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Experience with dose and schedule variations in germ cell tumors

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The majority of patients with metastatic germ cell tumors can be cured with currently available poly-chemotherapy. Based on presenting criteria three prognostic groups can be discerned. In patients with a good prognosis (> 90% probability of 5-year survival) attempts have been made to diminish the dose of the active compounds in the BEP regimen. The omission of bleomycin cannot be recommended on presently available data; and a total dose of at least 240 mg seems appropriate. Platinum at a dose intensity below 75 mg/m²/3 weeks compromised efficacy and the recommended dose is 100 mg/m². A true comparison between the two most frequently used etoposide doses has not been performed. Based on the available literature etoposide should be given in doses of at least 360 mg/m²/cycle when four courses are given and 500 mg/m²/cycle when three courses are given. For intermediate and high-risk patients alternating, accelerated and high-dose chemotherapy can be considered. None of the alternating and accelerated regimens has a proven advantage in randomized trials and they remain investigational. The addition of hematopoietic growth factors permits a higher dose intensity of BEP/EP and BOP/VIP; although to date there is no proven impact on outcome. The application of high-dose chemotherapy for one to four courses is feasible with the support of both hematopoietic growth factors and autologous bone marrow or peripheral stem cells. In true chemotherapy-resistant disease the value of this approach seems limited. Its role in patients with a first relapse should be further explored. The approach of high-dose chemotherapy in first line for patients with poor prognostic features should preferentially be investigated in a randomized fashion, but this will require extensive international collaboration in view of the low incidence and the expected advantage of the approach.

Introduction

The development of the treatment of germ cell tumors is a classic story in the modern era of chemotherapy and many lessons can be learned from it. Since the introduction of cisplatin (P)[1] major progress has been made, the majority of patients now obtaining cure even with far advanced metastatic disease. At the moment several active drugs are identified for this disease: cisplatin, bleomycin, vinblastine, etoposide, ifosfamide, carboplatin, cyclophosphamide; to a lesser extent adriamycin and actinomycin-d; and more recently paclitaxel.[2] The first breakthrough came from the combination of cisplatin, vinblastine (0.4 mg/kg) and bleomycin given q 3 weeks × 4 followed by 21 months vinblastine maintenance therapy. From this early experience it also became clear that additional courses after four courses of PVB (cisplatin, vinblastine, bleomycin) were clinically not inducing more complete remissions.[3] This indicated that a higher total dose of these drugs did not contribute and the standard number was established to be four. The total dose of vinblastine in this study was high and contributed significantly to the observed toxicity. In a subsequent study the higher dose of vinblastine (0.4 vs 0.3 mg/kg) resulted in similar therapeutic efficacy.[4] The number of patients treated in this study (26 vs 27) was low and therefore does not meet the statistical criteria for equivalence in outcome. It resulted, however, in the establishment of the reduced vinblastine dose as the standard. In another randomized study omission of the maintenance treatment with vinblastine was also shown not to compromise outcome.[5] These studies were among the first to look at dose intensity and total dose given in relation to treatment outcome. The subsequent discovery of etoposide as an active agent with a different toxicity profile led to the development of the BEP (bleomycin, etoposide, cisplatin) combination and this is the backbone of present chemotherapy for metastatic germ cell tumors.[6–8] This therapy results in the cure of approximately 70%–80% of patients. Factors associated with treatment failure have been analyzed in several large studies and

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include large tumor volume, the presence of liver, bone or brain metastases, grossly elevated tumor markers, and an extragonadal primary site, particularly in the mediastinum.[9–15] Based on these prognostic factors clinical trials have investigated either decreasing doses to diminish the toxicity of the standard of four BEP cycles in patients with good-risk disease (predicted cure rate > 90%), or improving the results by intensifying therapy in patients with intermediate-risk (predicted cure rate 80%) and poor-risk (predicted cure rate 50%) disease.

Studies of dose and response in germ cell tumours are not extensive and provide only limited evidence to support the dose–response model. Schedule dependency is quite often ignored in this context, as is synergy between drugs.[16] In studies applying alternating therapeutic agents it is important that active compounds with a different mechanism of action are used. It is against this background that the presently available literature should be assessed.

Chemotherapy in good-risk disease

As mentioned above, clinical trials in patients with a high probability of cure have focused on decreasing the toxicity of standard chemotherapy.[2,17] At present a 5-day regimen of BEP is considered the "gold standard", usually administered 3-weekly for a total of four cycles. During the past decade efforts towards decreasing toxicity have included: (1) defining the role of full-dose bleomycin (with well known toxicities including Raynaud's phenomenon and pulmonary fibrosis); (2) decreasing the dose of etoposide per cycle; (3) decreasing the duration of therapy (number of cycles and number of days per cycle); and (4) reducing toxicity by replacement of cisplatin by carboplatin (which is less emetogenic, neurotoxic and nephrotoxic). Approaches (1)–(3) are related to dose intensity and total dose in the treatment of this disease.

Bleomycin

The role of bleomycin in the management of non-seminomatous germ cell cancer (NSGCC) has been the subject of several randomized studies. The EORTC directly compared four cycles of BEP (etoposide 360 mg/m^2/cycle) with four cycles of EP (etoposide, cisplatin) in patients deemed to be good-risk by the criteria of the EORTC. This trial started in 1982. At that time the EORTC prognostic factor analysis indicated that good-prognosis patients were characterized by lymph nodes < 5 cm, lung metastasis < 2 cm, alpha-foetoprotein (AFP) < 1000 ng/ml, human chorionic gonadotrofin (HCG) < 10,000 IU/l. Today the cut-off values for the markers are still valid, but more recent prognostic factor analyses have shown that patients with more extensive metastases can still be categorized as having a good prognosis. With 393 patients entered into the study, 97% of the evaluable patients receiving BEP and 91% of patients receiving EP achieved complete remission. Of the complete responders, 6 receiving EP and 7 receiving BEP relapsed. Although there was no statistical difference between the two arms a few more patients progressed and died on the EP arm, even though the eligibility criteria actually selected for ultra-good prognostic patients. The number of events in this study is low and the study therefore lacks the power to give a final answer. At the same time an ECOG prospective randomized study comparing three courses of BEP (etoposide 500 mg/m^2/cycle) with three courses of EP in patients with minimal or intermediate disease by the Indiana classification showed progression-free survival of only 69% in the patients using the two-drug schedule compared to 85% with three drugs.[18] It is important to realize that the Indiana good-prognosis group also comprises patients of the intermediate group according to the EORTC classification. It is obvious that bleomycin cannot be omitted when three courses of chemotherapy are given. When four courses are delivered one could consider diminishing the dose of bleomycin. However, based on the data presently available a true threshold cannot be given.

Duration of therapy

The South Eastern Cancer Study Group (SECSG) investigated whether, in those with good-prognosis NSGCC, three courses of BEP was equivalent to the standard four-courses regimen.[19] The trial was designed to show a < 10% difference in the response rate for three courses compared with four courses. One hundred and eighty-four patients entered the study. Eighty-six of 88 patients (98%) randomized to three courses, and 93 of 96 randomized to four courses (97%) of BEP achieved disease-free status. There were 10 relapses (5%), five on each arm. After a median follow-up of only 19 months (range 13–30 months) 81 of 88 (92%) and 88 of 96 (92%) patients randomized to three vs four courses of BEP were free of disease. The authors reported that three courses of BEP could be regarded as standard treatment for favorable-prognosis NSGCC.

It has since been questioned whether this trial of only 184 patients had provided sufficient data to conclude that three BEP equals four BEP as far as progression-free survival and survival are concerned. Although the sample size was sufficient to detect a 10% difference at a power of 85%, it did not allow the detection of a clinically meaningful difference between 5% and 9%. Of equal importance was that the median follow-up of 19 months is probably not sufficient to make the result of this study definitive. There has been no formal update since (personal communication, P. Loehrer, study coordinator, 16 May 1994). In Europe three cycles are therefore not generally accepted as the standard treatment. In a disease where cure can be achieved in over 90% of patients a difference of 5%–9% is not acceptable and it is generally agreed that a new trial should be carried out to rule out a > 5% difference in progression-free survival, with sufficient follow-up. In March 1995 the MRC and EORTC embarked on a large randomized trial that is designed as an equivalence study comparing four vs three cycles of BEP in more than 700 patients, which enables exclusion of a small but meaningful difference.

Etoposide dose

Finally, the dose of etoposide in the BEP regimen remains subject to discussion. Whereas investigators in Europe have used etoposide 120 mg/m^2, days 1, 2, 3 (MRC) or 1, 3, 5 (EORTC), in the US 100 mg/m^2 per day, days 1–5 has always been the preferred schedule. No studies have addressed the issue of the optimal dose of etoposide per cycle in a comparative fashion.

Cisplatin vs carboplatin

The role of carboplatin as replacement for cisplatin is beyond the scope of this review and will therefore not be discussed in detail. Based on the available data cisplatin should be the drug of choice.[20,21]

In view of the fact that four courses of BEP is to be considered the gold standard chemotherapy in patients with good-risk germ cell tumors, the question arises whether the intended dose and schedule of BEP should be maintained vigorously if four cycles are being given. In general drug dose adherence will be regarded as critical if a two-drug regimen or only three cycles of BEP are being given. It is however unlikely that a 25% dose reduction of etoposide and/or cisplatin for one or two cycles will compromise treatment outcome in the case of a planned full-dose BEP regimen over four courses. In a series of 127 patients from the MRC with metastatic germ cell cancer who had been treated with four BEP cycles consisting of cisplatin 20 mg/m^2 per day on days 1–5, etoposide 120 mg/m^2 per day on days 1–3, and bleomycin 30 mg on days 2, 9 and 16, a white cell count nadir of < 1.0 × 10^9/l occurred in only 2% of 482 courses.[7] There were three episodes of neutropenic sepsis, with one death in a patient who had received additional high-dose methotrexate for poorly responding bulky disease. Significant thrombocytopenia was rarely seen and platelet counts < 50,000 × 10^9/l occurred in 2% of 482 courses. Eighteen patients had treatment delays of more than 2 weeks between the start of chemotherapy and the expected date of completion of the fourth course of therapy. Delays occurred predominantly in the earlier part of the series (1979–1983) when chemotherapy was withheld with total white cell counts < 2.5 × 10^9/l. The investigators reported that there was no relationship between these short treatment delays and stage of disease and no effect on recurrence or survival was apparent; the actuarial 5-year recurrence-free survival was 79% for no delay compared to 85% for delay > 1 week. It should be emphasized that the number of patients at risk was low (18) and therefore this observation, though reassuring, does not constitute scientific proof.

When a 5-day schedule of etoposide 100 mg/m^2 per day is used, the incidence of grade 3/4 leukocytopenia and neutropenia is more frequent, resulting in a white cell nadir < 1.0 × 10^9/l in 20% and incidence of fever during neutropenia in 15% of patients at some time during treatment. In a series of 123 patients treated at Indiana University over 50% of patients had an absolute neutrophil count < 0.5 × 10^9/l at some time during treatment.[22] Two patients died of sepsis while they had neutropenia. Fourteen per cent of patients had a platelet count < 50,000 × 10^9/l at some time during treatment. In the previously-mentioned study of 184 patients who received either three or four BEP cycles, one patient died from chemotherapy-related sepsis.[19] As it appears from this latter study that the efficacy of three BEP cycles is not clearly inferior to four cycles, this would lend support to the conclusion that minor dose modifications or some delay in a standard regimen of BEP courses are not critical, as long as four cycles are being administered.

At the Memorial Sloan-Kettering Cancer Center (MSKCC) the effect of duration of induction therapy on complete remission (CR) rate and disease-free survival (DFS) was evaluated by means of univariate and multivariate regression analyses in 162

good-risk patients treated with either VAB-6 (vinblastine, bleomycin, actinomycin-D, cyclophosphamide, cisplatin) at 28-day intervals for three cycles or four cycles of EP at 21-day intervals.[23] Treatment was routinely postponed for 7 days for leukocytes $< 3.0 \times 10^9$/l or platelets $< 100 \times 10^9$/l on the day of planned treatment and therapy was then administered regardless of blood count. The proportion of CR and DFS were not influenced by a ≤ 7-day delay resulting from chemotherapy-induced myelosuppression. The authors concluded that short, planned delays in chemotherapy for good-risk patients of ≤ 7 days per cycle did not compromise treatment outcome and therefore appear acceptable since they may prevent serious toxicity in this curable patient population.

In conclusion, four cycles of BEP is at the moment considered to be the gold standard chemotherapy in patients with good-risk germ cell cancer. Minor dose modifications or some delay do not appear to be critical, as long as four cycles are being given. Variations in the total dose of bleomycin over four courses may range from 270 to 360 mg. For etoposide these figures are 1440–2000 mg/m^2. Cisplatin in all these regimens is given at full dose, 400 mg/m^2.

Intermediate- and poor-prognosis disease

For this patient group treatment strategies include the use of: (1) alternating combinations of different regimens; (2) protocols with shorter intervals of standard doses between treatment cycles to intensify therapy (accelerating chemotherapy); and (3) increased dosages of the individual cytotoxic agents.

Alternating and accelerated chemotherapy

The rationale for alternating different chemotherapy combinations is based on the assumption that a tumor contains cell populations that are sensitive to one drug but resistant to another agent. Such heterogeneity may either exist at the initiation of cytostatic treatment, or develop during treatment as a result of biochemical modulation or genetic mutation.[24,25] In the case of germ cell cancer it is likely that natural resistance is involved since these tumors proliferate rapidly and the duration of induction chemotherapy is restricted to 3 or 4 months. These considerations favor the approach with alternating chemotherapy as the initial treatment in patients with poor-prognosis germ cell tumors.

Drug combinations in sequence have been explored at the Charing Cross Hospital with POMB/ACE chemotherapy (cisplatin, vincristine, methotrexate, bleomycin/actinomycin-D, cyclophosphamide, etoposide). Recently, an updated analysis was published concerning 206 patients treated between 1977 and 1988.[26] In a further study 106 out of 193 fully evaluable patients had large-volume metastatic disease (according to the Royal Marsden Hospital staging classification), i.e. Stage IIC (lymph node metastases > 5 cm) or L3 (lung metastases > 2 cm). These 106 patients with advanced disease had an overall survival of almost 80%. The efficacy of the POMB/ACE regimens was confirmed in a series of 60 patients with large or very-large volume metastases (according to the Royal Marsden Hospital staging classification), resulting in a 5-year survival rate of about 70%.[27] In one North American study 48 patients with advanced disease (according to M.D. Anderson criteria) treated with a combination of cyclophosphamide, doxorubicin and cisplatin (CISCA), and alternated with a combination of vinblastine and bleomycin (VB), 44 patients (92%) achieved a CR and an 85% durable CR rate was achieved in a series of 100 patients.[28] And in another study a 6-month schedule of alternating cycles of EP and VAB-6 in 41 poor-risk patients (predicted survival rate < 50%) resulted in a durable overall CR of 37%.[29] The response and survival of these patients was found to be identical to the results of 29 historical controls with poor-risk germ cell tumors treated with VAB-6 alone at the MSKCC. Based on these data this alternating was not further explored.

It is impossible to judge the relative merits of these alternating regimes as the studies were not randomized and different prognostic selection criteria were used. In 1982 the EORTC began a randomized study comparing four cycles of BEP vs an alternating regime of PVB and BEP for a total of four cycles for patients with 'high-volume' metastases (defined as lymph node metastases > 5 cm or lung metastases > 2 cm in diameter).[30] Two hundred and thirty-four eligible patients were randomized. The CR rates to PVB/BEP and BEP were similar: 76% and 72%, respectively ($p = 0.58$). In addition, there were no significant differences in relapse rate, disease-free and overall survival at an average follow-up of 6 years. The 5-year progression-free and survival rates in both treatment groups were approximately 80%. In 1990 the MRC/EORTC initiated a randomized trial comparing standard therapy with six cycles of bleomycin 30 mg weekly × 12, etoposide 100 mg/m^2 days 1–5 and cisplatin 20 mg/m^2 days

1–5 (BEP/EP) given 3-weekly, against three cycles of bleomycin 30 mg, vincristine 2 mg and cisplatin 50 mg/m^2 days 1 and 2 (BOP) given every 10 days, followed by three cycles of etoposide 100 mg/m^2 days 1, 3, 5, ifosfamide 1 g/m^2 days 1–5 and cisplatin 20 mg/m^2 days 1–5 (VIP) given 3-weekly in patients with poor-prognosis germ cell cancer.[31] The BOP/VIP schedule incorporates rapid induction, i.e. a form of accelerated chemotherapy followed by potentially non-cross resistant chemotherapy, and had previously been tested in a pilot study in 91 cases.[32] Between January 1990 and June 1994, 380 patients were randomized. Eligible patients had one or more of the following: liver/bone or brain metastases; βHCG ≥ 10,000 IU/l or AFP ≥ 1000 Ku/l; lung metastases ≥ 20; lymph node mass ≥ 10 cm maximum diameter below or ≥ 5 cm above the diaphragm. Two hundred and twenty-eight of the 229 patients (150 on BEP, 149 on BOP/VIP) for whom data are available are evaluable for response to date. Of these, 68/116 (59%) on BEP and 65/112 (58%) on BOP/VIP achieved CR. With a median follow-up of almost 1.5 years, 46/175 (26%) on BEP and 57/173 (33%) on BOP/VIP have progressed or died ($p = 0.15$). Among the patients who achieved CR, 10/68 (15%) on BEP and 7/65 (11%) on BOP/VIP have progressed or died ($p = 0.73$). There were a total of 14 deaths attributed to toxicity, 6 on BEP and 8 on BOP/VIP. This preliminary analysis suggests no advantage to the alternating and more intensive schedule, although longer follow-up is required. In a subgroup of 263 patients, a second randomization was performed in order to investigate whether the scheduled dose or either BOP/VIP or BEP/EP could be better maintained with the addition of granulocyte-colony stimulating factor (G-CSF). A preliminary analysis indicated that 10% better dose adherence was achieved with the addition of G-CSF, but that the better dose adherence did not result in a significant improvement of progression-free survival (69% vs 68%) or overall survival (76% vs 80%), no G-CSF vs plus G-CSF respectively.[33]

The main explanation for a lack of benefit from these chemotherapy combinations may be that cisplatin resistance is the crucial factor for treatment failure in testicular cancer, and that alternating vinblastine and etoposide or etoposide and ifosfamide will not have a substantial impact on the efficacy of these combinations.[34] Agents with more important activity in refractory disease such as the taxanes are alternative candidates for drug combinations which may merit further testing of alternating chemotherapy.[2] Although treatment with BEP remains the gold-standard therapy, randomized comparative trials with other schedules, given in either an alternating or a sequential fashion, with or without an intensive induction phase, are justified.

Increased dose per cycle

The rationale for the use of dose-intensified chemotherapy in intermediate- and poor-risk patients is based on preclinical evidence of a dose–response relationship. Because of dramatically improved response rates and survival with the introduction of cisplatin into combination chemotherapy regimens, escalation of cisplatin dose was one of the first attempts made to further improve clinical results.

The South Western Oncology Group (SWOG) conducted a randomized study with PVB at a cisplatin dose of either 120 mg/m^2 every 4 weeks or cisplatin 75 mg/m^2 every 4 weeks.[35] There was a significant increase in the complete response rate and survival for patients in the cisplatin 120 mg/m^2 arm. The clinical meaning of cisplatin dose intensity in this trial was hampered by the relatively low dose intensity of cisplatin in the 75 mg/m^2 arm of 0.58 compared to standard BEP. The relevance of this study is that it underlines the importance of maintaining the standard cisplatin dose intensity and that reduction to 75 mg/m^2 has a detrimental effect on treatment outcome.

The apparent improvement of increased-dose cisplatin was accentuated by a study performed by the National Cancer Institute (NCI) that was designed to determine whether superior results could be obtained by maximum doses of chemotherapy comprising cisplatin 200 mg/m^2, etoposide 500 mg/m^2, vinblastine 0.2 mg/kg per cycle every 3 weeks, and bleomycin 30 mg weekly, relative to a standard scheme of PVB, i.e. cisplatin 100 mg/m^2, vinblastine 0.3 mg/kg every 3 weeks and bleomycin 30 mg weekly.[36] Of the patients randomized to the high-dose arm, 88% obtained disease-free status compared to 67% in the standard arm. This study has frequently been cited to advocate the importance of cisplatin dose intensity in poor-risk germ cell cancer, but the results should be interpreted cautiously since the addition of full-dose etoposide was the other variable in the high-dose cisplatin regimen.

These studies were accompanied or followed by a number of phase II trials that invariably reported superior outcome but as mentioned earlier are difficult to interpret since a myriad of classification systems to assign poor risk were applied.[27,28,37] Trials have included patients that by other classification systems would be regarded as good-risk,

particularly in terms of the number of pulmonary metastases and the size of abdominal lesions.

One important randomized clinical trial of cisplatin dose intensity was performed by the SECSG and SWOG.[38] This study compared the efficacy of BEP at either a cisplatin dose of 100 mg/m^2 per cycle or cisplatin 200 mg/m^2 per cycle. Overall, 84% of patients in the high-dose arm received 80% or more of the projected dose of chemotherapy, and 90% of patients on the standard-dose arm received 80% or more of the projected dose. Of 76 eligible patients who received the high-dose cisplatin regimen, 52(68%) became disease-free with chemotherapy alone or with subsequent resection of residual lesions, whereas of 77 patients who received the standard regimen, 56 (73%) became disease-free. After a median follow-up of 24 months 63% of patients in the high-dose cisplatin arm and 61% in the standard-dose arm were continuously disease-free. Univariate logistic regression analyses investigating the relationship between dose intensity and outcome were unable to conclude that cisplatin dose intensity had an effect on response: cisplatin $p = 0.42$, cisplatin and etoposide $p = 0.33$, the three drugs $p = 0.15$. Therefore, comparison of the single variable of double-dose cisplatin with the standard dose as the control arm showed that the intensified cisplatin regimen did not translate into improved survival or cure. It should be noted that the number of patients entered into this trial is too low to state that equivalence has been shown beyond doubt.

Besides cisplatin, increased dosages of other agents have been incorporated into chemotherapy protocols. Since etoposide and ifosfamide are the two most active single agents apart from cisplatin, and the three-drug combination of cisplatin, etoposide, ifosfamide (PEI) had shown an efficacy in relapsed patients,[39] further exploration was warranted. The German Testicular Cancer Study Group has performed phase I/II dose-escalation studies of PEI with the addition of granulocyte macrophage-colony stimulating factor (GM-CSF), and subsequently studies with the support of G-CSF and autologous peripheral stem cells, as first-line therapy for poor-prognosis patients.[40] Without the use of a hematopoietic growth factor it appeared that cisplatin 25 mg/m^2, etoposide 120–150 mg/m^2 and ifosfamide 1.2 g/m^2 each given days 1–5 every 3 weeks was the maximum tolerated dose schedule, with myelosuppression being the dose-limiting toxicity. The use of GM-CSF allowed a moderate increase in the dose intensity of the schedule of 1.37 (cisplatin 30 mg/m^2, etoposide 200 mg/m^2 and ifosfamide 1.6 g/m^2, days 1–5 every 3 weeks). Dose-limiting toxicities were mucositis and prolonged thrombocytopenia.

No randomized data are available to date comparing standard BEP or ifosfamide-containing regimens with increased-dose protocols. Although minor modifications of the standard chemotherapy regimens with a 20%–50% increase in delivered dose intensity are not very likely to improve therapeutic outcome, further dose escalations of 2-fold or more with the use of hematopoietic growth factors plus bone marrow or peripheral stem cell support are new and interesting approaches.

High-dose chemotherapy in relapsed patients and up-front high-dose chemotherapy in poor-risk patients

The new means of circumventing hematological toxicity with the use of autologous bone marrow and peripheral stem cell support have provided opportunities for testing significantly more intensive treatment regimens. Initial studies were carried out in patients failing second- or third-line or even multiple platinum-containing regimens.[41] The cure of 10%–20% of these patients, in several cases overtly cisplatin-refractory at conventional doses, clearly supports the clinical relevance of a dose–response relationship in this disease when the dose of chemotherapy can be substantially augmented.

Initial investigations used high-dose carboplatin (900–2000 mg/m^2) and high-dose etoposide (1.2 g/m^2), two courses, with autologous bone marrow support. Subsequent studies incorporated ifosfamide (6–10 g/m^2) or cyclophosphamide (2–6 g/m^2) in this combination.[41–48] From these studies it was clear that durable remissions are rarely obtained in patients who are refractory to conventional-dose chemotherapy. Refractory means progressive disease during standard treatment. Furthermore, 10%–20% therapy-related deaths were observed in this pretreated group of patients. Further studies have focused on the earlier utilization of high-dose chemotherapy, i.e. in first line or at first relapse after adequate first-line therapy.

These efforts have included using autologous bone marrow, a combination of bone marrow and autologous peripheral stem cells obtained by leukapheresis, and peripheral stem cells only. Both single and double transplants have been applied as initial salvage treatment (upon first relapse) and as consolidation therapy for patients either incompletely responding to first-line conventional therapy or at high risk of treatment failure.[42–46,49]

High-dose chemotherapy as part of initial salvage chemotherapy has been reported on for 21 patients with poor-prognosis germ cell cancer (6 incomplete responders to initial induction therapy, and 15 with recurrent disease).[50] These patients were treated with a regimen of either carboplatin 1200 mg/m^2, etoposide 3.0 g/m^2 and ifosfamide 6.0 g/m^2, or carboplatin 800 mg/m^2, etoposide 2.4 g/m^2 and cyclophosphamide 7.2 g/m^2, followed by infusion of previously stored autologous marrow. Two patients died of treatment-related toxicity. Only one of the 17 patients who were autografted progressed despite an initial favorable response as reflected in marker decline. Fourteen patients remained well and free after a median follow-up of 3.3 years post-bone marrow transplantation (DFS 67%).

In another study 18 out of 23 patients in first relapse received two cycles of conventional cisplatin-based therapy, followed by a single high-dose regimen of carboplatin 1500–2100 mg/m^2 and etoposide 1200–2250 mg/m^2 with autologous bone marrow support.[44] This resulted in 11 complete remissions, including one patient who was rendered disease-free with additional surgery, and 5 who obtained partial remission for an overall response rate of 88%. The response rate of all patients entering the protocol was 72%. There was only one treatment-related death in this cohort. Of those completing high-dose therapy, 7 of 18 (39%) survived progression-free with a median follow-up of 26 months.

Siegert *et al.* have reported the results of high-dose carboplatin, etoposide and ifosfamide in patients with recurrent germ cell cancer following a median of six cycles of cisplatin-based chemotherapy.[51] Patients were given two induction courses of conventional PEI prior to receiving escalated therapy. Seventy-four patients received high-dose therapy consisting of carboplatin 1500–2000 mg/m^2, etoposide 1.2–2.4 g/m^2 and ifosfamide 0–10 g/m^2. Two patients died of treatment-related toxicity. Of 45 patients who responded to induction therapy, 24 (53%) were disease-free with a probability of DFS at 2 years of 50% (SD 8%).

Also at MSKCC, it was demonstrated that high-dose chemotherapy as first salvage or part of the initial treatment in selected patients is better tolerated. Of 13 patients who had relapsed or incompletely responded to cisplatin + ifosfamide based chemotherapy, 6 obtained an as yet complete response following two cycles of high-dose carboplatin and etoposide, with 3 durable responses at 8+, 20+ and 24+ months follow-up.[45] One patient died of treatment-related toxicity. Of 22 patients who were considered failures on conventional (VAB-6) therapy, based on an inappropriate slow decline of serum tumor markers after two cycles of VAB-6 therapy,[46] and were selected for two cycles of high-dose therapy, 12 achieved a complete response, 11 of these remaining disease-free at a median follow-up of 31 months. One patient died from treatment-related complications. Toxicity was not cumulative, and with the addition of G-CSF following bone marrow reinfusion recovery of blood counts was generally rapid. Although the predictive value of increased marker half-lives (and thus the rationale to proceed to high-dose chemotherapy) remains to be further defined,[51] this study again shows that early intervention with two cycles of high-dose chemotherapy is generally well tolerated in this patient group.

Based on their experience with dose-escalated PEI therapy the German Testicular Cancer Study Group has incorporated the separation and reinfusion of peripheral stem cells in addition to hematopoietic growth factor support into their treatment concept of up-front dose-intensified PEI chemotherapy.[52,53] Hematopoietic stem cells can easily be obtained by leukapheresis after stimulation with G- or GM-CSF during the recovery of the bone marrow following chemotherapy, resulting in the opportunity of harvesting stem cells for subsequent autologous stem cell support during repetitive cycles of high-dose chemotherapy. With this approach multiple cycles of considerably dose-intensified chemotherapy at 3- or 4-week intervals can be delivered, which—especially in the setting of salvage chemotherapy—may be more attractive than conventional reinduction followed by one or two high-dose courses. Notably, in several patients treated at Indiana University it was shown that disease-free status was obtained only after the second cycle of high-dose chemotherapy.[42] However, once optimal dose-escalated regimens are established, the true value of this approach has to be demonstrated in prospective randomized trials.

One such study has recently been completed. The addition of high-dose chemotherapy to conventional-dose induction therapy for patients with untreated poor-risk germ cell cancer was compared with a standard regimen.[54] The high-dose regimen was based on their initial experience with a salvage regimen of cisplatin 200 mg/m^2 over 5 days, etoposide 1.75 g/m^2 over 5 days and cyclophosphamide 6.4 g/m^2 over 4 days (PEC).[55] A total of 115 patients were randomized to either three or four conventional (PVeBV: cisplatin, vinblastine, etoposide, bleomycin) cycles or two PVeBV cycles followed by one PEC cycle with autologous bone marrow support. The 2-year survival was 82% in the standard

arm, whereas it was only 60% in the experimental arm. This difference was not statistically significant, though the power of this trial to detect differences was limited in view of the number of patients treated. It is however unlikely that a benefit will be detected in view of the data presented. Several aspects of this trial warrant discussion. The patients on the high-dose arm received an equivalent or lower total dose of cisplatin than the patients treated with three or four cycles of PVeBV. Carboplatin would permit a substantial higher total 'platinum' dose (1500–2000 mg/m^2) in view of the relative lack of non-hematologic toxicity of carboplatin, and should be considered first choice high-dose chemotherapy.

Conclusion

It is feasible to increase the dose intensity when hematopoietic growth factors are used. It is however questionable whether improved efficacy can be obtained with the modestly increased doses or shortened interval which can be obtained. The use of hematopoietic growth factors without other forms of support can result in a 20%–50% dose intensification. In combination with either autologous bone marrow or peripheral stem cells it has clearly been shown that adequate doses of chemotherapy can be given which may overcome 'chemotherapy resistance' in patients with advanced or relapsing germ cell tumors. This has now resulted in DFS rates higher than can be expected when using conventional cisplatin-based chemotherapy,[56,57] moreover with acceptable toxicity. Also, in selected cases of patients with multiple poor-prognosis factors with predicted survival rates of < 50% when using conventional regimens, the concept of high-dose therapy should be further explored. For true resistant patients, as defined earlier, it is obvious that only about 10% of patients will obtain a durable disease-free status and these are not appropriate candidates for further exploration of this approach.

As has been mentioned, the true value of optimal dose-escalated regimens has to be demonstrated in prospective randomized trials. The relative rarity of patients relapsing after modern cisplatin-based chemotherapy as well as patients presenting with multiple poor-prognostic features will complicate such clinical investigations. Since survival differences of more than 20% are not to be expected, such trials will require several hundreds of patients, which even in the case of collaborative efforts will lead to trial durations of at least 5 or 6 years.

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