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Recent strategies for the use of paclitaxel in the treatment of urological malignancies

Abstract Paclitaxel, a natural anticancer drug, has gained widespread acceptance as an active broad-spectrum antitumor agent, including its use in urological malignancies, particularly urothelial tract cancer and testicular cancer. The mechanism of action, based on the premature stabilization of the microtubule assembly with disruption of the cytoskeletal framework, is completely different from those of DNA-damaging agents, e.g., cisplatin and ifosfamide. As a single agent, paclitaxel is one of the most active drugs in metastatic bladder cancer, with an overall response rate of 40–50% being obtained in previously untreated patients. These promising single-agent results have prompted the use of combination regimens including, in particular, cisplatin and paclitaxel. A high degree of activity for the cisplatin-paclitaxel combination as reflected by responses in 50–80% of patients, including a substantial number of complete responses (>30%), has been identified. The role of other agents such as vinorelbine, methotrexate, 5-fluorouracil, or ifosfamide as additions to this two-drug combination currently remains open. The combination of paclitaxel plus ifosfamide or vinorelbine in the absence of a platinum derivative has yielded rather disappointing results. Of particular interest may be the combination of paclitaxel and carboplatin. Both drugs can be given to patients with impaired renal function. Overall response rates of 45–60% have been reported in phase II studies. The so-called *platelet-sparing effect* of paclitaxel given in combination with carboplatin has resulted in a surprisingly low frequency of myelotoxicity, particularly thrombocytopenia. The combination of paclitaxel with carboplatin is being compared in an ongoing trial against the current standard MVAC regimen (methotrexate/vinblastine/Adriamycin/cisplatin) in patients with metastatic disease. Furthermore, the activity of paclitaxel-based combinations is currently being explored in the neoadjuvant setting in phase II studies, and the potential for the combination with the other new promising agent – gemcitabine – will be evalutated in a phase I setting. In prostate cancer, estramustine phosphate is widely used as palliative treatment for patients with hormone-refractory disease. In vitro synergistic activity has been observed between estramustine and paclitaxel in prostate-cancer cell lines, although paclitaxel has not demonstrated single-agent activity in patients with hormone-refractory prostate cancer. In clinical trials the combination of the two agents was associated with increased gastrointestinal toxicity. The addition of etoposide as a third drug has yielded prostate-specific antigen (PSA)-response rates of > 50%, but data on quality of life and survival time have not been reported for these combinations. A true clinical role for paclitaxel in prostate cancer has therefore not been established. Paclitaxel has finally demonstrated single-agent activity in relapsed and/or cisplatin-refractory testicular cancer in recent phase II trials, indicating different mechanisms of resistance to cisplatin and paclitaxel. These results have formed the rationale for the introduction of paclitaxel as part of combination chemotherapy regimens in patients with relapsed but chemosensitive testicular cancer. Preliminary results demonstrate that paclitaxel can be safely included into these conventional-dose combination regimens. When it is used prior to high-dose chemotherapy, sufficient numbers of peripheral blood stem cells (PBSCs) for high-dose therapy can be collected. The final role of

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paclitaxel in risk-adapted chemotherapeutic strategies in testicular cancer is not defined, but it appears that paclitaxel-based combinations can achieve a substantial response rate in patients with relapsed disease.

Whereas no established chemotherapeutic regimen exists for hormone-refractory prostate cancer, cisplatin-based combination chemotherapy is considered standard treatment for patients with bladder and testicular cancer. Paclitaxel represents a natural anticancer drug with demonstrated activity in solid tumors such as ovarian, breast, and lung cancers [24, 26, 41]. Premature stabilization of microtubule assembly with disruption of the cytoskeletal framework represents the major mechanism of cytotoxicity of paclitaxel [49]. Paclitaxel's mechanisms of action and of resistance are different from those of DNA-damaging agents such as cisplatin and ifosfamide. Since patients who develop resistance to the DNA-damaging agent cisplatin have an extremely poor prognosis, the role of paclitaxel in bladder as well as testicular cancer is of particular interest [20]. Clinical investigations support the important role for paclitaxel in the treatment of these malignancies [3, 31, 44]. This review updates recent data on paclitaxel in patients with bladder cancer, prostate cancer, and testicular germ-cell tumors. The potential role of paclitaxel for the treatment of urological malignancies either as a single agent or as part of combination chemotherapy regimens is discussed.

Paclitaxel in the treatment of bladder cancer

Approximately 50,000 new cases of urothelial cancer are estimated to occur per year in the United States, of which 11,000 will result in death. Although 75% of all bladder cancers are initially limited to the mucosa, submucosa, or lamina propria, 10–25% of these superficial tumors will progress to muscle-invasive disease with a substantial risk for the development of distant metastases [48].

Prior to the development of effective chemotherapy the median survival of patients with metastatic urothelial tract cancer rarely exceeded 6 months. The use of different cytotoxic drugs and the development of combination chemotherapy regimens have clearly demonstrated the chemosensitivity of this disease [48]. Cisplatin, methotrexate, and, to a lesser degree, Adriamycin and vinblastine have been the most active drugs, with response rates (complete response, CR, plus partial response PR) being 34% for cisplatin and between 29% and 45% for methotrexate [21, 35, 48]. However, the overall rate of response to single-agent therapy in metastatic bladder cancer rarely exceeds 30% and, in particular, only few CRs are achieved. To improve response rates and survival in advanced bladder cancer, cisplatin-based combination chemotherapy is used. MVAC (methotrexate, vinblastine, Adriamycin, cisplatin) represents one of the most commonly employed combination regimens. In addition to overall response rates of 40–60%, CRs in 20% of patients have been reported [18, 56]. However, although cisplatin-based combination chemotherapy regimens are clearly associated with high response rates, median survival reaches only 12–14 months and most patients achieving a CR will nonetheless suffer a relapse. Survival beyond 5 years following CMV (cisplatin, vinblastine, methotrexate) chemotherapy has been reported in only 3–5% of patients [18].

The toxicity of cisplatin-based combination chemotherapy such as CISCA (cisplatin, cyclophosphamide, Adriamycin), MVAC, or CMV in patients aged mostly 60 years and older is substantial. Particularly, hematological toxicity involving grade III/IV granulocytopenia will occur in 40–60% of patients. Many trials have employed hematopoietic growth factors in addition to MVAC chemotherapy to reduce hematological toxicity [16, 18, 51]. Thus, it has been of major interest to develop less toxic but more effective new treatment regimens.

In recent years, new active agents such as gallium nitrate, gemcitabine, and paclitaxel have been identified as being effective in patients with bladder cancer [11, 28, 42, 44]. In particular, paclitaxel and gemcitabine appear to be very promising, their single-agent activities being at least as high as or even higher than that of cisplatin [12, 39, 44]. Table 1 summarizes the results of single-agent therapy in advanced urothelial bladder cancer.

The initial phase II trial of paclitaxel by the Eastern Cooperative Oncology Group (ECOG) has demonstrated significant activity in advanced urothelial cancer. A total of 26 patients received paclitaxel given at 250 mg/m^2 by 24-h continuous infusion every 21 days supported by granulocyte colony-stimulating factor (G-CSF) given at 5 μg/kg per day. In all, 11 of 26 patients (42%) demonstrated an objective response, with 7 patients (27%) achieving a CR. The median response duration in the 11 responding patients was 7+ months. Toxicity according to WHO criteria was mainly

Table 1 Summary of single-agent activity in urothelial cancer [12, 13, 28, 39, 42, 44, 48]

Drugs investigated	Remission rates (CR + PR)	Range
Paclitaxel	55%	50–60%
Methotrexate (low + high dose)	37%	23–50%
Cisplatin	34%	28–40%
Gemcitabine	31%	27–38%
Gallium nitrate	29%	13–45%
Adriamycin	17%	13–22%
5-Fluorouracil	17%	11–25%
Vinblastine	16%	4–28%
Carboplatin	15%	11–19%

Table 2 Results of phase II studies of paclitaxel/cisplatin-based combination chemotherapy in patients with advanced or metastatic bladder cancer

Reference	Regimen and schedule	Patients (*n*)	Remission rates
Murphy et al. [33]	175 mg/m^2 paclitaxel + 75 mg/m^2 cisplatin	20	15 (75%) (6 CR, 9 PR)
Burch et al. [5]	135 mg/m^2 paclitaxel + 70 mg/m^2 cisplatin	11	8 (82%) (4 CR, 4 PR)
Calvo et al. [6]	100 mg/m^2 paclitaxel + 3 × 20 mg/m^2 cisplatin	12	9 (75%) (1 CR, 8 PR)
	+ 3 × 800 mg/m^2 5-fluorouracil	14[a]	5 (45%) (0 CR, 5 PR)
McLaren et al. [27]	175 mg/m^2 paclitaxel + 70 mg/m^2 cisplatin + 2 × 3 mg/m^2 vinblastine	15	8 (47%) (2 CR, 5 PR)
McCaffrey et al. [25]	200 mg/m^2 paclitaxel + 70 mg/m^2 cisplatin + 3 × 1.5 mg/m^2 ifosfamide	24	20 (79%) (4 CR, 16 PR)

[a] Patients had received previous chemotherapy

hematological, with granulocytopenia of grade III/IV occurring in 21% of the patients; grade III neuropathy, in 11%; and grade III mucositis, in 11% [44].

The promising results of first-line single-agent therapy with paclitaxel in patients with advanced bladder cancer have prompted the use of combination regimens including cisplatin and paclitaxel. The results of these recent trials are summarized in Table 2. Paclitaxel given at 175 mg/m^2 as a 24-h continuous infusion was combined with cisplatin given at 75 mg/m^2 in 20 patients treated at Vanderbilt University. A response rate of 75% was observed, with 6 patients achieving a CR and 9 patients showing a PR [33]. The combination of paclitaxel, cisplatin, and ifosfamide (ITP) used by the Memorial Sloan Kettering Cancer Center has resulted in a 79% response rate in 24 currently evaluable patients, with 4 patients achieving a CR [25]. Further small phase II studies combining cisplatin, paclitaxel, and either vinblastine or 5-fluorouracil have also achieved response rates of about 50% in metastatic bladder cancer [6, 27]. Considering the high-level activity of the cisplatin-paclitaxel combination and the substantial number of CRs achieved by this combination, the role of further agents as additions to this two-drug combination currently remains open.

Paclitaxel-combination partners of potential interest include vinorelbine, ifosfamide, carboplatin, and gemcitabine. Preliminary results reported for the combination of paclitaxel plus vinorelbine have been rather disappointing in patients with bladder cancer [55]. The combination of paclitaxel given at 135 mg/m^2 on day 4 with ifosfamide given at 1.0 g/m^2 on days 1–4 has also not been very encouraging. In 12 previously untreated patients a response rate of only 33% (2 CRs/2PRs) was achieved, which is worse than the results initially reported for paclitaxel alone. In 12 pretreated patients an 18% response rat was achieved. This does not differ from previous experience with ifosfamide single-agent salvage therapy [45].

In contrast to the results obtained using paclitaxel-ifosfamide as salvage therapy, the combination of paclitaxel with cisplatin and methotrexate has yielded more promising results in 25 patients with metastatic refractory urothelial cancer when given as second- or third-line chemotherapy. Altogether, 10 patients (40%) have again obtained a PR, including 3 of 7 patients with liver metastases [57].

The ITP regimen has also been evaluated as neoadjuvant chemotherapy in 10 patients with locally advanced disease. In all, 5 patients (50%) whose disease was initially staged as T4aN1 have achieved a CR (2 pathologically confirmed). Disease-free survival in these patients ranges from 3+ to 12+ months. Further evaluation of paclitaxel-based chemotherapy in the neoadjuvant setting appears warranted [19, 25].

The role of paclitaxel may be of particular interest in patients with bladder cancer combined with renal insufficiency. Since only 3–5% of the drug is excreted by the kidneys, paclitaxel can be applied without dose reduction in patients with renal insufficiency. Using dosing models based on renal function, paclitaxel has recently been widely used in combination with carboplatin. Carboplatin was given according to area-under-the-curve (AUC) calculations [40, 50, 59]. The clinical results obtained with carboplatin-paclitaxel combinations in bladder cancer are summarized in Table 3. Overall response rates of 50–60% are achievable. However, it appears that the number of CRs reached may be slightly lower than those reported for the combination with

Table 3 Results of phase II studies of paclitaxel/carboplatin-based chemotherapy for advanced or metastatic bladder cancer

Reference	Regimen and schedule	Patients (*n*)	Remission rates
Vaughn et al. [59]	225 mg/m^2 paclitaxel + (AUC 6) carboplatin	24	12 (50%) (2 CR, 10 PR)
Redman et al. [40]	200 mg/m^2 paclitaxel + (AUC 5) carboplatin	19	10 (53%) (4 CR, 6 PR)
Schnack et al. [50]	175 mg/m^2 paclitaxel + (AUC 5) carboplatin	15	10 (66%) (5 CR, 5 PR)
Edelman et al. [14]	200 mg/m^2 paclitaxel + (AUC 6) carboplatin 10 mg/m^2 methotrexate[a]	12	4 (33%) (0 CR, 4 PR)

[a] Dose escalation of methotrexate at 10-mg/m^2 steps

cisplatin [5]. The overall toxicity of the paclitaxel/carboplatin combination was low. In contrast, peripheral neuropathy, myelosuppression, and fatigue were noted following administration of the cisplatin/paclitaxel combination [5, 47, 59]. Most studies have used carboplatin doses targeted at an AUC value of 5–6 mg/ml × min. Thus, it may be speculated that higher carboplatin doses could be safely explored and might be potentially even more effective when given in combination with paclitaxel. This may be of particular interest since the combination of paclitaxel and carboplatin is not associated with severe myelosuppression. A surprisingly low rate of thrombocytopenia has been observed for this combination. This so-called *platelet-sparing effect* may result from the protection of hematopoetic stem cells from the toxicity of carboplatin by paclitaxel [60].

In summary, in metastatic bladder cancer, paclitaxel used as a single agent as well as in combination regimens demonstrates high response rates. Paclitaxel-based combinations – most likely, carboplatin/paclitaxel – will be evaluated against the current standard MVAC regimen in a randomized trial by the Southwest Oncology Group (SWOG) in the United States. The activity of paclitaxel-based chemotherapy in the neoadjuvant and the adjuvant setting needs to be explored in future trials [23, 56]. The combination of paclitaxel with the other promising new agent in bladder cancer, such as gemcitabine, is currently being investigated in a phase I study at Indiana University. A definitive role for paclitaxel in the cytostatic armamentarium for the treatment of bladder cancer should be expected.

Paclitaxel in the treatment of prostate cancer

There is no standard chemotherapeutic approach to patients with hormone-refractory prostate cancer. In general, chemotherapy is poorly tolerated by the elderly population of men with limited bone marrow reserve and often coexisting medical illnesses. Recent investigations have evaluated the use of new cytotoxic agents such as vinorelbine, gemcitabine, or oral platinum derivatives (JM-216) or have focused on biological treatment approaches using, e.g., suramin or antibodies against the epidermal growth factor (EGF) receptor either alone or in combination with chemotherapeutic agents [7, 29, 38, 53, 58]. The first experience with paclitaxel given at 135–175 mg/m^2 as a 24-h infusion every 3 weeks during a phase II trial in 23 patients with hormone-refractory prostate cancer demonstrated almost no activity, with only 1 of 23 patients achieving a PR [43].

Estramustine phosphate (EMP) is widely used as palliative treatment for patients with hormone-refractory prostate cancer. In vitro specific binding of EMP to microtubule-associated proteins has been observed, and this acitivty appears to be synergistically potentiated by the application of paclitaxel [22]. This has been the rationale for clinical trials evaluating the combination of EMP and paclitaxel in metastatic prostate cancer patients. Among 23 evaluable patients treated with paclitaxel given at 120 mg/m^2 and EMP given at 600 mg/m^2 p.o. daily, 3 of 7 patients with measurable disease achieved a PR and, in addition, 11 patients had a >50% decline in prostate-specific antigen (PSA) values [22]. In another phase I trial using a dose escalation of paclitaxel combined with oral EMP, 10 of 16 patients had a >30% fall in PSA values. Gastrointestinal toxicity was substantial in this trial, and 4 patients had to discontinue the treatment [37]. Another trial demonstrated a >30% reduction in PSA values in 9 of 11 patients (82%) [61]. This line of investigation has recently been taken further, adding oral etoposide to the combination of paclitaxel plus estramusine [54]. 12 of 23 patients had a substantial decrease in PSA levels and 2 of 5 patients obtained a PR of soft-tissue metastases (Table 4).

In summary, although paclitaxel has not demonstrated single-agent activity in hormone-refractory prostate cancer, its combination with EMP appears to be active but is also associated with increased gastrointestinal toxicity. Future study concepts include the addition of carboplatin or mitoxantrone to the above-described two- or three-drug paclitaxel-based chemotherapy regimens, although the rationale for these three-drug combinations remains open. It might be that paclitaxel is more effective in prostate cancer when infused over a shorter period (1–3 h) [61]. The evaluation of paclitaxel as a part of combination treatment for prostate cancer is ongoing, and it currently remains open whether paclitaxel will possess a role in the treatment of this disease.

Table 4 Results of paclitaxel-based chemotherapy in hormone-refractory prostate cancer

Reference	Regimen and schedule	Remission rates
Roth et al. [43]	Paclitaxel 135–175 mg/m^2 (24 h)	1 PR in 23 patients
Hudes et al. [22]	Paclitaxel 120–140 mg/m^2 (96 h) estramustine 600 mg/m^2 p.o. daily	11/16 PSA reduction >50% 3/7 soft-tissue PR
Pereboom et al. [37]	Paclitaxel 70–200 mg/m^2 (3 h) estramustine 600 mg/m^2 p.o. daily	10/16 PSA reduction >30%
Wu et al. [61]	Paclitaxel 125–175 mg/m^2 (3 h) estramustine 600 mg/m^2 p.o. daily	9/11 PSA reduction >30%
Smith et al. [54]	Paclitaxel 135 mg/m^2 (1 h) estramustine 560 mg/m^2 daily etoposide 100 mg days 1–14	12/23 PSA reduction >50% 2/5 soft-tissue PR 5 stopped due to toxicity

Table 5 Single-agent activity of paclitaxel in patients with relapsed and/or cisplatin-refractory testicular cancer (*inf.* Infusion)

Reference	Dose and schedule (mg/m^2)	Patients (*n*)	Remission rates (CR/PR)
Bokemeyer et al. [2]	135–225; 3- to 6-h inf.	10	30% (0/3)
Motzer et al. [30]	250[a]; 24-h inf.	31	26% (3/8)
Bokemeyer et al. [3]	225; 3-h inf.	24	25% (2/4)
Christou et al. [10]	175; 24-h inf.	18	11% (0/2)
Total		83	26% (5/17)

[a] With routine use of G-CSF

Paclitaxel in the treatment of testicular cancer

Testicular germ-cell tumors serve as a model for a curable malignancy in the adult. Platinum-based combination chemotherapy such as the PEB regimen (platinum, etoposide, bleomycin) is considered standard treatment for patients with metastatic testicular cancer and achieves long-term cure in approximately 70–80% of patients [15]. However, patients who suffer a relapse after conventional cisplatin-based chemotherapy have a considerably worse prognosis, achieving only 20–30% long-term survival. High-dose chemotherapy followed by autologous stem-cell rescue is widely used as salvage treatment in these patients [1, 34, 52]. Patients who suffer a relapse even after high-dose therapy or who have absolutely platinum-refractory disease have almost no chance for long-term cure [1]. Identification of new agents with significant antitumor activity in this group of patients remains a priority [17].

The basis for the clinical investigation of paclitaxel has been its proven in vitro activity in the teratocarcinoma cell line 833K and in its cisplatin-resistant subline 833K 63CP10. A marked degree of cytotoxic activity was seen for paclitaxel in both the wild-type cell line and the cisplatin-resistant subline. Furthermore, synergistic activity for cisplatin and paclitaxel was observed [9, 31]. In recent phase II studies the activity of paclitaxel in relapsed and/or cisplatin-refractory testicular cancer has been confirmed [3, 30].

The German Testicular Cancer Study Group (GTCSG) has evaluated the dose and schedule of paclitaxel in relapsed testicular cancer patients using doses of between 175 and 225 mg/m^2 given as 3- to 6-h outpatient infusions. Among 10 patients treated, 3 achieved a PR, and 1 patient has remained in PR for more than 6 months [2]. The activity of paclitaxel in germ-cell cancer was confirmed in 31 patients who had relapsed after receiving one cisplatin-based chemotherapy regimen. Paclitaxel was applied at 250 mg/m^2 by 24-h continuous infusion followed by G-CSF, and treatment was recycled every 21 days. A response rate of 26%, involving 3 CRs and 8 PRs, was observed [30]. A subsequent trial by the GTCSG using 225 mg/m^2 given as a 3-h infusion without routine application of hematopoietic growth factors demonstrated a 25% response rate (2 CRs, 4 PRs) in 24 patients with multiply relapsed or cisplatin-refractory disease [3]. A somewhat lower level of activity was observed by the Indiana University Group, who treated 18 patients with 175 mg/m^2 paclitaxel given as a 24-h continuous infusion. Only 2 patients (11%) achieved a PR [10]. In total, among 83 patients reported in the literature a response rate of 26% was found in this heavily pretreated population. It is of particular interest that even CRs were observed (Table 5). In all studies, responses to paclitaxel have been rare following the use of high-dose chemotherapy regimens. However, at least single patients with mediastinal germ-cell tumors, who are also considered to possess a particularly poor prognosis, have responded to single-agent paclitaxel [2, 3, 10, 30, 36].

Neutropenia of grade III/IV was the main toxicity in approximately 50% of patients with heavily pretreated testicular cancer. Neutropenic fever and hospitalization occurred in approximately 20% of patients. Neurotoxicity due to previous cisplatin treatment has affected between 10% and 30% of patients receiving paclitaxel. However, in most cases the paclitaxel-related neuropathy was partially reversible. Severe allergic reactions have been reported in only 1 of the 83 patients treated [3, 10, 30, 47].

The favorable responses observed in patients with cisplatin-refractory disease appear very promising. Different mechanisms of resistance are suspected for cisplatin and paclitaxel [8, 49]. The development of platinum resistance has been attributed to an increased DNA-damage repair capacity [46].

The results achieved in cisplatin-refractory patients have formed the rationale for the introduction of paclitaxel as part of combination chemotherapy regimens

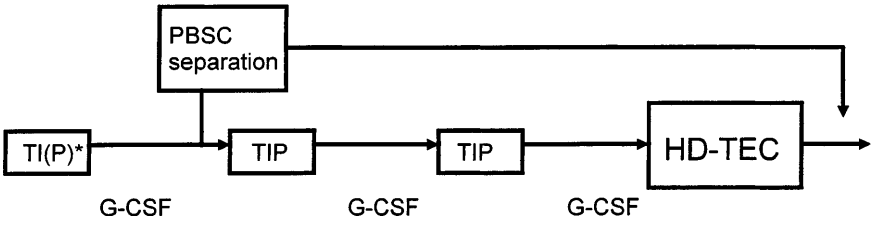

Fig. 1 Schematic outline of the phase II study of the GTCSG for patients with relapsed testicular cancer [4] (*TIP* Paclitaxel/ifosfamide/cisplatin, *HD-TEC* high-dose thiotepa/etoposide/carboplatin). *First course may be given without cisplatin

in patients with relapsed testicular cancer. Investigations at the MSKCC are using two different paclitaxel-based approaches for the treatment of patients with relapsed disease. Favorable-risk patients (primary testicular site and prior CR to first-line therapy) are treated with four cycles of TIP (paclitaxel, ifosfamide, cisplatin), with the paclitaxel dose being escalated from 175 to 250 mg/m^2, with G-CSF support. In all, 13 of 20 patients have responded to TIP and 11 (55%) remain in CR at 10 months of follow-up (range 4–30 months). Unfavorable-risk patients receive two cycles of TI (paclitaxel, ifosfamide) at 14-day intervals followed by peripheral blood stem-cell (PBSC) separation and three consecutive cycles of high-dose CE (carboplatin, etoposide), each involving PBSC retransfusion. Among 22 evaluable patients treated in this group, 10 (46%) remain disease-free at 11 months (range 4–32 months) of follow-up. Carboplatin doses are escalated according to an AUC-based model [32]. The GTCSG is investigating the use of the TIP regimen as salvage chemotherapy to reduce the tumor burden and at the same time mobilize PBSCs. Patients receive three cycles of TIP therapy followed by G-CSF and responders go on to receive high-dose carboplatin, etoposide, and thiotepa (TEC; Fig. 1). From the initial analysis of more than 70 patients treated, it appears that TIP chemotherapy can be considered at least as active as the established PEI regimen. Although no severe nephrotoxicity has been observed with TIP + high-dose TEC therapy, a considerable number of patients have developed significant neurotoxicity. The full analysis of approximately 100 subsequent patients will be necessary to determine whether a paclitaxel-based salvage strategy can be of benefit for particular subgroups such as patients with either chemotherapy-sensitive or chemotherapy-refractory relapses [1]. Separation of PBSCs following administration of the TIP regimen + G-CSF is feasible but appears to be less effective than the stem-cell yield obtained following the previous experience with PEI + G-CSF. However, separation of sufficient numbers of PBSCs appears possible after TI chemotherapy; therefore, the first cycle of chemotherapy is now given without cisplatin.

In summary, single-agent paclitaxel has demonstrated antitumor activity in germ-cell tumors and the drug is being studied in combination regimens as second-line treatment. Ongoing trials demonstrate that paclitaxel can be safely included in conventional chemotherapy regimens prior to high-dose chemotherapy. The use of paclitaxel combined with a standard PEB-type regimen as first-line treatment in patients with intermediate-prognosis non-seminomatous germ-cell tumors, a subgroup of patients with a long-term survival chance of 70–80%, may be studied by the European Organization on Research and Treatment of Cancer (EORTC) Genitourinary Tumor (GU) Group. It remains to be seen which role this new anticancer drug will finally achieve in modern risk-adapted treatment strategies for the highly curable group of patients with testicular cancer.

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