

Michael A. Bookman

2.1

Trials that Define Primary Treatment

Current optimal management of advanced-stage ovarian cancer includes maximal cytoreductive surgery and a program of chemotherapy with carboplatin and paclitaxel, generally administered for six cycles. While the chemotherapy has been validated by phase III trials, there are areas of controversy, as well as gaps in knowledge, contributing to acceptable variations in clinical practice as applied to individual patients. A number of strategies have been evaluated with the goal of improving treatment outcomes, including dose intensity, maintenance-consolidation, schedule variations, intraperitoneal administration, regional hyperthermia, and incorporation of additional cytotoxic agents. Many of the phase III trials that have defined current treatment options are summarized in Table 2.1.

Platinum compounds remain dominant as the most active cytotoxic agents currently utilized in the treatment of ovarian cancer. Over the last 30 years, the therapeutic ratio of platinum-based primary chemotherapy has been improved through the development of less toxic analogs (carboplatin) and the determination of optimal dose, schedule, sequence, and duration of treatment [1–4]. In general, the administration of higher doses of chemotherapy with hematopoietic support, or extended administration of multiple cycles of chemotherapy (beyond six cycles), has not improved long-term outcomes, and these strategies carry an increased risk of serious cumulative toxicity [5–7].

M.A. Bookman
Arizona Cancer Center, 1515 N. Campbell Avenue, 2942F,
P.O. Box 245024, Tucson, AZ 85724-5024, USA
e-mail: mbookman@azcc.arizona.edu

Table 2.1 Principles of optimal primary therapy

<i>Platinum agents</i>	Cisplatin vs. carboplatin	Carboplatin dosing optimized using renal clearance [2] Carboplatin-based combinations associated with equivalent long-term outcomes, reduced nonhematologic toxicity, and increased hematologic toxicity, especially thrombocytopenia [1, 3, 4]
	Carboplatin dose intensity	No evidence of improved long-term outcomes within ranges achieved using conventional therapy or hematopoietic progenitor cell support [5–7]
	Duration of treatment	Optimal number of cycles not defined, without differences in long-term outcomes between 4, 6, 8, 10, or 12 cycles within individual trials. Cumulative hematologic and nonhematologic toxicity observed with extended therapy, and most patients receive six cycles
<i>Taxanes</i>	Dose intensity and infusion duration	No evidence for dose-response relationship within practical dose range [76–78] Extended infusion duration correlates with hematologic toxicity, but not efficacy [79, 80]
	Primary combinations with cisplatin or carboplatin	Improved median survival with paclitaxel and platinum [8–10] “Platelet-sparing effect” in combination with carboplatin raises questions of drug–drug antagonism [28] Sequential single-agent therapy appropriate for some patients [12, 13]
	Optimal scheduling	Improved therapeutic ratio (phase I-II) associated with weekly therapy in recurrent disease [16, 17] Improved progression-free survival with dose-dense weekly paclitaxel in combination with carboplatin as primary treatment [18]
	Docetaxel vs. paclitaxel	Different toxicity profile without improved long-term outcomes [15]
<i>Intraperitoneal therapy</i>	Intraperitoneal cisplatin	Improved survival validated in phase III trials, but with increased nonhematologic toxicity [81–83] Metaanalysis [84, 85] Commentary [86, 87]
	Intraperitoneal carboplatin	Reduction in nonhematologic toxicity, but activated more slowly, compared to cisplatin. Potential role as intraperitoneal therapy currently under phase III evaluation (GOG 0252)
	Intraperitoneal paclitaxel	Incorporated as component in GOG 0172, but individual contribution of route vs. schedule unclear [82]

Table 2.1 (continued)

<i>Incorporation of additional agents with primary therapy</i>	Integration of cytotoxic agents including gemcitabine, epirubicin, PEG-liposomal doxorubicin, topotecan	Extensively evaluated through international phase III trials involving multiple GCIG members. No evidence for improved progression-free or overall survival with any new regimen [22–26]
	Integration of agents that target angiogenesis	Positive phase II data with single-agent bevacizumab, front-line phase III trials ongoing (GOG 0218, OV7) [50, 51]
<i>Maintenance – consolidation</i>	Extended cytotoxic therapy evaluated with topotecan, epirubicin, paclitaxel, or IP platinum	No improvement in survival from completed trials [88–92]. Phase III trial in progress with paclitaxel and polyglutamated paclitaxel (GOG 0212)
	Extended biologic therapy evaluated with interferon- α , [46]Y-anti-HMFG1 antibody, murine anti-CA125	No improvement in survival from completed trials [93–95]. Trials in progress with anti-MUC16 antibody, bevacizumab, and inhibitors of VEGF receptor signaling
<i>Surgical interventions</i>	Extent of cytoreductive surgery	Extent of postoperative residual disease correlated with outcome in retrospective studies, although cytoreductive surgery has not been prospectively validated in a randomized trial [96–98]
	Timing of cytoreductive surgery	Initial surgery followed by interval cytoreduction in appropriate patients is not inferior to initial cytoreduction alone [99–101] For patients with advanced IIIC-IV disease, neoadjuvant chemotherapy with interval cytoreduction achieves equivalent survival to initial cytoreduction, with improved safety (EORTC 55971)
	Role of secondary surgical assessment	Secondary surgical assessment for patients in clinical complete remission provides prognostic information, but surgery has not been shown to have an impact on survival or optimization of secondary treatment [102]

2.2 Optimal Integration of Taxanes

Mature results from Gynecologic Oncology Group (GOG) protocol GOG 0111 and the National Cancer Institute of Canada (NCIC) and European Organization for Research and Treatment of Cancer (EORTC) trial, protocol OV10, established the superiority of cisplatin plus paclitaxel as compared to cisplatin plus cyclophosphamide [8–10]. In addition, GOG 0158 and Abeitsgemeinschaft Gynäkologische Onkologie-Ovarialkarzinom

(Gynecologic Oncology Ovarian Cancer Study Group, AGO-OVAR) studies established that carboplatin plus paclitaxel was at least as effective as cisplatin plus paclitaxel [3, 4]. Based on these findings, the Gynecologic Cancer InterGroup (GCIG) published consensus guidelines favoring carboplatin and paclitaxel as the preferred comparator arm for clinical trials [11]. However, the GOG 0132 and International Collaborative Ovarian Neoplasm (ICON3) trials have suggested that sequential therapy with platinum followed by paclitaxel at progression can achieve equivalent long-term outcomes for some patients, supporting a role for individualized selection criteria while reinforcing the primary activity of platinum compounds [12, 13].

Taxanes have clearly emerged as the second most important class of cytotoxic agents. In addition to data from front-line trials, a phase III trial in the setting of platinum-sensitive recurrent disease, ICON4, also demonstrated superiority of a combination of carboplatin and paclitaxel compared to carboplatin regimens without paclitaxel, but without directly addressing the role of sequential single-agent therapy [14].

Substitution of docetaxel is an acceptable alternative to paclitaxel in the front-line setting with a reduced risk of neuropathy and hypersensitivity, but with an increased risk of dose-limiting hematologic toxicity, based on a phase III trial [15]. In spite of interesting molecular pharmacodynamics, there are no data to indicate clinical superiority of docetaxel when compared to paclitaxel in the management of newly diagnosed or recurrent epithelial ovarian cancer.

With paclitaxel, longer infusions (≥ 24 h) increase mucosal and bone marrow toxicity, but without improved efficacy. Shorter infusions (< 3 h) are generally better-tolerated from a hematologic perspective, although higher individual doses can increase the risk of arthralgia-myalgia and neuropathy. Weekly scheduling permits higher cumulative dose delivery, while avoiding hematologic toxicity and alopecia, and has demonstrated consistent activity in patients who have recurred within 6 months of primary therapy with conventional carboplatin and paclitaxel [16, 17].

The Japanese Gynecologic Oncology Group (JGOG) conducted a phase III trial in women with newly diagnosed advanced-stage ovarian cancer, demonstrating superiority of weekly dose-dense paclitaxel in combination with standard doses of carboplatin compared to standard scheduling of the same drugs [18]. This is an important finding, illustrating the need to carefully examine how we use standard agents, as well as strategies to incorporate new agents. Ongoing phase III trials through GOG and other groups aim to extend the JGOG findings, including integration with intraperitoneal chemotherapy and bevacizumab.

2.3

Integration of a Third Cytotoxic Agent

A number of nonplatinum cytotoxic agents have well-defined activity in the management of recurrent disease, including topotecan, pegylated liposomal doxorubicin (PLD), prolonged oral etoposide, and gemcitabine. Each of these agents has a unique molecular target, mechanism of action, and pathways of resistance. In view of the central role of platinum, there has been particular interest in the incorporation of agents that may

accentuate the platinum response, through increased formation of platinum-deoxyribonucleic acid (DNA) adducts or inhibition of DNA repair. Early nonrandomized clinical trials reported high response rates using triple-drug platinum-based combinations, particularly with gemcitabine [19, 20]. However, randomized studies were clearly needed to determine whether new platinum-based combinations could achieve meaningful clinical benefit when balanced against the increased risk of host toxicity.

Recognizing that a large number of patients would be required for a definitive analysis of newer cytotoxic agents, many of the cooperative groups engaged in collaborative relationships through GCIg, which provided a framework for sharing preliminary clinical data, coordinated planning of international phase III trials and standards for collaboration on larger studies [21]. While some international trials emerged with overlapping treatment regimens, the cumulative global experience provides a robust analysis of multiple platinum-based chemotherapy regimens for primary therapy of advanced-stage disease.

Based on multiple phase III trials involving more than ten thousand women, we can conclude that the addition of a third cytotoxic agent has clearly been associated with increased host toxicity, but has not been shown to improve long-term clinical outcomes [22–26]. Some agents, such as topotecan and gemcitabine, exhibit schedule- and sequence-dependent hematologic toxicity, particularly when combined with carboplatin. These agents can interfere with repair of damage from platinum-DNA adducts, which could be advantageous, but only if there was a reliable method to circumvent hematologic toxicity. Of note, the relationship between increased hematologic toxicity and optimum tumor cell-kill has remained unclear, and one may not always correlate with the other [27].

In contrast, combinations of paclitaxel with carboplatin are well-tolerated, with capability of administering full doses of both drugs. This has been attributed to a “platelet-sparing” effect of paclitaxel on carboplatin-mediated thrombocytopenia, raising questions about possible drug–drug antagonism which have not been resolved [28].

2.4

New Approaches Targeting the Mitotic Apparatus

Disruption of the mitotic apparatus is thought to be the primary mechanism of action for paclitaxel, which promotes tubulin aggregation. The clinical development of paclitaxel has been challenged by poor solubility, hypersensitivity reactions, and peripheral neuropathy. Various formulations have been developed to optimize delivery, including liposomes, nanoparticle albumin-bound (NAB) paclitaxel, polyglutamated paclitaxel, and emulsions. NAB-paclitaxel has regulatory approval for the treatment of metastatic breast cancer and phase II activity in ovarian cancer [29]. While a front-line phase III trial of NAB-paclitaxel in combination with carboplatin would be of interest, there are many competing priorities, including novel cytotoxic and molecular-targeted agents, as well as the utilization of non-conjugated paclitaxel on a dose-dense weekly schedule.

Alternative agents under development include potent epothilone derivatives (ixabepilone and patupilone) that also target tubulin, but are less susceptible to some resistance strategies, such as increased expression of tubulin beta-III isoforms or multidrug resistance (MDR)

mediated by p-glycoprotein (pGP) [30]. These agents are associated with varying degrees of myelosuppression, stomatitis, diarrhea, and neuropathy. Another approach has been to develop molecules that inhibit proteins associated with the mitotic spindle apparatus, including the kinesin spindle protein (KSP). These agents, if proven to be effective, would eliminate the risk of neuropathy, which is caused by damage to nonmitotic tubulin. There has also been interest in targeting aurora kinase, which is frequently overexpressed in tumors and associated with regulation of chromosome segregation and cytokinesis during mitosis.

2.5

Development of Alternative Cytotoxic Agents

While the combination of carboplatin and paclitaxel remains a well-tolerated and effective standard treatment for newly diagnosed ovarian cancer, there is continued interest in the discovery of new targets, as well as new approaches for inhibiting old targets. DNA damage, replication, and repair offer a number of important targets for ongoing drug development. For example, trabectedin, a marine-derived antineoplastic agent, was initially isolated from the tunicate *Ecteinascidia turbinata*. It binds covalently to the minor groove of DNA, bending DNA toward the major groove, disrupting transcription, and leading to G2-M cell cycle arrest and apoptosis. Trabectedin is particularly active in recurrent platinum-sensitive ovarian cancer [31]. However, unlike carboplatin, trabectedin is more cytotoxic in cells with efficient transcription-coupled nucleotide excision repair (NER).

Folate metabolism is another pathway under reexamination, with the development of pemetrexed, a multitargeted antifolate that is also an excellent substrate for polyglutamation, thereby increasing retention within tumor cells. Pemetrexed, in combination with cisplatin, is utilized for the treatment of mesothelioma, and single-agent pemetrexed has activity in recurrent platinum-resistant ovarian cancer, with expected hematologic toxicity managed with dose selection and utilization of vitamin supplementation [32, 33].

Although there is great interest in molecular-targeted biology, cytotoxic chemotherapy remains an essential element in the treatment of advanced-stage disease. New cytotoxic agents with novel targets should be fully evaluated in parallel with biologic agents.

2.6

Biologic Principles with an Impact on Primary Therapy

Primary disease management has been guided not only by phase III trials, but also by emerging knowledge of cancer biology, including histopathology. For example, although primary ovarian mucinous tumors are rare, collaborative retrospective review of international data has verified that mucinous tumors are not generally responsive to platinum-based chemotherapy, and patients with advanced mucinous tumors have inferior long-term survival, compared with serous or endometrioid subtypes [34, 35]. International studies have been initiated through the GCIG to evaluate alternative interventions, modeled after mucinous colorectal cancer (Table 2.2).

Table 2.2 Biologic observations guiding development of front-line trials

<i>Type I/II tumors</i>	Clinical and molecular characteristics of low-grade (type I) and high-grade serous tumors (type II)	Verified distinct origin of low-grade serous tumors in association with borderline tumors of low malignant potential, compared to high-grade serous tumors, reinforcing targeted development of clinical trials [39, 40]
<i>Early-stage disease</i>	Clinical features, pathologic subtypes, and risk factors associated with early-stage disease	Recognition of distinct distribution of histologic subtypes in early-stage disease, relationship of complete surgical staging to chemotherapy outcomes, risk of recurrence associated with high-grade serous histology and/or positive peritoneal cytology, reduced risk associated with well-staged clear cell tumors [36–38]
<i>Advanced-stage disease</i>	Analysis of histologic factors, molecular subtypes, and activated pathways	Verification that mucinous tumors are poorly-responsive to platinum-based therapy with inferior long-term clinical outcomes [34, 35] Identification of epithelial-mesenchymal transition, including mesenchymal gene activation profile with more aggressive behavior [44, 45]
<i>Stem cell hypothesis</i>	Presence of treatment-resistant regenerative subpopulations	Recognition of limitations associated with platinum-based primary therapy and the need to explore alternatives guided by molecular and genomic analysis of treatment-resistant subpopulations [61, 62]
<i>Synthetic lethal paradigms</i>	Genetic and epigenetic silencing of pathways involved in DNA repair	Opportunity to exploit synthetic lethality using PARP inhibition ($\pm$ chemotherapy) in tumors with loss of BRCA function and deficient homologous recombination repair of double-strand DNA breaks [70, 71] Somatic and epigenetic silencing of BRCA, expanding the proportion of patients that might benefit from PARP inhibition [72, 73] Recognition of secondary mutations in BRCA associated with PARP resistance [74, 75]
<i>Immunologic regulation</i>	Intratumoral T lymphocytes	Improved survival associated with higher number of tumor infiltrating lymphocytes and lower ratios of immunoregulatory T lymphocytes, prompting prospective trials with vaccination, antibodies, and cytokines [103, 104]
<i>Drug resistance</i>	Platinum-resistance	Multifactorial, including transport, detoxification, damage tolerance, reduced damage detection, defective apoptotic signaling [55–57, 60]
	Multidrug resistance	Drug efflux pumps (p-glycoprotein) for natural products, no therapeutic advantage from inhibition [64]
	Other specific adaptations	Examples include isoforms of β tubulin associated with taxane resistance, downregulation of targets (topoisomerase I), reduced phosphorylation of gemcitabine, amplification of ribonucleotide reductase

It is also apparent that early-stage ovarian cancer has a distinct biologic profile, characterized by an increased proportion of nonserous tumors, including endometrioid and clear cell histology [36–38]. When patients undergo complete surgical staging and have a tumor that is limited to the ovary, the finding of clear cell histology, in and of itself, does not appear to carry an independent adverse prognosis, and cure would be expected in the vast majority of cases. In contrast, early-stage serous tumors are often high-grade and more likely to have occult peritoneal or nodal spread. As such, they have a greater risk of recurrence and are perhaps more likely to benefit from adjuvant chemotherapy.

In advanced-stage serous tumors, distinct molecular profiles have been associated with low-grade (Type I) compared to high-grade (Type II) neoplasia [39, 40]. Low-grade invasive adenocarcinoma generally arises in conjunction with borderline tumors of low malignant potential. These tumors are not generally sensitive to platinum-based chemotherapy, retain functional p53, and harbor activating mutations of either B-ras or K-raf [39, 40]. Activated RAS triggers phosphorylation and activation of RAF kinase, which then phosphorylates cytoplasmic mitogen-activated protein kinases (MAPK) that include MEK-1/2 [41]. Activated MEK then phosphorylates ERK-1/2, which dimerizes and translocates to the nucleus where it can regulate cellular proliferation [42]. This important pathway is activated by a diverse group of extracellular signals including integrins, receptors for epidermal growth factor, platelet-derived growth factor, and insulin-like growth factor-1, as well as various cytokines. Specific tyrosine kinase inhibitors, such as AZD6244, have been developed to target MEK-1/2, a central pathway component [43]. The GOG completed a phase II study of AZD6244, a MEK inhibitor, in low-grade ovarian adenocarcinoma (GOG 0239), and this may provide an important strategy to build new combinations.

In contrast, high-grade serous tumors tend to have inactivation of p53 through chromosomal deletion and/or mutation, without activating mutations of B-raf or K-ras, and are initially sensitive to platinum-based chemotherapy [39, 40]. Some high-grade ovarian cancers are associated with sarcomatous differentiation, recognized as carcinosarcomas or mixed Müllerian tumors. This is thought to occur through a process of epithelial-mesenchymal transition (EMT) and is associated with downregulation of epithelial markers (such as epithelial membrane antigen) and upregulation of mesenchymal markers (such as vimentin) [44]. These changes contribute to cellular motility, production of proteolytic enzymes, and invasive behavior. Aggressive mesenchymal features have also been identified through the analysis of gene expression profiles, even without visible evidence of sarcoma [45]. Core components of EMT are under control of src kinase, prompting clinical evaluation of dasatinib and other inhibitors of src kinase.

Advanced-stage clear cell tumors exhibit more aggressive patterns of metastatic spread and are frequently resistant to platinum-based chemotherapy. Analysis of gene expression profiles have identified characteristic patterns associated with clear cell tumors from other primary sites, but optimal treatment strategies for clear cell tumors of ovarian origin remain to be defined [46].

2.7

Targeting Angiogenesis

High-grade serous ovarian cancer is characterized by overexpression of vascular endothelial growth factor (VEGF), which drives abnormal tumor angiogenesis, contributing to high interstitial pressure and production of ascites [47]. Direct targeting of this pathway can be achieved by sequestration of VEGF protein using monoclonal antibodies (bevacizumab) or engineered binding site molecules (aflibercept), blockade of the VEGF receptor-2 (VEGFR2) with monoclonal antibodies (IMC-1C11), or inhibition of receptor-associated tyrosine kinase with small molecular weight inhibitors (axitinib, cediranib, pazopanib, sorafenib, BIBF 1120). Indirect strategies include targeting genes involved in the regulation of VEGF expression, such as hypoxia inducible factor 1-alpha (HIF1a), antibody-based blockade of angiopoietin-2 (CVX-060), inhibition of cytoplasmic tyrosine kinases that are activated following VEGF receptor-mediated phosphorylation, inhibition of protein kinase-c β (enzastaurin), or interference with other convergence pathways, such as the serine-threonine specific protein kinase (AKT) or the mammalian target of rapamycin (mTOR) [48, 49].

Thus far, the most widely studied agent has been bevacizumab, initially as a single agent, and subsequently in phase III trials with concurrent chemotherapy and maintenance [50, 51]. When evaluated in combination with chemotherapy in other tumor types, bevacizumab was associated with improved long-term outcomes, achieving regulatory approval in colon cancer, nonsquamous lung cancer, and breast cancer. These observations have been attributed to improved drug delivery as a result of pseudonormalization of tumor vasculature and a reduction in interstitial pressure [52]. Single-agent activity with bevacizumab in recurrent ovarian cancer is more substantial than previously observed in these other tumor types, and it is anticipated that combinations of bevacizumab with carboplatin and paclitaxel will improve long-term outcomes for women with ovarian cancer. These combinations are currently under evaluation in several phase III trials, both in the setting of primary therapy for newly diagnosed disease (GOG 0218, ICON7), as well as recurrent disease (GOG 0213).

2.8

Chemotherapy Resistance

The dominant pattern of resistance observed in ovarian cancer is related to platinum compounds (cisplatin and carboplatin), with extension to traditional alkylating agents and radiation [53, 54]. Resistance is multifactorial, involving decreased active transport, increased drug efflux, rapid detoxification of platinum through glutathione conjugation, increased DNA damage tolerance, reduced detection of DNA damage, accelerated removal of platinum-DNA adducts, enhanced DNA repair, and defective apoptotic signaling, often associated

with loss of tumor suppressor protein p53, but also independent of p53. Resistance can be intrinsic or evolve in response to selective pressures from chemotherapy exposure. As such, some components of resistance may be reversible over a period of time.

Preclinical models have suggested a variety of strategies to prevent or overcome resistance. Frequently, these models are based on targeting one aspect of platinum-resistance using short-term data from established cell lines, and they have not successfully translated to clinical practice. Actual human tumors have lower growth fractions, greater biologic heterogeneity, and diverse adaptation strategies.

Currently, there are no compounds with the ability to specifically target platinum-resistant tumors in the clinical setting. Some chemotherapy agents, such as gemcitabine and topotecan, can interfere with DNA repair and reliably increase platinum-mediated toxicity. However, these effects are not tumor-specific, and combinations are also associated with increased hematologic toxicity, limiting their clinical application. A sterically-hindered platinum compound (picoplatin) was developed to avoid thiol-mediated inactivation, but did not achieve superior clinical outcomes in patients with recurrent disease [55]. It was also thought that oxaliplatin might retain activity in resistant tumors because it forms DNA adducts that are not detected by the mismatch repair system, but only a 7% response rate was observed in patients with a platinum-free interval of less than 6 months [56]. In addition, components of the mismatch repair system, such as MLH1, can be suppressed by gene methylation in resistant tumors, prompting studies with a demethylating agent (decitabine) and carboplatin, but without improved efficacy at the expense of increased hematologic toxicity [57].

NER is the primary mechanism to remove platinum-DNA adducts, and excision repair cross-complementing-1 (ERCC1) is a critical NER component. Resistance to platinum has been linked to ERCC1 mRNA expression in ovarian cancer and other tumors, and ERCC1 levels are predictive of clinical outcomes in lung cancer patients treated with platinum-based chemotherapy [58, 59]. Whether ERCC1, or other markers, could be used to guide chemotherapy selection in woman with ovarian cancer is unknown.

Recent efforts have focused on the biology of platinum influx, largely mediated by copper transporter-1 (CTR1), which can be downregulated after platinum exposure [60]. Strategies are also under evaluation to restore damage detection and apoptotic signaling in tumor cells via intrinsic or extrinsic pathways, such as restoration of the tumor suppressor gene protein p53, regulation of the antiapoptotic protein Bcl-2, activation of the tumor necrosis factor receptor (TNFR), and TNF-related apoptosis-inducing ligand (TRAIL) R1. There has also been interest in tumor stem cell biology as it relates to the emergence of drug resistant populations, and this may provide some new molecular markers and targets with greater specificity [61, 62].

The second pattern is related to MDR for natural products mediated primarily by the drug efflux pump, pGP. Natural substrates for pGP include taxanes, anthracyclines, and vinca alkaloids. A number of inhibitors of pGP MDR function have been developed [63]. The most extensively studied agent has been valspodar, an analog of cyclosporine A, which showed no clinical benefit in a phase III trial with paclitaxel and carboplatin [64]. While these agents can block drug efflux at the cellular level, the effects are not tumor-specific, and it has been necessary to utilize lower doses of chemotherapy to avoid serious toxicity, minimizing any potential therapeutic advantage. The breast cancer resistance protein (BCRP), or adenosine triphosphate (ATP)-binding cassette protein G2 (ABCG2), dimerizes

to form a membrane-associated energy-dependent efflux pump that is also associated with MDR, primarily to mitoxantrone and camptothecins, including topotecan [65].

The third pattern represents a collection of specific cellular adaptations associated with resistance to individual cytotoxic agents used in the treatment of ovarian cancer. These include mutations in β tubulin subunits or alterations in the ratio of tubulin isoforms that have an impact on taxane sensitivity. Downregulation of topoisomerase-I can prevent the formation of cleavable complexes with topotecan. Resistance to gemcitabine can be mediated by decreased active membrane transport, reduced phosphorylation related to the depletion of deoxycytidine kinase, or amplification of the gene for the M2 subunit of ribonucleotide reductase [66–68].

Our understanding of the biology surrounding drug resistance continues to improve, with interesting predictive markers of tumor response, and potential targets for intervention, but drug resistance still remains a central problem in the treatment of advanced-stage ovarian cancer.

2.9

Synthetic Lethal Strategies

Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) is a key component in the process of base excision repair of single-strand DNA breaks. Inhibition of PARP leads to the accumulation of DNA single-strand breaks, which can lead to potentially lethal DNA double-strand breaks at replication forks [69]. However, these breaks are usually repaired by the double-strand homologous recombination pathway, which incorporates the tumor suppressor proteins BRCA1 and BRCA2. Germ-line mutations in either BRCA1 or BRCA2 have been associated with an increased risk of developing ovarian cancer, and tumor cells that harbor loss-of-function BRCA mutations (affecting the remaining wild-type allele) are deficient in homologous repair. Importantly, this repair defect is not shared by normal tissues in the same patient, due to the presence of the remaining wild-type allele.

Inhibition of PARP in a patient with a BRCA1/2 mutation has the potential to create a “synthetic lethal” situation, generating unrepaired single-strand breaks, accumulation of double-strand breaks, and collapse of the replication fork. This single-agent treatment strategy is well-tolerated and effective in a proportion of women with BRCA1/2 mutations [70, 71]. However, inheritable germ-line mutations only account for perhaps 5% of all ovarian cancers. Additional patients may benefit if they have tumors with somatic (non-germ line) mutations or with hypermethylation or epigenetic silencing of key genes involved in DNA homologous recombination repair [72, 73]. Allowing for all three scenarios might account for 30% of women with ovarian cancer. Of interest, laboratory studies have documented the appearance of secondary mutations in tumor-associated BRCA1 that can restore expression and overcome the effects of PARP inhibition [74, 75].

PARP inhibitors (olaparib, ABT-881, BSI-201) can also be utilized to enhance the effects of cytotoxic chemotherapeutics that target DNA, such as carboplatin, gemcitabine, and topotecan. However, as with other strategies to overcome drug resistance, there can be increased host toxicity, particularly bone marrow suppression, and randomized trials will be needed to evaluate long-term clinical benefits.

2.10
Discussion

Optimal primary chemotherapy of advanced ovarian cancer has not substantially changed over the last few years, in spite of the extensive evaluation of new cytotoxic agents and diverse treatment strategies (Table 2.3). Almost all patients undergo at least one attempt at

Table 2.3 Clinical impact of strategies to improve outcomes in primary therapy

Clinical paradigm and representative trials	Stage	Patients (n)	Hazard ratio for progression-free survival (95% CI)	p Value
Substitution of docetaxel for paclitaxel (SCOTROC) [15]	Ic–IV	1,077		
Paclitaxel+Carboplatin		538	1.0 (reference)	
Docetaxel+Carboplatin		539	0.97 (0.83–1.13)	p=0.707
Incorporation of a third cytotoxic agent (i.e GOG 0182/ICON5) [22]	III–IV	4,312		
Paclitaxel+Carboplatin		864	1.0 (reference)	
Gemcitabine triplet		864	1.028 (0.924–1.143)	p=0.610
Gemcitabine doublet		861	1.037 (0.932–1.153)	p=0.503
PEG-liposomal doxorubicin		862	0.984 (0.884–1.095)	p=0.796
Topotecan doublet		861	1.066 (0.958–1.186)	p=0.239
Intraperitoneal chemotherapy (GOG 0172) [82]	Optimal III	415		
Intravenous		210	1.0 (reference)	
Intraperitoneal		205	0.80 (0.64–1.00)	p=0.05
Dose-dense weekly paclitaxel with carboplatin (JGOG) [18]	II–IV	631		
Standard paclitaxel		319	1.0 (reference)	
Dose-dense paclitaxel		312	0.71 (0.58–0.88)	p=0.0015
Incorporation of bevacizumab				
GOG 0218	III–IV	1,873	Accrual complete, analysis in progress	
MRC-ICON7	Ic–IV	1,528	Accrual complete, analysis in progress	

maximal cytoreductive surgery, and the combination of carboplatin and paclitaxel remains a well-tolerated and widely utilized standard treatment regimen. Emerging data favor the selected utilization of neoadjuvant chemotherapy in patients with bulky disease, and dose-dense weekly paclitaxel in combination with carboplatin appears superior to standard dosing of paclitaxel. Intraperitoneal cisplatin and paclitaxel can be administered to patients with small-volume residual disease, and new trials are evaluating intraperitoneal delivery of carboplatin to improve patient safety and tolerability.

The integration of emerging biologic principles with the development of molecular-targeted reagents is starting to achieve meaningful results, especially with regard to inhibition of angiogenesis and interference with PARP-mediated DNA repair. Biologic observations have also contributed to our understanding of tumor classifications and prompted the evaluation of individualized treatments. However, the rapid development of drug resistance remains a major clinical challenge for the majority of patients with advanced-stage disease, prompting studies that target regenerative subpopulations of resistant cells.

The next few years will see mature data from phase III trials targeting VEGF, including integration with intraperitoneal chemotherapy, as well as numerous phase II trials with diverse molecular-targeted agents. Comparative data among these agents are limited, and selection of high-priority combinations will remain challenging. Future phase III trials will depend on carefully designed randomized phase II studies with criteria for the selection of promising combinations, based on feasibility, tolerability, and efficacy.

References

1. Alberts DS, Green S, Hannigan EV et al (1992) Improved therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase III randomized trial in stages III and IV ovarian cancer. *J Clin Oncol* 10:706–717
2. Calvert AH, Newell DR, Gumbrell LA et al (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 7:1748–1756
3. du Bois A, Luck HJ, Meier W et al (2003) Arbeitsgemeinschaft Gynakologische Onkologie Ovarian Cancer Study Group. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 95:1320–1329
4. Ozols RF, Bundy BN, Greer BE et al (2003) Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 21:3194–3200
5. Gore M, Mainwaring P, A'Hern R et al (1998) Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. *J Clin Oncol* 16:2426–2434
6. Jakobsen A, Bertelsen K, Andersen JE et al (1997) Dose-effect study of carboplatin in ovarian cancer: a Danish Ovarian Cancer Group study. *J Clin Oncol* 15:193–198
7. Möbus V, Wandt H, Frickhofen N et al (2007) Phase III trial of high-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: intergroup trial of the AGO-Ovar/AIO and EBMT. *J Clin Oncol* 25:4187–4193

8. McGuire WP, Hoskins WJ, Brady MF et al (1996) Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 334:1–6
9. Piccart MJ, Bertelsen K, James K et al (2000) Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 92:699–708
10. Piccart MJ, Bertelsen K, Stuart G et al (2003) Long-term follow-up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide-cisplatin combination in advanced ovarian cancer. *Int J Gynecol Cancer* 13(suppl 2):144–148
11. du Bois A, Quinn M, Thigpen T et al (2005) 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol* 16(Suppl 8):viii7–viii12
12. International Collaborative Ovarian Neoplasm Group (2002) Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. *Lancet* 360:505–515
13. Muggia FM, Braly PS, Brady MF et al (2000) Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. *J Clin Oncol* 18:106–115
14. Parmar MK, Ledermann JA, Colombo N et al (2003) ICON and AGO Collaborators. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 361:2099–2106
15. Vasey PA, Jayson GC, Gordon A et al (2004) Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 96:1682–1691
16. Fennelly D, Aghajanian C, Shapiro F et al (1997) Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol* 15:187–192
17. Markman M, Blessing J, Rubin SC et al (2006) Phase II trial of weekly paclitaxel (80 mg/m²) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol* 101:436–440
18. Katsumata N, Yasuda M, Takahashi F et al (2009) Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 374:1331–1338
19. du Bois A, Belau A, Wagner U et al (2005) A phase II study of paclitaxel, carboplatin, and gemcitabine in previously untreated patients with epithelial ovarian cancer FIGO stage IC-IV (AGO-OVAR protocol OVAR-8). *Gynecol Oncol* 96:444–451
20. Look KY, Bookman MA, Schol J et al (2004) Phase I feasibility trial of carboplatin, paclitaxel, and gemcitabine in patients with previously untreated epithelial ovarian or primary peritoneal cancer: a Gynecologic Oncology Group study. *Gynecol Oncol* 92:93–100
21. Trimble EL, Davis J, DiSaia P et al (2007) Clinical trials in gynecological cancer. *Int J Gynecol Cancer* 17:547–556
22. Bookman MA, Brady MF, McGuire W et al (2009) Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup (GCIG). *J Clin Oncol* 27:1419–1425
23. du Bois A, Weber B, Rochon J et al (2006) Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. *J Clin Oncol* 24:1127–1135

24. Hoskins PJ, Vergote I, Stuart G et al (2008) Phase III trial of cisplatin plus topotecan followed by paclitaxel plus carboplatin versus standard carboplatin plus paclitaxel as first-line chemotherapy in women with newly diagnosed advanced epithelial ovarian cancer (EOC) (OV.16). A Gynecologic Cancer Intergroup Study of the NCIC CTG, EORTC GCG, and GEICO. *J Clin Oncol* 26:Abstract LBA5505
25. Kristensen GB, Vergote I, Stuart G et al (2003) First-line treatment of ovarian cancer FIGO stages IIB-IV with paclitaxel/epirubicin/carboplatin versus paclitaxel/carboplatin. *Int J Gynecol Cancer* 13(suppl 2):172–177
26. Scarfone G, Scambia G, Raspagliesi F et al (2006) A multicenter, randomized, phase III study comparing paclitaxel/carboplatin (PC) versus topotecan/paclitaxel/carboplatin (TPC) in patients with stage III (residual tumor >1 cm after primary surgery) and IV ovarian cancer (OC). *J Clin Oncol* 24(suppl 18S):Abstract 5003
27. Bookman MA, McMeekin DS, Fracasso P (2006) Sequence-dependence of hematologic toxicity using carboplatin and topotecan for primary therapy of advanced epithelial ovarian cancer: A phase I study of the Gynecologic Oncology Group. *Gynecol Oncol* 103: 473–478
28. Guminski AD, Harnett PR, deFazio A (2001) Carboplatin and paclitaxel interact antagonistically in a megakaryoblast cell line – a potential mechanism for paclitaxel-mediated sparing of carboplatin-induced thrombocytopenia. *Cancer Chemother Pharmacol* 48:229–234
29. Teneriello MG, Tseng PC, Crozier M et al (2009) Phase II evaluation of nanoparticle albumin-bound paclitaxel in platinum-sensitive patients with recurrent ovarian, peritoneal, or fallopian tube cancer. *J Clin Oncol* 27:1426–1431
30. Dumontet C, Jordan MA, Lee FF (2009) Ixabepilone: targeting beta III-tubulin expression in taxane-resistant malignancies. *Mol Cancer Ther* 8:17–25
31. Krasner CN, McMeekin DS, Chan S et al (2007) A Phase II study of trabectedin single agent in patients with recurrent ovarian cancer previously treated with platinum-based regimens. *Br J Cancer* 97:1618–1624
32. Miller DS, Blessing JA, Krasner CN et al (2009) Phase II evaluation of pemetrexed in the treatment of recurrent or persistent platinum-resistant ovarian or primary peritoneal carcinoma: a study of the Gynecologic Oncology Group. *J Clin Oncol* 27:2686–2691
33. Vergote I, Calvert H, Kania M et al (2009) A randomised, double-blind, phase II study of two doses of pemetrexed in the treatment of platinum-resistant, epithelial ovarian or primary peritoneal cancer. *Eur J Cancer* 45:1415–1423
34. Hess V, A'Hern R, Nasiri N et al (2004) Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. *J Clin Oncol* 22:1040–1044
35. Winter WE 3rd, Maxwell GL, Tian C et al (2007) Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 25:3621–3627
36. Chan JK, Tian C, Monk BJ et al (2008) Prognostic factors for high-risk early-stage epithelial ovarian cancer. A Gynecologic Oncology Group study. *Cancer* 112:2202–2210
37. Trimbos JB, Parmar M, Vergote I (2003) International Collaborative Ovarian Neoplasm 1 (ICON1) and European Organisation for Research and Treatment of Cancer Collaborators–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION). International Collaborative Ovarian Neoplasm trial and Adjuvant Chemo Therapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst* 95:105–112
38. Trimbos JB, Vergote I, Bolis G et al (2003) For the EORTC–ACTION collaborators. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst* 95:113–125
39. Pohl G, Ho CL, Kurman RJ et al (2005) Inactivation of the mitogen-activated protein kinase pathway as a potential target-based therapy in ovarian serous tumors with KRAS or BRAF mutations. *Cancer Res* 65:1994–2000

40. Singer G, Stöhr R, Cope L et al (2005) Patterns of p53 mutations separate ovarian serous borderline tumors and low- and high-grade carcinomas and provide support for a new model of ovarian carcinogenesis: a mutational analysis with immunohistochemical correlation. *Am J Surg Pathol* 29:218–224
41. Ahn NG, Nahreini TS, Tolwinski NS, Resing KA (2001) Pharmacologic inhibitors of MKK1 and MKK2. *Meth Enzymol* 332:417–431
42. Khokhlatchev AV, Canagarajah B, Wilsbacher J et al (1998) Phosphorylation of the MAP kinase ERK2 promotes its homodimerization and nuclear translocation. *Cell* 93:605–615
43. Davies BR, Logie A, McKay JS et al (2007) AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamics relationship, and potential for combination in preclinical models. *Mol Cancer Ther* 6:2209–2219
44. Larue L, Bellacosa A (2005) Epithelial-mesenchymal transition in development and cancer: role of phosphatidylinositol 3' kinase/AKT pathways. *Oncogene* 24:7443–7454
45. Tothill RW, Tinker AV, George J et al (2008) Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. *Clin Cancer Res* 14:5198–5208
46. Zorn KK, Bonome T, Gangi L et al (2005) Gene expression profiles of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. *Clin Cancer Res* 11:6422–6430
47. Byrne AT, Ross L, Holash J et al (2003) Vascular endothelial growth factor-trap decreases tumor burden, inhibits ascites, and causes dramatic vascular remodeling in an ovarian cancer model. *Clin Cancer Res* 9:5721–5728
48. Kumaran GC, Jayson GC, Clamp AR (2009) Antiangiogenic drugs in ovarian cancer. *Br J Cancer* 100:1–7
49. Martin L, Schilder R (2007) Novel approaches in advancing the treatment of epithelial ovarian cancer: the role of angiogenesis inhibition. *J Clin Oncol* 25:2894–2901
50. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI (2007) Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 25:5165–5171
51. Cannistra SA, Matulonis UA, Penson RT et al (2007) Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol* 25:5180–5186
52. Grothey A, Galanis E (2009) Targeting angiogenesis: progress with anti-VEGF treatment with large molecules. *Nat Rev Clin Oncol* 6:507–518
53. Martin LP, Hamilton TC, Schilder RJ (2008) Platinum resistance: the role of DNA repair pathways. *Clin Cancer Res* 14:1291–1295
54. Muggia F (2009) Platinum compounds 30 years after the introduction of cisplatin: implications for the treatment of ovarian cancer. *Gynecol Oncol* 112:275–281
55. Gore ME, Atkinson RJ, Thomas H et al (2002) A phase II trial of ZD0473 in platinum-pre-treated ovarian cancer. *Eur J Cancer* 38:2416–2420
56. Fracasso PM, Blessing JA, Morgan MA et al (2003) Phase II study of oxaliplatin in platinum-resistant and refractory ovarian cancer: a gynecologic group study. *J Clin Oncol* 21:2856–2859
57. Glasspool RM, Gore M, Rustin G et al (2009) Randomized phase II study of decitabine in combination with carboplatin compared with carboplatin alone in patients with recurrent advanced ovarian cancer. *Clin Oncol* 27(suppl; abstr 5562):15s
58. Gossage L, Madhusudan S (2007) Current status of excision repair cross complementing-group 1 (ERCC1) in cancer. *Cancer Treat Rev* 33:565–577
59. Vilmar A, Sørensen JB (2009) Excision repair cross-complementation group 1 (ERCC1) in platinum-based treatment of non-small cell lung cancer with special emphasis on carboplatin: a review of current literature. *Lung Cancer* 64:131–139
60. Holzer AK, Howell SB (2006) The internalization and degradation of human copper transporter 1 following cisplatin exposure. *Cancer Res* 66:10944–10952

61. Glinsky GV (2008) "Stemness" genomics law governs clinical behavior of human cancer: implications for decision making in disease management. *J Clin Oncol* 26:2846–2853
62. Szotek PP, Pieretti-Vanmarcke R, Masiakos PT et al (2006) Ovarian cancer side population defines cells with stem cell-like characteristics and Mullerian Inhibiting Substance responsiveness. *Proc Natl Acad Sci USA* 103:11154–11159
63. Fojo T, Bates S (2003) Strategies for reversing drug resistance. *Oncogene* 22:7512–7523
64. Lhommé C, Joly F, Walker JL et al (2008) Phase III study of valsopodar (PSC 833) combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone in patients with stage IV or suboptimally debulked stage III epithelial ovarian cancer or primary peritoneal cancer. *J Clin Oncol* 26:2674–2682
65. Sharom FJ (2008) ABC multidrug transporters: structure, function and role in chemoresistance. *Pharmacogenomics* 9:105–127
66. Bookman MA (2005) Gemcitabine monotherapy in recurrent ovarian cancer: from the bench to the clinic. *Int J Gynecol Cancer* 15(suppl 1):12–17
67. Galmarini CM, Mackey JR, Dumontet C (2001) Nucleoside analogues: mechanisms of drug resistance and reversal strategies. *Leukemia* 15:875–890
68. Mini E, Nobili S, Caciagli B et al (2006) Cellular pharmacology of gemcitabine. *Ann Oncol* 15(suppl 5):v7–v12
69. Bolderson E, Richard DJ, Zhou BB, Khanna KK (2009) Recent advances in cancer therapy targeting proteins involved in DNA double-strand break repair. *Clin Cancer Res* 15:6314–6320
70. Bryant HE, Schultz N, Thomas HD et al (2005) Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 434:913–917
71. Fong PC, Boss DS, Yap TA et al (2009) Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 361:123–134
72. Esteller M, Silva JM, Dominguez G et al (2000) Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. *J Natl Cancer Inst* 92:564–569
73. Hilton JL, Geisler JP, Rathe JA et al (2002) Inactivation of BRCA1 and BRCA2 in ovarian cancer. *J Natl Cancer Inst* 94:1396–1406
74. Edwards SL, Brough R, Lord CJ (2008) Resistance to therapy caused by intragenic deletion in BRCA2. *Nature* 451:1111–1115
75. Sakai W, Swisher EM, Karlan BY et al (2008) Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature* 451:1116–1120
76. Bolis G, Scarfone G, Polverino G, Raspagliesi F et al (2004) Paclitaxel 175 or 225 mg per meters squared with carboplatin in advanced ovarian cancer: a randomized trial. *J Clin Oncol* 22:686–690
77. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD et al (1994) European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol* 12:2654–2666
78. Omura GA, Brady MF, Look KY et al (2003) Phase III trial of paclitaxel at two dose levels, the higher dose accompanied by filgrastim at two dose levels in platinum-pretreated epithelial ovarian cancer: an intergroup study. *J Clin Oncol* 21:2843–2848
79. Markman M, Rose PG, Jones E et al (1998) Ninety-six-hour infusional paclitaxel as salvage therapy of ovarian cancer patients previously failing treatment with 3-hour or 24-hour paclitaxel infusion regimens. *J Clin Oncol* 16:1849–1851
80. Spriggs DR, Brady MF, Vaccarello L et al (2007) Phase III randomized trial of intravenous cisplatin plus a 24- or 96-hour infusion of paclitaxel in epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 25:4466–4471
81. Alberts DS, Liu PY, Hannigan EV et al (1996) Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 335:1950–1955

82. Armstrong DK, Bundy B, Wenzel L et al (2006) Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 354:34–43
83. Markman M, Bundy BN, Alberts DS et al (2001) Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 19:1001–1007
84. Hess LM, Benham-Hutchins M, Herzog TJ et al (2007) A meta-analysis of the efficacy of intraperitoneal cisplatin for the front-line treatment of ovarian cancer. *Int J Gynecol Cancer* 17:561–570
85. Jaaback K, Johnson N (2006) Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev* 25:CD005340
86. Ozols RF, Bookman MA, du Bois A et al (2006) Intraperitoneal cisplatin therapy in ovarian cancer: comparison with standard intravenous carboplatin and paclitaxel. *Gynecol Oncol* 103:1–6
87. Swart AM, Burdett S, Ledermann J, Mook P, Parmar MK (2008) Why i.p. therapy cannot yet be considered as a standard of care for the first-line treatment of ovarian cancer: a systematic review. *Ann Oncol* 19:688–695
88. Bolis G, Danese S, Tateo S et al (2006) Etoposide versus no treatment as consolidation therapy in advanced ovarian cancer: results from a phase II study. *Int J Gynecol Cancer* 16(suppl 1):74–78
89. De Placido S, Scambia G, Di Vagno G et al (2004) Topotecan compared with no therapy after response to surgery and carboplatin/paclitaxel in patients with ovarian cancer: Multicenter Italian Trials in Ovarian Cancer (MITO-1) randomized study. *J Clin Oncol* 22:2635–2642
90. Markman M, Liu PY, Wilczynski S et al (2003) Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy: a Southwest Oncology Group and Gynecologic Oncology Group trial. *J Clin Oncol* 21:2460–2465
91. Pfisterer J, Weber B, Reuss A et al (2006) Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a gynecologic cancer intergroup trial of the AGO-OVAR and GINECO. *J Natl Cancer Inst* 98:1036–1045
92. Piccart MJ, Floquet A, Scarfone G et al (2003) Intraperitoneal cisplatin versus no further treatment: 8-year results of EORTC 55875, a randomized phase III study in ovarian cancer patients with a pathologically complete remission after platinum-based intravenous chemotherapy. *Int J Gynecol Cancer* 13(suppl 2):196–203
93. Alberts DS, Hannigan EV, Liu PY et al (2006) Randomized trial of adjuvant intraperitoneal alpha-interferon in stage III ovarian cancer patients who have no evidence of disease after primary surgery and chemotherapy: an intergroup study. *Gynecol Oncol* 100:133–138
94. Berek JS, Taylor PT, Gordon A et al (2004) Randomized, placebo-controlled study of oregovomab for consolidation of clinical remission in patients with advanced ovarian cancer. *J Clin Oncol* 22:3507–3516
95. Verheijen RH, Massuger LF, Benigno BB et al (2006) Phase III trial of intraperitoneal therapy with yttrium-90-labeled HMFG1 murine monoclonal antibody in patients with epithelial ovarian cancer after a surgically defined complete remission. *J Clin Oncol* 24:571–578
96. Dowdy SC, Loewen RT, Aletti G, Feitoza SS, Cliby W (2008) Assessment of outcomes and morbidity following diaphragmatic peritonectomy for women with ovarian carcinoma. *Gynecol Oncol* 109:303–307
97. Eisenkop SM, Spiros NM, Lin WC (2006) “Optimal” cytoreduction for advanced epithelial ovarian cancer: a commentary. *Gynecol Oncol* 103:329–335

98. Winter WE 3rd, Maxwell GL, Tian C et al (2008) Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 26:83–89
99. Bristow RE, Eisenhauer EL, Santillan A, Chi DS (2007) Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. *Gynecol Oncol* 104:480–490
100. Rose PG, Nerenstone S, Brady MF et al (2004) Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med* 351:2489–2497
101. van der Burg ME, van Lent M, Buyse M et al (1995) The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 332:629–634
102. Greer BE, Bundy BN, Ozols RF et al (2005) Implications of second-look laparotomy in the context of optimally resected stage III ovarian cancer: a non-randomized comparison using an explanatory analysis: a Gynecologic Oncology Group study. *Gynecol Oncol* 99:71–79
103. Curiel TJ, Coukos G, Zou L et al (2004) Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med* 10:942–949
104. Zhang L, Conejo-Garcia JR, Katsaros D et al (2003) Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med* 348:203–213

Intraperitoneal Therapy for Ovarian Cancer

Alberts, D.; Clouser, M.C.; Hess, L.M. (Eds.)

2010, VIII, 153 p., Hardcover

ISBN: 978-3-642-12129-6