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REVIEW

Clinical trials and progress with paclitaxel in ovarian cancer

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Abstract: Paclitaxel is a front-line agent for ovarian cancer chemotherapy, along with the platinum agents. Derived from the Pacific yew tree, *Taxus brevifolia*, paclitaxel has covered significant ground from the initial discovery of its antineoplastic properties to clinical applications in many forms of human cancers, including ovarian cancer. Although much has been published about the unique mechanism of action of this agent, several issues remain to be resolved. Finding the appropriate dosage schedule for paclitaxel in chemo-naïve and recurrent ovarian cancer, defining the role of paclitaxel in maintenance chemotherapy, and elucidating the mechanisms of taxane resistance are areas of intense research. Newer forms of taxanes are being manufactured to avoid troublesome adverse effects and to improve clinical efficacy. These issues are reviewed in detail in this paper with an emphasis on clinically relevant evidence-based information.

Keywords: paclitaxel, clinical trials, ovarian cancer, treatment

Epithelial ovarian cancer

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the US. An estimated 21,650 new cases and 15,520 deaths were attributed to ovarian cancer, representing 6% of all cancer deaths recorded in the US in 2008.[1] One woman in 70 will develop ovarian cancer, and one woman in 100 will die of the disease.[1,2] The incidence of ovarian cancer increases with age. There is a particularly steep rise in incidence starting from the fifth decade of life, peaking in the eighth decade.

Serous carcinoma is the most common histologic type of ovarian cancer in all racial and ethnic groups, followed by mucinous, endometrioid, and clear cell carcinoma.[2] Transitional, mixed, and undifferentiated histology are the uncommon types of ovarian cancer. Symptoms of the disease are nonspecific and there are no effective screening tests available for the general population. As a result, diagnosis often occurs when the disease is already at an advanced stage, and hence the prognosis is poor. Abdominal pain/discomfort, abdominal distension, or gastrointestinal symptoms (eg, nausea, vomiting, and dyspepsia) are the most frequent presenting complaints but, occasionally, urinary symptoms or vaginal bleeding predominates. Physical examination usually detects ascites and pelvic mass. Imaging in the form of ultrasound and computed tomography scans confirm the findings in the abdomen and pelvis.

Risk factors for ovarian cancer include family history of ovarian/breast cancer, nulliparity, early menarche, late menopause, white race, and higher socioeconomic status.[3] Protective factors include multiparity, use of the oral contraceptive pill, and tubal ligation.[3,4] Although ovarian cancer still carries an extremely high case fatality ratio, the five-year relative survival in the US has increased from 37% during 1975–1977

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to 45% during 1996–2002.[1] Age is associated with significant prognostic implications in ovarian cancer. The five-year survival rates by age groups are 78.8%, 58.8%, and 35.3% for very young (<30 years), young (30–60) and older (>60) individuals, respectively.[5]

Historic overview

The National Cancer Institute (NCI) initiated a screening program to identify the biologic antitumor activity of thousands of naturally occurring plants in the 1960s, during which time a crude extract from the bark of the Pacific yew, *Taxus brevifolia*, showed activity against many tumor types.[6] This is a slow-growing evergreen plant found in the old-growth forests of the Northwest Pacific. In 1971, investigators were able to isolate the active ingredient, paclitaxel, from the crude bark extract.[6] In 1979, Horwitz et al noted that the drug prevented cell division by promoting the assembly of microtubules without inhibiting their disassembly.[7] In the initial phases, development was slow because paclitaxel did not appear to be more effective than other agents under development, and the procurement of this potentially scarce natural product in adequate quantities was deemed to be labor- and cost-intensive. However, paclitaxel displayed impressive activity in human tumor xenografts in nude mice and, by the mid-1980s, the NCI had initiated the clinical Phase I trials.[8]

Structure

The chemical name of paclitaxel is 5β, 20-epoxy-1,2α,4, 7β,10β,13α-hexahydroxytax-11-en-9-one4, 10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. The chemical formula of paclitaxel is $C_{47}H_{51}O_{14}$, with a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at 217°C. The structure of paclitaxel is in the form of a complex ring system that is linked to a four-member oxetan ring at positions C4 and C5 and to an ester side chain at C13. Some studies suggested that this side chain is responsible for the unique effect of paclitaxel on microtubules.[9,10] In contrast, other studies showed that the side chain is not an absolute requirement for the biologic activity of paclitaxel, but lack of this may confer a structure that is not as active as paclitaxel.[10,11]

Mechanism of action

Microtubules play a key role in the initiation of DNA synthesis, mitosis, meiosis, motility, maintenance of cellular shape, and intracellular trafficking of macromolecules and organelles. Paclitaxel binds selectively and reversibly to the B subunit of tubulin, promoting tubulin polymerization and formation of stable microtubules even in the absence of the energy source, guanosine triphosphate. This effect leads to disruption of the equilibrium between the tubulin dimer-polymer in favor of polymer assembly.[12,13] Paclitaxel-induced microtubules have unusual stability and resist depolymerization by calcium, cold temperature, and dilution. Cells exposed to the drug exhibit an accumulation of arrays of disorganized microtubules which cause profound cell cycle arrest at the G2/M phase and eventually result in cell death through an apoptotic pathway.[12,13] Paclitaxel induces two distinct microtubular structures, ie, bundles and esters, which can be visualized by antitubulin antibody staining. Cells with esters produced by paclitaxel exposure are in mitosis and cells with paclitaxel-induced bundles are in the G0/G1, S, and G2 phases.[9] At high concentration, paclitaxel increases polymer mass and induces microtubule bundle formation, while at low concentration the principal effect is suppression of microtubule dynamics without altering the polymer mass.[14,15] At a molecular level, paclitaxel-induced apoptosis and drug resistance is thought to be mediated through alteration in function of p53, p21, Bcl-2, and Bcl-xL.[16,17] Specifically, apoptosis mediated by caspase 3 and caspase 8, hyperphosphorylation of Bcl-2, and increased expression of Bax have been shown to be partly responsible for paclitaxel-associated cytotoxicity.[18,19]

Pharmacokinetics

Paclitaxel is a large complex structure, insoluble in water, and >95% bound to protein. Therefore, paclitaxel uptake in the brain and testes is minimal, as demonstrated by radiolabeled drug studies.[20] The bioavailability of paclitaxel is poor after oral administration due to enterocyte expression of P-glycoprotein (Pgp) and first-pass metabolism in the liver. Parental administration is therefore required. Early studies with prolonged infusions of paclitaxel were suggestive of linear pharmacokinetics. However, later studies showed that paclitaxel followed nonlinear pharmacokinetics due to saturable distribution, metabolism, and elimination. This is especially evident with shorter durations of infusion and/or high dose levels.[21] At higher doses and administration rates, the plasma concentration of paclitaxel begins to exceed the metabolic capacity of the elimination pathways, thereby disproportionately increasing the area under the plasma-time curve.[22,23] The clinical implication of nonlinearity is that dose escalation may result in a disproportionate increase in toxicity, whereas dose reduction may result in a disproportionate

decrease in efficacy. The pharmaceutical vehicle used to dissolve paclitaxel, ie, Cremopher® EL, may affect the disposition of the drug and contribute to the reduction in plasma clearance observed at higher doses of paclitaxel.[22] Pharmacodynamic analyses have strongly indicated that there is a relationship between percentage decrease in white blood cell count or absolute neutrophil count and the time for which plasma paclitaxel concentration is above the threshold level of 0.1 μmol/L.[22,23]

Metabolism

The major pathway of elimination for paclitaxel is hepatic metabolism followed by biliary excretion. Renal clearance is minimal, with less than 15% of the drug excreted in urine. Paclitaxel is metabolized by CYP3A4 and CYP2C8; 6α-hydroxy-paclitaxel is the major metabolite of paclitaxel that is formed by hydroxylation of C6 in the taxane ring by CYP2C8. This metabolite is approximately 30-fold less active than the parent drug, as evident from the *in vitro* studies. Another minor metabolite of paclitaxel is 3'-para-hydroxypaclitaxel, which is produced by cytochrome P450 3A4. These more polar metabolites penetrate the cells poorly, hence they are either inactive or much less cytotoxic than the parent compound.[22,24,25]

Dosing strategy for paclitaxel

Paclitaxel has been used in doses ranging from 60–250 mg/m^2, over 1–96 hours and from 1–3 weekly intervals. However, no ideal dosing strategy for paclitaxel exists in ovarian cancer, even after almost two decades of its clinical use. Intense research efforts are underway to find the least toxic, least expensive, and most efficacious paclitaxel dosing strategy. Preclinical data suggested that prolonged exposure (96 hours) might have greater efficacy, but this was conclusively refuted by large prospective studies.[26,27]

Initial studies used arbitrarily selected 24-hour infusions to reduce the risk of hypersensitivity reactions, but the development of effective premedication regimens led to evaluation of a broad range of more convenient dosing schedules (Table 1).[28]

In a landmark Canadian-European trial designed to find the best clinically relevant dose of paclitaxel, 407 patients were randomized to receive 175 or 135 mg/m^2 of paclitaxel over either 24 or three hours in a 2 × 2 design. Major

Table 1 Major studies with dose variations of paclitaxel in ovarian cancer (MOS and PFS in months unless otherwise indicated)

Study	Agents/Schedule	Eligibility	n	Response (%)	MOS (month)	PFS (month)	Comments
Spriggs et al[27] 2007 GOG166	Paclitaxel 135 mg/m^2/24 h + Cisplatin 75 mg/m^2 vs Paclitaxel 120 mg/m^2/96 h + Cisplatin 75 mg/m^2	Suboptimal stage III or IV	280	62 70	2.5 yr 2.5 yr	1 yr 1 yr	Grade 4 neurotoxicity-79% vs 54% Grade 3 anemia – 6% vs 18% Concluded that longer infusions are not better.
Omura et al[31] 2003	Paclitaxel 135 or 175 mg/m^2/24 h vs Paclitaxel 250 mg/m^2/24 h	Relapsed ovarian cancer	330	27 36	12.3 13.1	4.8 5.5	Thrombocytopenia, neuropathy, and myalgia-greater with 250 mg/m^2 dose, which exhibited a better response rate. But no survival benefit to justify paclitaxel 250 mg/m^2 + filgrastim.
Bolis et al[30] 2004	Paclitaxel 175 mg/m^2 + Carboplatin AUC 6 vs Paclitaxel 225 mg/m^2 + Carboplatin AUC 6	IIB-IV	207 219	64 56	4-year survival 46% 47%	4 year PFS 42% 39%	Concluded that 175 mg/m^2 preferred regimen.
Katsumata et al[32] 2009	Paclitaxel 80 mg/m^2/1h/wk × 6 cycles + Carboplatin-AUC 6/3 wks vs Paclitaxel 180 mg/m^2/3 h/3 wk × 6 cycles + Carboplatin AUC 6/3 wks	II-IV	631	56 53	3-year survival 72% 65%	28 17	Neutropenia 92% vs 88%. Grade 3/4 anemia 69% vs 44%. Withdrawal because of toxicity – higher in dose-dense regimen than in the conventional regimen (n =113 vs n =69)

Abbreviations: AUC, area under curve; n, number; MOS, median overall survival; PFS, progression-free survival.

endpoints were the frequency of significant hypersensitivity reactions and objective response rate. This trial showed equivalent efficacy of the three-hour versus 24-hour infusion schedules for paclitaxel in recurrent ovarian cancer, with reduced bone marrow toxicity and an increased incidence of neuropathy with the shorter infusions. Subsequently, the three-hour infusion schedule became the new standard due to its convenience and lesser cost compared with the other schedules.[29] Furthermore, no clinically relevant advantage has been found with paclitaxel at a dose of 135 mg/m^2 as compared with 225–250 mg/m^2 in the setting of either upfront chemotherapy[30] or relapsed disease.[31] These observations paved the way for the concepts of weekly low-dose one-hour infusion and dose-dense paclitaxel.[32] These strategies are believed to reduce the risk of serious toxicity and alopecia markedly, with maintenance of clinical efficacy.[33]

Katsumata et al recently reported a Phase III study of dose-dense paclitaxel in front-line ovarian cancer comparing standard chemotherapy including paclitaxel 180 mg/m^2 over three hours every three weeks with a dose-dense regimen which included paclitaxel 80 mg/m^2 over one hour every week in a three-week cycle. There was prolongation of progression-free survival (PFS), as well as median survival, in the dose-dense arm at the cost of a significant increase in toxicity (Table 1).[32] This study suggests that dose-dense paclitaxel may be of clinical benefit, but that toxicities must be mitigated before it can be adopted widely.[34] Others have reported different doses on a weekly schedule as well.[35–37] Suffice it to say that a weekly dosing strategy for paclitaxel in ovarian cancer remains under investigation.

Drug interactions

Because paclitaxel has saturable distribution and elimination at the currently used dosage, small changes in its pharmacokinetics could potentially cause serious effects, especially if the toxic effect is enhanced or, conversely, if the cytotoxic antitumor effect is diminished by drug interaction.

Interaction with other cytotoxic drugs

Cisplatin

The sequence of cisplatin 75 mg/m^2 followed by paclitaxel infusion at 135 mg/m^2 over 24 hours is associated with more profound neutropenia and less *in vitro* antitumor activity.[38] The hepatic clearance of paclitaxel may be decreased by 33% when it is preceded by cisplatin.[38] The precise mechanism is unclear, but this could be caused by cisplatin-induced modulation of cytochrome P450 metabolism or damage to the kinestin heavy chain gene which plays a role in the cytotoxicity of many natural-based antitumor drugs.[39] Sequence dependence is unlikely to be clinically relevant with shorter paclitaxel infusion schedules. Moreover carboplatin, the more commonly used platinum agent, does not appear to modulate cytochrome P450 systems or the pharmacokinetics of paclitaxel.[40–42]

Doxorubicin

Paclitaxel exhibits a sequence- and schedule-dependent interaction with doxorubicin.[43] It increases the area under the curve (AUC) of doxorubicin by 30% when given before or immediately after doxorubicin and consequently increases the incidence of doxorubicin-induced cardiotoxicity and myelosuppression, however, neither sequence of drug infusion significantly influenced the AUC of paclitaxel.[43,44] Based on these observations, it was recommended to restrict the cumulative dose of doxorubicin to 360 mg/m^2, to administer doxorubicin 24 hours before paclitaxel,[43] and to use dexrazoxane with the combination as well.[44]

Etoposide

Paclitaxel and etoposide exhibit schedule-dependent interaction and optimal synergism with sequential 24-hour use, without the impact of an intervening drug-free period. In contrast, less than additive inhibitory cytotoxicity is observed with concurrent administration of these agents in *in vitro* experiments.[45] Other studies have reported independent antagonism with these two agents.[46] However, the clinical relevance of these observations remains to be elucidated.

Topotecan

The sequential combination of paclitaxel and topotecan resulted in severe dose-limiting myelosuppression, although there is no established pharmacodynamic or pharmacokinetic interaction between the two agents to explain this observation.[43]

Trastuzumab

In breast cancer patients, the incidence of congestive heart failure has been higher with the trastuzumab-paclitaxel combination than with paclitaxel alone. Data are preliminary and the reason for this association is unknown.[47]

Interaction with noncytotoxic drugs

The maximum tolerated dose of paclitaxel in cancer patients receiving anticonvulsant therapy, such as phenytoin and phenobarbital, is higher compared with those on no anticonvulsant therapy (200 mg/m^2 versus 140 mg/m^2).[48] This may be due to enhanced hepatic clearance which could result in reduction of the cytotoxic and antitumor effects of paclitaxel.[48] Explanation involves induction of cytochrome P450 mixed-function oxidases by the anticonvulsants.[49]

Paclitaxel in early ovarian cancer

The treatment strategy for early-stage ovarian cancer has evolved differently compared with that of late-stage disease, which is reflective of the higher relative prevalence and mortality of the latter compared with the former. Currently, the suggested treatment for early-stage ovarian cancer (FIGO I and II) in the US is optimal surgical staging followed by either chemotherapy or expectant management, depending on the stage and grade of the disease.[50] Patients with Stage IA or IB disease with Grade I and II tumor have a greater than 90% cure rate, and require no further postoperative treatment, while patients with a Stage I Grade 3 lesion or Stage II disease have a recurrence rate of approximately 25%–40% and will need additional postoperative chemotherapy.[50] The duration of chemotherapy has been addressed by GOG protocol 157, where the investigators enrolled 427 stage I and II high-risk patients and compared three versus six cycles of paclitaxel at 175 mg/m^2 for three hours plus carboplatin-AUC 7.5.[51] Both arms in the study had similar death rates, and the estimated probability of recurrence within five years was 20.1% (six cycles) versus 25.4% (three cycles), respectively. The respective Grade 3 or 4 neurotoxicity was 11% versus 2%. Six cycles also caused significantly more severe anemia and granulocytopenia. In other words, this study showed a minimal reduction in risk of recurrence, with a significant increase in toxicity due to the six cycles, and thus it is advocated for only three cycles of combination therapy in this setting. Several limitations of the study have been highlighted, and some continue to argue for the use of more chemotherapy in early-stage ovarian cancer, especially if the initial three cycles are tolerated without significant toxicity in patients with high-risk features.[52] Also, a subsequent idea originating from this study was the GOG 175 protocol where the same patient population with high-risk, early-stage ovarian cancer is being randomized to either three cycles of carboplatin-(AUC 6) with paclitaxel 175 mg/m^2 or three cycles of the same regimen followed by weekly paclitaxel 40 mg/m^2 for 24 weeks. Results of this study are pending.

Paclitaxel in advanced ovarian cancer

Encouraged by successful completion of several Phase I trials safely administering paclitaxel and the subsequent response in other tumor types, several groups started using paclitaxel for ovarian cancer in Phase II trials.[53–55] In the initial studies, an extremely high rate of hypersensitivity reactions of up to 30% was noted. To ameliorate this, longer infusion (24–96 hours)[53,56] and pretreatment with antihistamine agents and steroids became necessary. These strategies, when used in combination, reduced the risk of severe hypersensitivity reactions to 5% or less, but marked the emergence of dose-limiting neutropenia. It is noteworthy that some of the initial trials of paclitaxel included both platinum-sensitive as well as platinum-refractory patients, with response rates ranging from 20% to 37%.[57,58]

Due to the excellent response rates seen in these studies, the next logical step was to combine paclitaxel with platinum compounds, which are arguably the agents with the best activity in ovarian cancer. Validating this notion was a Phase I study[38] showing that paclitaxel and cisplatin could be given safely in combination, with paclitaxel administered first as a 24-hour infusion.

Subsequently, four major trials have been reported which compared platinum-paclitaxel doublets with other agents (Table 2). The first two of these (GOG 111[59] and OV-10[60]) helped to establish platinum-paclitaxel as front-line therapy in ovarian cancer, whereas the subsequent two trials (GOG 132[61] and ICON3[62]) have questioned whether the addition of paclitaxel to platinum provides any additional benefit.

In GOG 111, a cyclophosphamide-cisplatin doublet was compared with paclitaxel-cisplatin in patients with stages III and IV ovarian cancer. The authors reported a response rate of 60% versus 73%, a PFS of 13 versus 18 months, and median survival of 24 versus 38 months, respectively, favoring the paclitaxel-cisplatin doublet compared with the cyclophosphamide-cisplatin doublet. On the other hand, OV-10 showed an overall survival of 26 versus 36 months and a PFS of 12 versus 16 months ($P < 0.05$), both favoring the paclitaxel-cisplatin doublet (Table 2).

In GOG 132, 648 suboptimally debulked stage III and IV epithelial ovarian cancer patients were randomized to receive cisplatin or paclitaxel or the combination of paclitaxel-cisplatin. This trial concluded that cisplatin alone or in combination yielded superior response rates and a PFS relative to paclitaxel. However, the OS (overall survival) was similar in all three arms, and the combination therapy had a better toxicity profile. Therefore, the authors argued

Table 2 Phase III trials of paclitaxel and platinum compounds in front-line chemotherapy for advanced ovarian cancer

Study	Agents/Schedule	Eligibility (Stage)	n	Response (%)	MOS (months)	PFS (months)	Comments
McGuire et al[59] 1996 GOG-111	Paclitaxel 135 mg/m^2/24 h + Cisplatin 75 mg/m^2; six cycles vs Cyclophosphamide 750 mg/m^2 + Cisplatin 75 mg/m^2; six cycles	Suboptimal III, IV	386	73 vs 60	38 24	18 13	
Piccart et al[60] 2000 OV-10	Paclitaxel 135 mg/m^2/3 h + Cisplatin 75 mg/m^2 vs Cyclophosphamide 750 mg/m^2 + Cisplatin 75 mg/m^2	Optimal or suboptimal IIB–IV	680	59 vs 45	36 26	16 12	Neurotoxicity 19% vs 1%
Muggia et al[61] 2000 GOG132	Paclitaxel 135 mg/m^2/24 h + Cisplatin 75 mg/m^2 vs paclitaxel 200 mg/m^2/24 h vs cisplatin 100 mg/m^2	Suboptimal III, Any IV	614	67 vs 42 vs 67	26 26 30	14 11 16	
ICON3[62] 2002	Paclitaxel 175 mg/m^2/3 h + Carboplatin AUC 6 Vs CAP or Carboplatin	I–IV	2075	NA	36 35	17 16	

Abbreviations: AUC, area under curve; n, number; CAP, cyclophosphamide-doxorubicin-cisplatin combination; MOS, median overall survival (in months unless otherwise indicated); PFS, progression free survival (in months unless otherwise indicated).

that the cisplatin-paclitaxel combination should remain the preferred initial treatment option. Perhaps the best rationale for lack of observed superior response with the platinum-paclitaxel doublet was the inclusion of a suboptimal control arm due to more than half of the patients in the single-agent arms crossing over to the other agents subsequently on a nonprotocol basis.[61]

The results of ICON3 were reported in 2002 in which paclitaxel-carboplatin versus carboplatin or cyclophosphamide-doxorubicin-cisplatin (CAP) were compared. No difference was found in OS between the paclitaxel-carboplatin and control groups. The trial concluded that single-agent carboplatin and CAP are as effective as the paclitaxel-carboplatin doublet. Also, the favorable toxicity profile of single-agent carboplatin suggested that this drug may be a reasonable option as first-line chemotherapy for ovarian cancer.[62] This trial called into question the additional benefit offered by paclitaxel over the platinum compounds, but was not successful in changing the practice on a large scale in patients due to several limitations which are analyzed by Sandercock et al in detail.[63]

Several theoretical arguments support the concurrent use of paclitaxel with platinum in ovarian cancer. Firstly, addition of a second agent may be useful in reducing the possibility of development of resistant clones. Secondly, a greater cell kill might be achieved at the start of the treatment, which may mean a higher proportion of patients becoming tumor-free at induction chemotherapy. Thirdly, the dual agent approach may help to lower the doses, and hence the toxicity of each of the single agents involved, and still preserve acceptable efficacy. Support for these notions comes from a meta-analysis in which the platinum-paclitaxel doublet still had an edge over the other agents.[63] Consequently, platinum and paclitaxel remain the preferred front-line chemotherapy for ovarian cancer in the US.

Due to the significant side effects of cisplatin, including nausea/vomiting, neurotoxicity, and nephrotoxicity, several trials have looked at substituting cisplatin with carboplatin, a better tolerated platinum compound. A study by Neijt et al[64] compared paclitaxel at 175 mg/m^2 for three hours with cisplatin or carboplatin, and a study by du Bois et al[65] compared paclitaxel at 185 mg/m^2 with either cisplatin or carboplatin as front-line chemotherapy in ovarian cancer. Both these studies showed similar response rates, PFS, and OS in the cisplatin and carboplatin arms. Similar findings were reported by Ozols et al in a GOG study.[66] As expected, more gastrointestinal and neurologic toxicity was found in patients receiving cisplatin and more myelosuppression in patients randomized to carboplatin, but overall, the latter resulted in lesser toxicity, more convenient dosing, and no inferiority when compared with the former agent. Hence, intravenous (IV) carboplatin has replaced IV cisplatin in clinical practice around the world.

Paclitaxel in recurrent ovarian cancer

Approximately two-thirds of patients will respond to front-line chemotherapy in ovarian cancer, but the majority of these women will have disease recurrence. Cure is rare and, therefore, the goals of treatment in recurrent ovarian cancer

Table 3 Major trials employing a third agent with the paclitaxel-carboplatin doublet

Study	Schedule/Agents	n	PFS/MOS	Comments
du Bois et al[102]	**TEC arm** Paclitaxel 175 mg/m^2+ carboplatin AUC-5 + epirubicin 60 mg/m^2 Every 3 wks x 6 cycles vs Paclitaxel 175 mg/m^2 + carboplatin AUC-5 Every 3 wks × 6 cycles	1282	18/46 18/41	Grade 3–4 hematological toxicities and grade 3–4 febrile neutropenia-more frequent in the first group. Nausea, vomiting, stomatitis/mucositis and infections-significantly less frequent in the second group. Inferior quality of life in TEC arm
Scarfone et al[103]	Paclitaxel 175 mg/m^2 D1 Carboplatin AUC-5 D1 Topotecan 1 mg/m^2 D1–3 Every 3 weeks for 6 cycles vs Paclitaxel 175 mg/m^2 D1 Carboplatin AUC-5 D1 Every 3 weeks for 6 cycles	326	Median PFS 72 vs 70 weeks	Grade ¾ neutropenia 40% vs 24%. Alopecia 72% vs 78.2% and nausea/vomiting 51% vs 44%
GOG182-ICON5[104] Phase III	**ARM 1** Control Paclitaxel 175 mg/m^2 D1 Carboplatin AUC 6 D1 Every 3 wks for 8 cycles **ARM 2** Gemcitabine triplet Paclitaxel 175 mg/m^2 D1 Carboplatin AUC 5 D1 Gemcitabine 800 mg/m^2 D1,8 Every 3 wks for 8 cycles. **ARM 3** Doxil triplet Paclitaxel 175 mg/m^2 D1 Carboplatin AUC 5 D1 Doxil 30 mg/m^2 (cycle 1, 3, 5, 7) Every 3 wks for 8 cycles. **ARM 4** Topotecan doublet Carboplatin AUC 5 D3 (Cycle 1–4) Topotecan 1.25 mg/m^2/day D1–3 (cycle 1–4) Paclitaxel 175 mg/m^2 in 3 h D1(cycle 5–8) Carboplatin AUC 6 D1(cycle 5–8) **ARM 5** Gemcitabine doublet Carboplatin AUC 6 D8 (cycle 1–4) Gemcitabine 1000 mg/m^2/day D1–8 (cycle 1–4) Paclitaxel 175 mg/m^2 in 3 h D1(cycle 5–8) Carboplatin AUC 6 D1(cycle 5–8)	4412	No significant difference in the PFS and OS	Increased hematologic toxicity with triplet regimens. Increased thrombocytopenia with gemcitabine. Neuropathy decreased in doublet group which included only four cycles of Paclitaxel.
Penson et al[105] Phase II	Paclitaxel 175 mg/m^2 in 3 h-cycle 1–6 Carboplatin AUC 6 cycle 1–6 Bevacizumab 15 mg/kg in cycle 2–6 then continued for 1 year	62	PFS at 36 months 58%. Radiographic response rate 75%	2 cases of pulmonary embolism and 2 of GI perforations.
Micha et al[106] Phase II	Paclitaxel 175 mg/m^2 in 3 h-cycle 1–6 Carboplatin AUC 6 cycle 1–6 Bevacizumab 15 mg/kg cycle 2–6	20	80% Overall response	Grade 3 and 4 neutropenia 23% and 25% cycles. No GI perforation, 2 cases of grade 3 hypertension and 2 cases of DVT

Abbreviations: AUC, area under curve; DVT, deep vein thrombosis; MOS, median overall survival (in months unless otherwise indicated); n, number; PFS, progression-free survival (in months unless otherwise indicated); TEC, paclitaxel-etoposide-cyclophosphamide combination; GI, gastrointestinal.

are maintaining an acceptable quality of life, control of symptoms, and prolonging survival, if possible.[67]

It has been established that a longer time interval to relapse after the initial platinum-based therapy (the platinum-free interval) was associated with a higher response rate to retreatment with platinum as well as other drugs.[68,69] Accordingly, patients who relapsed within six months of completing initial platinum-based therapy were classified as platinum-resistant whereas those who relapsed after six months were considered to be platinum-sensitive.

In addition to platinum and taxanes, several agents have shown activity in relapsed ovarian cancer, including bevacizumab,[70] altretamine (hexamethylmelamine),[71] liposomal doxorubicin,[72,73] topotecan,[74,75] gemcitabine,[76–78] oral etoposide,[79,80] ifosfamide,[81] navelbine, capecitabine, tamoxifen, and pemetrexed. Research in this area continues to grow

as more anticancer agents are discovered. Whereas the best response rates in platinum-resistant patients have been in the 10%–20% range, response rates for platinum-sensitive disease have generally been much higher.

Paclitaxel in platinum-sensitive recurrence

Studies in platinum-sensitive patients can be classified into one of three groups, ie, non-platinum single-agent treatment, non-platinum combinations, and platinum-containing combinations (see Table 4A). In 1997 ten Bokkel Huinink et al published a trial[82] comparing topotecan with paclitaxel and did not find significant differences between the two groups for response rates or survival.[83] However, paclitaxel was much less toxic to bone marrow than topotecan. The European Organisation for Research and Treatment of Cancer (EORTC) randomized 86 women to either single-agent paclitaxel or oxaliplatin. Response in the 63 platinum-resistant group was 16% versus 6% in the paclitaxel versus oxaliplatin arms, respectively, and for the platinum-sensitive group was 20% versus 38%, respectively.[84]

In one Phase II study of a platinum-free interval (PFI) >12 months, paclitaxel 175 mg/m^2 IV over three hours was compared with the CAP regimen. Although the overall response rates were similar, CAP was associated with significant increases in response duration (16 versus 9 months) and median survival (35 versus 26 months). The authors concluded that single-agent paclitaxel may not be as active as platinum-based chemotherapy in recurrent ovarian cancer.[85]

A body of evidence supports the use of a platinum-paclitaxel doublet in women with platinum-sensitive relapse. Although the best response is seen in patients with a PFI of >24 months, response rates as high as 60% and a complete response rate of up to 25% may be achieved. A retrospective study of patients treated with paclitaxel-carboplatin reported a response rate of 84%. The PFS and OS were 9.7 and 13.1 months, respectively.[86] In a Phase II study, the Spanish Ovarian Cancer Research Group (GEICO) compared carboplatin with the paclitaxel-carboplatin doublet. With no significant difference in Grade 3–4 hematologic toxicity, the response rate favored

Table 4A Paclitaxel in platinum-sensitive recurrent ovarian cancer

Study	Agent/Schedule	n	Response (%)	Comments
ten Bokkel Huinink et al[82,83]	Topotecan (1.5 mg/m^2) as a 30-minute infusion daily for 5 days q21 days vs paclitaxel (175 mg/m^2)/3 h q21 days	226	20.5 vs 13.2 ($P = 0.138$)	Neutropenia was significantly more frequent on the topotecan arm 79% vs paclitaxel arm 23% ($P < 0.01$). Median survival 63 vs 53 weeks
Piccart et al[84]	Paclitaxel at 175 mg/m^2/3 h q3 weeks, vs oxaliplatin at 130 mg/m^2/2 h q3 weeks	86	20 vs 38 for sensitive disease 16 vs 6 for resistant disease	Neutropenia 22% vs none Neurotoxicity 7% vs 9%
Cantu et al[85]	Paclitaxel 175 mg/m^2 IV/3 h q3 weeks vs cyclophosphamide, Doxorubicin, and cisplatin (CAP)	97	45 vs 55	Leukopenia 4% vs 34%, neutropenia 13% vs 36% MOS 25.8 vs 34.7 months ($P < 0.043$)
Buda et al[89]	Epidoxorubicin + paclitaxel 175/3 h, q21 days for 4–6 cycles vs paclitaxel 175 mg/m^2/3 h, q21 days for 4–6 cycles	212	37 vs 47	Neutropenia: 37% vs 18%
Pujade-Lauraine et al 2009 ASCO CALYPSO study	Carboplatin with PLD vs carboplatin with paclitaxel	976	NA	PFS 11 vs 9 months, $P < 0.05$ PLD arm had fewer infusion reactions, less alopecia and less chronic neurotoxicity
Gronlund et al[86]	Paclitaxel (175 mg/m^2)/3 h followed by carboplatin AUC 5, q3 weeks	241	84	Retrospective MOS 13.1; PFS 9.7
Gonzalez-Martin et al[87]	Carboplatin AUC 5 vs paclitaxel 175 mg/m^2 + carboplatin AUC 5	81	50 vs 76	No differences in hematological toxicity. Mucositis, myalgia/arthralgia and peripheral neuropathy were more frequent in combination therapy.
Parmar et al[88]	Paclitaxel 175–185 mg/m^2 + cisplatin 50 mg/m^2/carboplatin AUC 5–6 vs cisplatin 75 mg/m^2/carboplatin AUC 5–6	802	78 vs 69 $P = 0.06$	MOS 29 vs 24

Abbreviations: AUC, area under curve; CAP, cyclophosphamide-doxorubicin-cisplatin combination; IV, intravenous; MOS, median overall survival (in months unless otherwise indicated); n, number; NA, not applicable; PFS, progression free survival (in months unless otherwise indicated); PLD, pegylated liposomal doxorubicin.

the platinum-paclitaxel doublet (75.6% and 50%).[87] The best evidence yet in favor of using a platinum-paclitaxel doublet for platinum-sensitive relapse comes from the ICON4 trial where 802 patients with platinum-sensitive relapse were randomized to paclitaxel-platinum or single-agent platinum. The trial showed a two-year survival rate of 57% versus 50%, favoring the combination (hazard ratio 0.82; 95% confidence interval [CI] 0.69–0.97, $P = 0.02$). There was a higher incidence of Grade 2–4 neurologic effects (20% versus 1%), alopecia (86% versus 25%), and a lower rate of myelosuppression in the paclitaxel-treated patients.[88]

An Italian trial compared an epidoxorubicin-paclitaxel doublet with paclitaxel alone and favored the latter based on a better response rate.[89] More recently, the CALYPSO study compared carboplatin plus either pegylated liposomal doxorubicin (PLD) or paclitaxel in 976 women with relapsed platinum-sensitive disease. In preliminary findings presented at the 2009 ASCO meeting,[90] PLD-carboplatin was not inferior to paclitaxel-carboplatin, was associated with a significant prolongation in PFS (11.3 versus 9.4 months), and was less toxic. The investigators concluded that PLD-carboplatin could be considered a valid alternative to carboplatin-paclitaxel for treatment of platinum-sensitive disease.

Paclitaxel in platinum-resistant disease

Single-agent taxanes have produced response rates in the 20% range for platinum-resistant disease in Phase II and III studies[57,58,91,92] (see Table 4B). There is no agreement on the optimal schedule and dose of paclitaxel in recurrent ovarian cancer. In one trial, doses of 135 to 175 mg/m^2 every three weeks, either as a three-hour or 24-hour infusion, showed similar response rates. Three-hour infusions were associated with more neurotoxicity but less myelosuppression.[29] Others have used higher doses of paclitaxel in the Phase III setting (250 versus 175 mg/m^2 per dose) with hematopoietic growth factor support and reported higher response rates, and significantly more thrombocytopenia, neuropathy, and myalgia, but no improvement in survival with the higher dosage ($P < 0.05$).[31] Thigpen et al used longer infusions of paclitaxel at 170 mg/m^2 IV once over 24 hours every three weeks, and reported Grade 4 neutropenia in 73%.[57] Weekly paclitaxel may maintain antitumor efficacy while minimizing toxicity, especially myelosuppression. This concept has been tested by several studies in the setting of relapsed ovarian cancer. Markman et al reported two Phase II studies of weekly paclitaxel with response rates of 20%–25%.[93,94] In the first study, five of 53 patients discontinued therapy because of toxicity (four due to peripheral

Table 4B Paclitaxel in platinum-resistant recurrent ovarian cancer

Study	Agent/Schedule	n	Response (%)	Comments
McGuire et al[91]	Paclitaxel 110 to 250 mg/m^2/24 h q22 days	40 total 25 resistant	24	Myelosupression dose limiting toxicity; 2 fatal cases of sepsis.
Thigpen et al[57]	Paclitaxel 170 mg/m^2/IV/24 h/q3 weeks	43 total 27 resistant	33	Neutropenia 73%
Trimble et al[143]	Paclitaxel 135 mg/m^2/IV/24 h/q3 weeks	652	22	Leucopenia 78% fever 33%, infection 12%.
Markman et al[93]	Weekly paclitaxel 80 mg/m^2	53	25	5 patients dropped due to toxicity, 4 due to peripheral neuropathy, and 1 because of painful fingernail beds
Markman et al[94]	Weekly paclitaxel 80 mg/m^2	48	21	Grade 3 neuropathy: 4%; grade 3 fatigue: 8%
Kita et al[95]	Paclitaxel 80 mg/m^2/week in 1-h infusion, 3 weeks on, 1 week off, and repeated at least twice	37 total 14 resistant	29	Neutropenia 24%
Kaern et al[96]	Weekly paclitaxel 80 mg/m^2/h infusion	57	56	Grade 2 neutropenia 2 patients
Rosenberg et al[97]	Weekly paclitaxel 67 mg/m^2 vs 3 weekly Paclitaxel 200 mg/m^2	208	Similar efficacy in two arms	Grade 3–4 hematological and non-hematological toxicity occurred more frequently in 3-weekly arm
Havrilesky et al[98]	Carboplatin AUC 2 and paclitaxel at 80 mg/m^2 on days 1, 8, and 15 on a 28-day cycle	28 Total 8 Resistant	38	Neutropenia 32%

Abbreviations: AUC, area under curve; IV, intravenous.

neuropathy and one due to painful fingernail beds).[93] In the second study, serious adverse events were relatively uncommon.[94] Similarly, Kita et al used weekly paclitaxel by hourly infusion, with a 29% response in the platinum-resistant setting. They reported Grade 3 or 4 neutropenia in 24% of their patients but there were no hospital admissions for neutropenic fever.[95] In another study, 57 patients were treated with weekly paclitaxel with a response rate of 56%, a median PFS of five months, and median OS of 13.7 months. Only two patients had Grade 2 neutropenia, and no neutropenic fever was recorded.[96] Rosenberg et al compared three-weekly paclitaxel with one-third of the total dose used per week, the goal being to have similar total doses of paclitaxel in both arms of the trial. There was no difference in efficacy between the two arms, but less toxicity (other than fingernail toxicity) was observed in the weekly arm.[97] In an innovative study of combination chemotherapy, Havrilesky et al used a reduced dose of carboplatin-paclitaxel on a weekly basis. In this study, eight platinum-refractory patients had a response rate of 37.5%, while 21 platinum-sensitive patients had a 100% response rate. Major toxicity in the form of Grade 3 neutropenia was seen in 32% of patients.[98]

Paclitaxel maintenance therapy

A randomized trial of 12 versus three months of maintenance paclitaxel at 175 mg/m^2 over three hours every 28 days in 277 women after a complete response to initial therapy improved PFS (28 versus 21 months), but no difference in OS was observed either in the initial report or subsequent updates of the data. This study was stopped early by the Data Monitoring Committee when approximately half the proposed accrual had occurred due to the observed benefit in PFS, which was the proposed endpoint of the study. It was speculated that the lack of difference in the OS was due to underpowering of the study due to its early closure. In addition, treatment at relapse might have equalized the outcome. It is also noteworthy that the initial dose of paclitaxel was reduced in the trial from 175 to 135 mg/m^2. The overall Grade 2/3 neuropathy rate in the trial was 14% and 18% in the control and treatment groups, respectively.[99,100] In contrast, an Italian study reported by Pecorelli et al in 2009 randomized 200 women after initial complete response to either observation (ie, control) or six courses of paclitaxel 175 mg/m^2 every three weeks and found no difference in PFS or OS.[101]

The GOG 212 trial is in progress comparing 12 cycles of paclitaxel versus 12 cycles of paclitaxel poliglumex versus observation until documented relapse, after a complete response to front-line therapy is achieved. This trial will hopefully resolve the controversy relating to the benefit of maintenance therapy.

Addition of a third agent to carboplatin-paclitaxel

Recently, several groups have tried to add a third agent to the paclitaxel-carboplatin doublet to exploit any potential clinical benefit. Du Bois et al added epirubicin and reported no benefit,[102] whereas Scarfone et al added topotecan without any clinical benefit.[103] In a landmark study of collaborative management of clinical trials, the GOG 182/ICON5 reported no evidence of clinical benefit from addition of topotecan, gemcitabine, or liposomal doxorubicin in the front-line treatment setting.[104] However, encouraging results have been reported with addition of bevacizumab, the humanized monoclonal antibody against vascular endothelial growth factor. Two small Phase II trials reported good results and manageable toxicities.[105,106] The "litmus test" of bevacizumab addition will be provided by GOG 218 and ICON7. GOG 218 is a randomized, double-blind, placebo-controlled, multicenter study, which is evaluating the paclitaxel-carboplatin doublet ± bevacizumab, either for six courses or for 22 courses (http://clinicaltrials.gov/ct/show/NCT00262847). ICON7 is testing a similar hypothesis, but the dose and duration of bevacizumab are different. This study finished recruiting 1528 patients in February 2009 and the results are pending.

Paclitaxel in intraperitoneal chemotherapy

Intraperitoneal (IP) spread presents one of the main routes of metastasis in epithelial ovarian cancer. Hence, the delivery of IP chemotherapy has always held theoretical promise, which investigators have tried to explore in at least three major randomized trials, two of which included paclitaxel.

Alberts et al[107] reported a trial of IV cisplatin-cyclophosphamide compared with IP cisplatin-cyclophosphamide, with a survival benefit in the IP arm of the study (41 versus 49 months). The main limitation of this study is that it preceded the paclitaxel era, and thus did not reflect contemporary therapy. Interestingly, the subset of patients with the lowest volume of disease did not demonstrate benefit from the IP approach.

In 2001, Markman et al[108] reported a second major trial of 462 patients randomized to receive either IV paclitaxel 135 mg/m^2 over 24 hours followed by IV cisplatin 75 mg/m^2 every three weeks for six courses or IV carboplatin-AUC 9

every 28 days for two courses, then IV paclitaxel 135 mg/m^2 over 24 hours followed by IP cisplatin 100 mg/m^2 every three weeks for six courses. This study reported a survival advantage in the IP arm (52.5 versus 63.2 months). This study has been criticized on the basis that more chemotherapy, rather than the IP route, may have resulted in the benefit because the patients in the IP arm received IV carboplatin-AUC 9 for two cycles before the IP therapy, representing a significant difference from the regimen used in the standard arm.

In January 2006, Armstrong et al published the results of GOG 172[109] in which patients with optimally debulked Stage III ovarian carcinoma were randomly assigned to receive 135 mg/m^2/24 hours of IV paclitaxel followed by either 75 mg/m^2 of IV cisplatin or 100 mg/m^2 of IP cisplatin on day 2 and 60 mg/m^2 of IP paclitaxel on day 8 (IP group). Treatment was given every three weeks for six cycles. Although only 42% of the patients in the IP arm completed six cycles of the assigned therapy. The median PFS was 18.3 versus 23.8 months, and the median OS was 49.7 versus 65.6 months, favoring the IP arm. Note that in this trial, the experimental arm used 24-hour IV paclitaxel followed by IP cisplatin on day 2 and IP paclitaxel on day 8. The added day 8 paclitaxel regimen introduces another set of variables in addition to the mode of delivery of the therapy. Some argue that the results seen with GOG 172 are not significantly better than what can be achieved with the IV carboplatin and three-hour paclitaxel regimens.[110–112] It is noteworthy that neutropenia, gastrointestinal toxicity, fatigue, pain, and metabolic events were increased in the IP arm. In addition, quality of life was significantly worse in the IP arm while on therapy but improved at the one-year follow-up. In addition, IP chemotherapy catheters caused abdominal pain, nausea, vomiting, infection, and fever.

On the basis of findings of increased survival with IP therapy in these three studies, the NCI issued a clinical advisory notice that recommended IP therapy be considered for women with ovarian cancer. Apart from the fact that IP therapy is more toxic, no IP regimen has so far been compared with what many consider to be the current standard, ie, IV carboplatin and paclitaxel.[112,113]

Resistance to paclitaxel

Several mechanisms have been described to explain resistance to paclitaxel. The foremost are increased expression of the efflux transporter Pgp, multidrug resistance-associated protein 2, and decreased expression of the influx transporter, ie, the organic anion transporting polypeptide 1 B3 (OATP1B3/SLCO1B3).[24] Other possible mechanisms include overexpression of the paclitaxel-metabolizing enzyme CYP2C8,[30] hypo-stable microtubules, mutations in tubulin that alter binding of paclitaxel, and alteration in the signaling pathways associated with microtubule function.[21,24] Kavallaris et al demonstrated that resistance of epithelial ovarian cancer cell lines to paclitaxel is correlated with increased levels of Class I, III, and IVa B-tubulin isotypes.[114] HER2/neu(c-erbB2) overexpression has also been implicated in paclitaxel resistance.[115,116]

MDR phenotype, which can be mediated by several multidrug transporters, particularly the 170-kDa Pgp efflux pump encoded by the *mdr1* gene, structurally altered α- and β-tubulins, and an impaired ability to polymerize tubulin dimers into microtubules. For example, high levels of the βIII isotype, a minor component of cellular β-tubulin that increases the dynamic instability of microtubules, impairs rates of microtubule assembly, and increases resistance to taxanes.[117–119]

Toxicity

Hematologic

The major adverse effect of paclitaxel is myelosuppression, which mainly consists of neutropenia, whereas thrombocytopenia and anemia are uncommon.[120] Neutropenia is more profound with higher doses, prolonged infusion, or if prior myelosuppressive therapy was used (eg, paclitaxel given after cisplatin). In the European-Canadian trial, the incidence of myelosuppression was 71% and 18% with 24-hour and 3-hour infusion, respectively, while febrile neutropenia was documented only in patients who received the 24-hour infusion.[29] The neutropenia begins a week after paclitaxel infusion, nadirs in the second week, with complete recovery by the third week. Neutropenia does not reach lower levels with subsequent cycles, suggesting that toxicity is noncumulative. Paclitaxel has a platelet-sparing effect on thrombocytopenia produced by carboplatin.[121] It is believed that clinically relevant doses of paclitaxel can be given without bone marrow supporting agents.[122]

Hypersensitivity reactions

Historically, the incidence of major hypersensitivity reactions to paclitaxel approached 30%, but the incidence is down to 1% to 3% following widespread prophylactic use of steroids and antihistamine pretreatment. The vast majority of these events are minor (dyspnea, bronchospasm, urticaria, hypotension, rash, and itching). They typically occur within

the first 10 minutes after the first or second cycle, respond well to supportive measures, and do not require cessation of therapy. Major reactions on the other hand are generally severe, eg, anaphylaxis, angioedema, or shock, and require cessation of therapy followed by emergent treatment. Usually, minor reactions do not indicate development of a major event. The hypersensitivity reactions are most likely caused by the polyoxyethylated castor oil vehicle, but the taxane moiety may also be contributory. It is noteworthy that in one large trial the incidence of major events was reported to be similar, irrespective of the infusion schedule used.[29] Evidence suggests that the vast majority of patients may be successfully retreated with slow, low-dose infusions of paclitaxel after premedication with appropriate desensitization schedules. Markman et al reported a 100% success rate with taxane rechallenge in 44 patients with their regimen.[123]

Neuromuscular

In contrast with myelosuppression, peripheral neuropathy is cumulative and progressive with increasing exposure to the drug, but usually disappears several weeks or months after discontinuation of paclitaxel. Neuropathy due to paclitaxel presents as numbness and paresthesia in a glove-and-stocking distribution. It is usually symmetric, sensory as well as motor, and affects proprioception, vibration, temperature, and pinprick sensation. The time of onset is typically several weeks at conventional doses (135 to 250 mg/m^2), and quicker (24–72 hours) at higher doses (>250 mg/m^2). The most commonly affected sites include the limbs, face (perioral numbness), optic nerve (scintillating scotoma), joints, and the autonomic nervous system. Risk factors include longer treatment, higher doses, alcohol, diabetes, and preexisting neuropathy. Transient muscle pains are common, and frank myopathy may occur at doses higher than 250 mg/m^2 or in combination with platinum agents. Unlike hematologic toxicity, neuropathy is observed more frequently with shorter infusion schedules (less than three hours).

The management of paclitaxel-induced neuropathy is a matter of intense research. Although multiple agents have been proposed to ameliorate nerve damage, few have been studied, and with mixed results. Amitriptyline and gabapentin have been used in neuropathic pain with success. Neuroprotective agents in the form of high dose vitamin E, glutamine, lamotrigine, and disodium 2,20-dithio-bisethanesulfonate (BNP7787, which is reduced to mesna) all have preliminary data in their support but await large-scale trials to validate their widespread use.[124]

Cardiac

In the initial clinical trials of paclitaxel, routine cardiac monitoring was performed due to a high rate of hypersensitivity reactions. This led to the detection of a relatively high rate of cardiac rhythm disturbances, the relevance of which is doubtful because the vast majority of patients remained asymptomatic. Therefore, routine cardiac monitoring of patients receiving paclitaxel is no longer required. Nevertheless, the most common rhythm disturbance appears to be asymptomatic transient bradycardia. Mobitz Type I (Wenckebach phenomenon), Mobitz Type II, and third-degree heart block have also been noted, but the incidence in a large NCI database was only 0.1%.[125]

There is no evidence that chronic paclitaxel use causes cardiac dysfunction. However, cardiac monitoring should be considered for patients with atrioventricular conduction disturbances or ventricular dysfunction. Doxorubicin used with paclitaxel increases cardiac toxicity more than what would be expected with the former alone. Dexrazoxane may help reduce cardiotoxicity in this setting but the data remain preliminary.[126–129] In a Phase III trial of trastuzumab-paclitaxel in breast cancer, the incidence of cardiotoxicity was increased, warranting careful patient monitoring.[130]

Gastrointestinal

Paclitaxel-induced gastrointestinal effects are generally uncommon and limited to mild nausea, mucositis, diarrhea, and elevated liver function tests, so routine use of antiemetics is not recommended. Rare cases of neutropenic enterocolitis, gastrointestinal necrosis,[131] typhlitis,[132] hepatotoxicity,[133] and pancreatitis[134] have been reported, especially with high doses of paclitaxel in combination with doxorubicin or cyclophosphamide.

Dermatologic

Paclitaxel induces reversible alopecia of the scalp. Extravasations of large volumes can cause moderate soft tissue injury, and rare reports of nail disorders and recall reactions at previously irradiated sites have also been noted, although mostly with weekly schedules only.[23]

Newer forms of paclitaxel

Several newer forms of paclitaxel have been manufactured, aimed at decreasing toxicity, increasing efficacy, and improving ease of administration. Abraxane® is an albumin-bound form of paclitaxel which delivers paclitaxel as a suspension of albumin nanoparticles in saline, eliminating the need for Cremophor EL, the traditional carrier for the drug.

Cremophor EL is considered a key factor in hypersensitivity reactions to paclitaxel, leading to slower infusion rates and a need for premedication. Abraxane may eliminate these limitations and offers the additional advantages of delivery of a relatively higher dose of paclitaxel. Fader et al successfully treated five patients with severe hypersensitivity reactions to traditional paclitaxel with 80 to 100 mg/m^2 of Abraxane in gynecologic cancers.[135]

Abraxane may also increase intratumoral concentration of paclitaxel by a receptor-mediated transport process across the endothelial cell wall, thereby breaching the blood/tumor interface.[136] Although Abraxane has demonstrated a high degree of activity in metastatic breast and lung cancer,[137,138] its toxicity profile and response rates in ovarian cancer remain to be elucidated in a large number of patients. In a Phase II study, Teneriello et al treated patients with recurrent platinum-sensitive disease using Abraxane 260 mg/m^2 for 30 minutes on day 1 of a 21-day cycle for six cycles or until disease progression. The response rate was 64% (15 complete and 13 partial responses among 44 assessable patients). Estimated median PFS was 8.5 months. The most frequent Grade 3–4 toxicities were neutropenia (24%) and neuropathy (9%).[139] Several other trials of this formulation are in progress.

Taxoprexin® is paclitaxel bound to docosahexaenoic acid (DHA), a fatty acid that is easily taken up by tumor cells. Upon entry of this prodrug into the cell, normal metabolism cleaves the fatty acid moiety to yield the active drug. The main advantage of DHA-paclitaxel is its ability to carry much higher concentrations of paclitaxel to the cells.[140]

Paclitaxel poliglumex is a conjugate of paclitaxel and poly-L-glutamic acid which accumulates in tumor tissue due to enhanced permeability of the tumor vasculature and lack of lymphatic drainage. Paclitaxel poliglumex prolongs exposure to the active drug and minimizes systemic exposure. In a Phase II GOG study of relapsed ovarian cancer, a response rate of 16% was seen, with Grade 3 and 4 toxicities being neutropenia (24% and 20%, respectively), constitutional symptoms (8% and 0%), gastrointestinal disturbance (6% and 0%), and neuropathy (24% and 0%).[141]

ANG1005, another newer form of paclitaxel, is made up of one molecule of angiopep-2 (brain peptide vector) joined together with three molecules of paclitaxel. ANG1005 enters the brain to a greater extent than paclitaxel and bypasses the Pgp efflux pump mechanism.[142] This formulation gives new hope for treatment of brain metastasis from various forms of tumors.

Patient perspectives

Quality of life, although an important consideration, has not in the past been the primary endpoint of front-line chemotherapy trials, because OS is considered the most important issue. It is believed that patients will prefer a therapy which prolongs life at the expense of nonthreatening toxicities impacting quality of life. However, this notion is not true for recurrent ovarian cancer where cure is not yet possible and therefore palliation of symptoms and toxicities is of critical value. Because the dosing strategy for paclitaxel has a great impact on its toxicity profile and hence quality of life, the better tolerated weekly low-dose paclitaxel regimens are fast emerging as the preferred therapy in recurrent ovarian cancer.[99,100]

Conclusions

In past two decades, taxanes have emerged as front-line chemotherapy agents in several types of human cancers. Paclitaxel for ovarian cancer epitomizes this notion and is the current standard front-line therapy along with carboplatin. Having already learned about the efficacy of paclitaxel in ovarian cancer, future areas of active exploration include finding the optimal dosing schedule, investigating newer and potentially better forms of paclitaxel, and identifying the optimal route of administration.

Disclosure

The authors declare no conflicts of interest in this work.

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