through applying molecular tools/approaches in clinical and pathological analyses of this malignancy, which will provide additional therapeutic targets. To test these experimental therapeutic options, pre-clinical murine models of ovarian cancer are being developed. Ultimately, treatment of ovarian cancer will benefit from the careful alignment of appropriate target, drug, patient, and trial design [160]. Mucin 1 (***MUC1***) is associated with cellular transformation and tumorigenicity and is considered as an attractive therapeutic target for cancer therapy owning to its overexpression in most adenocarcinomas including epithelial ovarian cancer. Tumor-associated MUC1 plays an important role in epithelial ovarian cancer metastasis and progression. In neoplastic tissues, MUC1 is under-glycosylated and reveals epitopes that are masked in the normal cells. This feature makes it possible to target tumor-associated MUC1 with antibodies, toxins, or radionuclides or use a vaccine targeting tumor-associated MUC1 antigen. The shed tumor-associated MUC1 in blood can be used as a diagnostic biomarker for epithelial ovarian cancer detection and monitoring. Recent results have shown that overexpression of MUC1 plays a very important role in epithelial ovarian cancer progression and MUC1 is an ideal target for targeted therapy to control metastatic and recurrent epithelial ovarian cancer [161].

In the last decades, advances in molecular biology have lead to the development of techniques that permit the manipulation of mammalian cell DNA for diagnostic

and therapeutic purposes. Gene therapy has subsequently evolved as a treatment option in patients with malignancies [162]. Only a small number of distinct genetic mutations are known to contribute to ovarian carcinogenesis. Furthermore, understanding mechanistic genotype-phenotype links is complicated by frequent aneuploidy. Epigenetic deregulation is even more prominent, and ovarian cancers are replete with such aberrations that repress tumor suppressors and activate proto-oncogenes. Epigenetic therapies are emerging as promising agents for re-sensitizing platinum-resistant ovarian cancers. These drugs may also have the potential to alter epigenetic programming in cancer progenitor cells and provide a strategy for improving therapy of ovarian cancer [163]. Advances in molecular virology and biotechnology have led to the engineering of vectors that can efficiently transfer genes to target cells. Gene therapy strategies were developed along two lines:

1) cytotoxic approaches involve the transfer of genes that encode enzymes, which convert inactive prodrugs into cytotoxic drugs; and

2) corrective gene therapy approaches aim to repair specific molecular alterations in signal transduction mechanisms that control the cell cycle or induce apoptosis.

Clinical evidence suggests that gene therapies are best suited for patients with minimal residual disease. Multimodality approaches with conventional strategies and novel therapeutic tools in various combinations will most likely prove advantageous, compared to single-modality treatments [164]. The field of gene therapy presents exciting new opportunities for advances in the management of ovarian cancer. Clinical trials of gene therapy for ovarian cancer have explored the feasibility of delivering a variety of agents as well as highlighted problems with the delivery of therapeutic constructs. Major challenges include enhancing gene transfection with improved vectors, minimizing immunogenicity of viral vectors *via* novel molecular alterations, effecting tumor-selective gene delivery by targeting genetic alterations present only in tumor cells, and utilizing tissue-specific promoters for selective transcription of gene products. Gene therapy research presents unique opportunities for extending the spectrum of ovarian cancer treatment possibilities, either alone or in combination with conventional chemotherapy regimens [165]. The different strategies of gene therapy (molecular chemotherapy [prodrugs], mutation compensation, immune-therapy approaches [immune-potentiation], altered drug sensitivity, and virotherapy) for cancer treatment involve Coxsackie-Adenovirus receptor (CAR) independent pathways to improve infectivity and specificity to ovarian tumor cells, the potential of utilizing gene therapy as an imaging modality in detecting cancer, and incorporating the recently described technique of ribonucleic acid (RNA) interference (RNAi). Due to the advancements in detection and targeting of ovarian cancer, coupled with the containment to the intraperitoneal cavity, gene therapy remains a promising treatment modality for ovarian cancer [166]. Improvements in delivery vehicles and in evaluation of gene transfer and viral replication remain important areas of investigation [167, 168].

The recent identification of the Fallopian tube secretory epithelial cells (FTSEC) as the cell-of-origin for most cases of this disease has led to studies aimed at elucidating new candidate therapeutic pathways through profiling of normal FTSEC and serous carcinomas. Transcriptional profiles identify the loss of the tumor suppressive transcription factor forkhead box protein O3 (FOXO3a) in a vast majority of high-grade serous ovarian carcinomas. FOXO3a loss is a hallmark of the earliest stages of serous carcinogenesis and occurs both at the DNA, RNA, and protein levels. Several mechanisms are responsible for FOXO3a inactivity, including chromosomal deletion (chromosome 6q21), upregulation of micro RNA (miRNA)-182, and destabilization by activated PI3K and MEK. The identification of pathways involved in the pathogenesis of ovarian cancer can advance the management of this disease from being dependant on surgery and cytotoxic chemotherapy alone to the era of targeted therapy. These data strongly suggest FOXO3a as a possible target for clinical intervention [169-171].

Müllerian-inhibiting substance (MIS) is a gonadal hormone that causes regression of the Müllerian ducts. A series of studies have demonstrated that MIS also has multiple extra-Müllerian functions including inhibition of epithelial ovarian cancer cells *in vitro* and *in vivo*. Accumulating evidence has shown that many human cancers are organized hierarchically and contain a small population of cancer stem cells (CSC) that are inherently resistant to common chemotherapy and radiation therapy. The effect of MIS on ovarian CSC seems to be particularly useful in rescuing ovarian cancer patients with resistance to conventional treatment [172]. A cornerstone of preclinical cancer research has been the use of clonal cell lines.

However, this resource has underperformed in its ability to effectively identify novel therapeutics and evaluate the heterogeneity in a patient's tumor. The PDX model retains the heterogeneity of patient tumors, allowing a means to not only examine efficacy of a therapy, but also basic tenets of cancer biology in response to treatment. PDX tumors are not simply composed of tumor-initiating cells, but recapitulate the original tumor's heterogeneity, oncogene expression profiles, and clinical response to chemotherapy. Combined carboplatin/paclitaxel treatment of PDX tumors enriches the CSC populations, but persistent tumors are not entirely composed of these populations. RNA sequencing (RNA-Seq) analysis of six pair of treated PDX tumors compared to untreated tumors demonstrated a consistently contrasting genetic profile after therapy, suggesting similar, but few, pathways are mediating chemoresistance. Pathways and genes identified by this methodology represent novel approaches to targeting the chemoresistant population in ovarian cancer [173].

TROPHOBLASTIC DISEASE

Gestational trophoblastic diseases (GTD) are interrelated conditions characterized by abnormal growth of chorionic tissues with various propensities for local invasion and metastasis. Complete mole is a unique conception in that all nuclear DNA is paternally derived and all cytoplasmic DNA is maternally derived. In contrast, partial mole generally has a triploid karyotype, where the extra haploid set of chromosomes is paternally derived: these diseases are characterized by altered expression of several growth regulatory factors and oncogenes. While differences in expression of oncoproteins may be important to the development of GTD, the precise molecular changes that are critical to pathogenesis remain unknown [174]. Based on the expression of various oncogenes and growth factors, partial mole appears to be more like normal placenta, while complete mole seems to be more like choriocarcinoma. These results may have both prognostic and therapeutic consequences and provide insight into the relationship between normal placenta and GTD [175].

UTERINE SARCOMA

Uterine sarcomas are rare malignancies accounting for 8-10% of all uterine ones, but are significantly more aggressive and have worse prognosis. They are treated similarly to endometrial cancers. Uterine sarcomas are a heterogeneous group of tumors. Little is known of epidemiologic risk factors for sarcoma: similarly, little work has been performed assessing molecular alterations in sarcomas. Because of their rarity, uterine sarcomas are not suitable for screening. Chemoprevention studies might target those at risk for recurrence or a second neoplasm [176]. The most common include uterine leiomyosarcoma (LMS) and the endometrial stromal neoplasms. The diagnosis requires pathologic review of the uterus in order to characterize extent of myometrial invasion. However, molecular diagnosis has aided the classification of endometrial stromal neoplasms, especially in helping to discriminate between endometrial stromal and undifferentiated endometrial sarcoma. The prognosis of these tumors following surgery varies, with endometrial stromal sarcoma (ESS) associated with a better prognosis compared to LMS or undifferentiated endometrial sarcoma. For aggressive sarcomas, there is interest in adjuvant treatment, which has focused on the evaluation of systemic agents. However, the rarity of these tumors makes the conduct of prospective trials difficult and no consensus adjuvant regimen has emerged. In the absence of level I data, the use of chemotherapy is based on institutional preferences. Ongoing clinical trials will help inform the standard treatment approach for these tumors, and patients with uterine sarcoma should be encouraged to participate in well-designed clinical trials [177]. The World Health Organization (WHO) revised their histopathologic classification in 2003. A new staging system has been recently designed by the FIGO. Currently, there is no consensus on risk factors for adverse outcome. Since carcinosarcomas (malignant mixed mesodermal tumors [MMMT]) are currently classified as metaplastic carcinomas, LMS remain the most common uterine sarcomas. Exclusion of several histologic variants of leiomyoma, as well as "smooth muscle tumors of uncertain malignant potential", frequently misdiagnosed as sarcomas, has made apparent that LMS are associated with poor prognosis even when seemingly confined to the uterus. ESS are indolent tumors associated with long-term survival. Undifferentiated endometrial sarcomas exhibiting nuclear pleomorphism behave more aggressively than tumors showing nuclear uniformity. Adenosarcomas have a favorable prognosis except for tumors showing myometrial invasion or sarcomatous overgrowth. Adenofibromas may represent well-differentiated adenosarcomas. The prognosis of carcinosarcomas is usually worse than that of grade 3 endometrial carcinomas. IHC expression of Ki67, TP53, and TP16 is significantly higher in LMS and undifferentiated endometrial

sarcomas than in ESS. Evaluation of hematoxylin and eosin (H&E) stained sections has been equivocal in the prediction of behavior of uterine sarcomas. IHC studies of oncoproteins as well as molecular analysis of non-random translocations will undoubtedly lead to an accurate and prognostically relevant classification of these rare tumors [178].

Patients with uterine LMS typically present with vaginal bleeding, pain, and a pelvic mass. Atypical presentations with hypercalcemia or eosinophilia have been reported. Radiographic evaluation with combined positron emission tomography (PET)/computed tomography (CT) may assist in diagnosis and surveillance in women with uterine LMS. Stage and tumor grade continue to appear valid prognostic indicators. A recently developed risk-assessment index is highly predictive of disease-specific survival. Ovarian preservation does not appear to negatively influence outcome. The addition of adjuvant therapy after surgical management does not seem to improve survival. A recently developed nomogram was demonstrated to predict disease recurrence in patients with LMS that may allow us to identify a subset of patients who are likely to recur and target this population for adjuvant systemic therapy. Novel therapies may result from continued improvements in our knowledge of the molecular biology of uterine LMS. Despite the infrequency of uterine LMS, several recent investigations have advanced our understanding of the disease [179]. The management of patients with advanced uterine LMS is divided between those with localized and those with disseminated disease. Selected patients with localized or single-organ oligometastatic disease may benefit from surgical resection. For patients with disseminated disease, fixed-dose-rate gemcitabine plus docetaxel is an appropriate first-line chemotherapy regimen. Other active cytotoxic agents include doxorubicin, ifosfamide, and dacarbazine. The role of trabectedin, approved by the European Medicine Agency (EMA) to be marketed for advanced or metastatic soft tissue sarcoma, is being explored. Trials are also underway for targeted therapy in uterine LMS. Currently, the only approved targeted therapy for advanced soft tissue sarcoma is pazopanib. In patients with small volume and slowly progressive ER/PR-positive disease, anti-estrogen therapy with an AI is a reasonable alternative to observation alone. Despite recent advances, OS for advanced disease remains poor and identification of novel agents with activity in LMS is clearly needed [180].

Cytogenetic abnormalities have been identified that allow differentiation of ESS from high-grade undifferentiated sarcomas (HGUS) which may be useful in pathologically difficult cases. To date, limited advancements have been made in discovering targeted therapies to these tumors [181]. HGUS are rare uterine malignancies arising from the endometrial stroma. They are poorly differentiated sarcomas composed of cells that do not resemble proliferative-phase endometrial stroma. HGUS are characterized by aggressive behavior and poor prognosis. Cyclin D1 has been reported as a diagnostic immune-marker for high-grade ESS, which represents a clinically aggressive subtype of ESS classified as high-grade endometrial sarcomas, and its distinction from the usual low-grade ESS and from HGUS with no identifiable molecular aberration may be important in guiding clinical management. Median age of the patients is between 55 and 60 years. The most common symptoms are vaginal bleeding, abdominal pain, and increasing abdominal girth. Disease is usually advanced with approximately 70% of the patients staged III to IV according to the FIGO classification. Preferential metastatic locations include peritoneum, lungs, intra-abdominal lymph nodes, and bone. Median PFS ranged from 7 to 10 months, and median OS ranged from 11 to 23 months. There is no clear prognostic factor identified for HGUS, not even stage. The standard management for HGUS consists of total hysterectomy and bilateral salpingo-oophorectomy. Systematic lymphadenectomy is not recommended. Adjuvant therapies, such as chemotherapy and radiotherapy, have to be discussed in multidisciplinary staff meetings [182]. Carcinosarcomas are rare aggressive neoplasms with a poor prognosis. The recent FIGO 2009 categorizes uterine carcinosarcoma into the endometrial carcinoma group. Therefore, uterine carcinosarcomas are staged and treated similarly to high-grade epithelial endometrial carcinomas and are no longer considered uterine sarcomas. The primary treatment is surgery. Lymphadenectomy as part of the surgical procedure has shown to prolong survival even for early-stage disease. A combined chemo-radiotherapeutic approach has shown a survival benefit. Radiotherapy from various studies has shown a significant effect on local control of the disease, with no obvious benefit on OS. Various trials led by the Gynecologic Oncology Group (GOG) looking into different chemotherapeutic combinations have showed differing response rates. In the future, the emergence of combination of chemotherapeutic agents with molecular-targeted agents may show promising results [183, 184].

VAGINAL AND VULVAR CANCER

Vaginal cancer is infrequent, but the morbidity associated with treatment is high. Delays in diagnosis account for presentations in advanced stages. Screening is probably not warranted given the low incidence, but inspection of the vagina should be performed at the time of Pap smear screening. No molecular markers are currently promising. Chemoprevention with retinoids may be feasible [185]. Cervical and vaginal cancers remain serious health problems. Worldwide, more than 530,000 women annually are diagnosed with these diseases, with most new incident cases occurring in nations with limited health resources and underdeveloped screening programs. For women whose disease is too bulky or widespread for surgery, radio-chemotherapy should be looked upon as the standard of care. RCT have indicated that radio-chemotherapy strategies that disrupt the repair of damaged DNA are key to the management of advanced stage cervical and vaginal cancers [186].

While the majority of studies regarding the health benefits from HPV vaccination have focused on cervical neoplasia and cancer, few have investigated how the epidemiology of vaginal and vulvar disease may be affected. To better understand how occurrence rates for vaginal and vulvar neoplasias and carcinomas may change in the future, we must have an understanding of the overall disease prevalence within a given population, the efficacy of vaccination, and the proportion of cases attributable to HPV types administered in the vaccine. While precise projections of exactly how vaginal and vulvar disease prevalence will change with vaccination will require more studies, the preliminary data are promising [187, 188].

CANCER AND PREGNANCY

McAb are the cornerstone of the treatment of several types of tumors, but their use in pregnant women is not clearly defined. There are very few data on the use of bevacizumab in pregnant women. However, owing to its anti-angiogenic effects and possible consequences on fetal development, it should be avoided during pregnancy. Trastuzumab administration has been associated with an elevated incidence of oligohydramnios and poor neonatal outcomes, particularly when prescribed after the first trimester for repeated infusions, and therefore it is not recommended. Rituximab does not seem to be teratogenic, but a transient prolonged neutropenia in the newborns was reported, without major infectious consequences in most cases. Few data are available about other McAb, and hence their use during pregnancy remains discouraged [189, 190].

CONCLUSIONS

Through advances in human genomic sequencing, the unique molecular biology that predisposes certain individuals to either health or disease has now been illuminated. Although many malignancies behave similarly on a phenotypic level, biologically there exist multiple layers of interconnected molecular and cellular pathways that may make each patient's disease significantly more unique than previously appreciated. Gynecologic cancer is a major burden in both developed and developing countries. Almost a half million deaths from gynecologic cancer are reported each year. Understanding the molecular biology of cancer is a principle resource leading to the identification of new potential therapeutic targets, which may be parlayed into novel therapeutic options in gynecologic cancer. In gynecologic oncology, the most progress in developing targeted biologics has been in the treatment of ovarian cancers. Future investigations will see further development in endometrial and cervical cancers. Technology such as whole genome sequencing can theoretically identify the individual tumor's genetic profile. However, identifying the priority pathways for therapeutic interventions and subsequent complex interactions remains a significant challenge. New therapeutic technologies such as siRNA and immune modulators will also play a promising role in the movement toward individualized therapies. It is hoped that the identification and use of targeted agents will lead to individualized care that in turn will lead to significantly improved outcomes manifested by more cures and better QOL through amelioration of toxicities [191]. The curative regimens that have been developed for gynecologic cancers, even those in more advanced stages, have included combinations of surgery and/or radiation with chemotherapy. The Cancer Genome Atlas (TCGA) has revealed complexities in the biology of these tumors that underscore the fact that reliance on selective DNA-damaging agents such as platinums, anti-metabolites, and anti-mitotic agents will continue for some time. The therapeutic progress that may arise from the study of molecular pathways will be due not only to the development of new targeted therapies, but also to a better understanding of older drugs developed empirically in the past. Taken together, these two types of advance illustrate the remarkable overall effect of modern cancer therapeutics' focus on tumor biology and tumor immunology [192].

In summary, among major clinical research achievements in gynecologic oncology in the last years, there have been:

1) for breast cancer, the identification of a promising target has led to successful preliminary applications, and eventually to further advances through drug development and the fine tuning of patient selection: as a result, the percentage of patients with breast cancer who are benefiting from targeted agents has steadily increased, even if the majority are still treated with conventional cytotoxic regimens; positive results of some outstanding phase III RCT have been reported;

2) for cervical cancer, long-term benefit of HPV test and efficacy of paclitaxel/carboplatin versus paclitaxel/cisplatin in stage IVB, persistent, or recurrent disease; in addition, three dimensional (3-D) image-based high-dose rate brachytherapy; several therapeutic agents showed viable anti-tumor clinical response in recurrent and metastatic disease: bevacizumab, cediranib, and immune-therapies including HPV-tumor infiltrating lymphocytes and Z-100; HPV test received Food and Drug Administration (FDA) approval as the primary screening tool of cervical cancer in women aged 25 and older, based on the results of the Addressing the Need for Advanced HPV Diagnostics (ATHENA) trial, which suggested that HPV test was a more sensitive and efficient strategy for cervical cancer screening than methods based solely on cytology;

3) for endometrial cancer, targeted agents including mTOR inhibitors and bevacizumab; radiation therapy “sandwiched” between combination chemotherapy schedules for the treatment of uterine papillary serous carcinoma; preoperative prediction of lymph node metastasis, definition of low-risk group, and recurrence and survival outcomes of laparoscopic approaches were addressed;

4) for ovarian cancer, bevacizumab studies were followed by PARP inhibitors and other molecular targeted agents such as EGFR TK inhibitor and trebananib (AMG 386); for the development of genomic study in gynecologic cancers, BRCA mutations were covered in epithelial ovarian cancer; and

5) for vulvar cancer, sentinel lymph node biopsy [193-195].

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