



Joanna Zjawinska. *My Brilliant Career*. Serigraph, 32" × 40". Courtesy of the Hanson Gallery, New Orleans, Louisiana.

High-dose chemotherapy is being investigated as first-line therapy for poor prognosis germ-cell tumors and for salvage therapy where first-line treatment has failed.

High-Dose Chemotherapy in Adult Patients With Germ Cell Tumors

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Background: Approximately 80% of patients with advanced germ cell tumors (GCTs) can be cured with cisplatin-based chemotherapy. Patients with poor-prognosis disease have a cure rate of only 50%, whereas patients with first relapse have only a 25% chance of prolonged survival and potential cure following standard therapy. High-dose chemotherapy (HDC) is being investigated in patients with GCTs to improve the results of salvage treatment and in first-line setting for poor prognosis disease.

Methods: The authors review the results of the clinical trials that have evaluated the role of HDC in GCT patients. Data were obtained using a computer-assisted MEDLINE search, and meeting abstracts with clinical relevance in this field were hand-searched. Open randomized phase III studies are described and examined.

Results: Several phase II studies have shown a possible benefit for patients with recurrent disease, but the preliminary results of a phase III randomized trial did not demonstrate a survival advantage for HDC after three courses of standard-dose chemotherapy in the salvage therapy of patients in whom first-line treatment has failed. Three prospective, randomized trials are evaluating the role of HDC in a first-line setting.

Conclusions: New HDC strategies are emerging, involving new drugs (eg, paclitaxel), intensive induction regimens, and upfront and/or multiple courses of HDC. The evaluation of mature data of randomized trials will better define the role of HDC in this disease.

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Introduction

Approximately 80% of patients with advanced germ cell tumors (GCTs) are cured with first-line cisplatin-based chemotherapy.^{1,3} Of the 20% to 30% of patients not achieving disease-free status, nearly 25% may be cured with salvage cisplatin plus ifosfamide-based chemotherapy.^{4,7}

In 1997, the International Germ Cell Cancer Collaborative Group (IGCCCG) provided a prognostic classification for patients with advanced GCTs at the time of diagnosis (Table 1).⁸ Patients with poor prognosis GCTs were defined as those with nonseminomatous GCTs with any of the following characteristics: mediastinal primary tumor or nonpulmonary visceral metastases or elevation of beta-human chorionic gonadotropin (β hCG) to $>50,000$ IU/L, α -fetoprotein to $>10,000$ ng/mL, or lactate dehydrogenase (LDH) to >10 times the upper limit of normal. The long-term survival rate in this population following standard-dose chemotherapy (SDC) and surgery, when necessary, is approximately 50%.⁸⁻¹⁰ Therefore, treatment options for patients with GCTs with poor prognosis at diagnosis still need improvement.

Because GCTs are the most chemosensitive solid tumors, the concept of dose intensity has been developed to improve the results of chemotherapy in patients with poor prognosis in the first-line setting and in patients with relapsed or refractory GCTs. In the past few years, high-dose chemotherapy (HDC) has been intensively investigated in patients with GCTs, and a number of prospective randomized clinical trials are ongoing. This review presents the results of the

clinical trials that have improved the outlook of HDC in GCT patients. A discussion of the recent developments in first-line and salvage HDC strategies is also included.

The History of High-Dose Chemotherapy in Patients With Germ Cell Tumors

The use of HDC in the treatment of GCTs began in the mid 1970s as a modality to circumvent drug resistance. The clinical and biological characteristics of candidates for HDC included young age (mainly between 20 and 35 years), good performance status in most of the cases, rare bone marrow involvement, and sensitivity to chemotherapeutic drugs even after recurrence.¹¹

Initially, HDC consisted of high-dose cyclophosphamide or etoposide or both.¹²⁻¹⁴ In the early 1980s, after introducing cisplatin, HDC regimens combined cisplatin with cyclophosphamide, etoposide, or melphalan and were supported by autologous bone marrow transplantation (ABMT).¹⁵⁻¹⁸ However, a large randomized trial demonstrated that doubling the dose of cisplatin did not improve the survival rate.¹⁹ Moreover, evidence that carboplatin was also active in GCTs and also more easily dose escalated than cis-

Table 1. — Prognostic Classification by the International Germ Cell Cancer Collaborative Group for First-Line Treatment of Germ Cell Tumors

Prognosis	Nonseminoma	Seminoma
Good	Testis/retroperitoneal primary No nonpulmonary visceral metastases AFP <1000 ng/mL hCG <5000 IU/L LDH $<1.5 \times$ ULN	Any primary site No nonpulmonary visceral metastases Normal AFP Any hCG Any LDH
Intermediate	Testis/retroperitoneal primary No nonpulmonary visceral metastases AFP ≥ 1000 and $\leq 10,000$ ng/mL or hCG ≥ 5000 and $\leq 50,000$ IU/L or LDH $\geq 1.5 \times$ ULN and $\leq 10 \times$ ULN	Any primary site Nonpulmonary visceral metastases Normal AFP Any hCG Any LDH
Poor	Mediastinal primary or Nonpulmonary visceral metastases or AFP $>10,000$ ng/mL or hCG $>50,000$ IU/L or LDH $>10 \times$ ULN	No patients classified as poor prognosis

AFP = α -fetoprotein
hCG = human chorionic gonadotropin
LDH = lactate dehydrogenase
ULN = upper limit of normal

Data from the International Germ Cell Cancer Collaborative Group.⁸

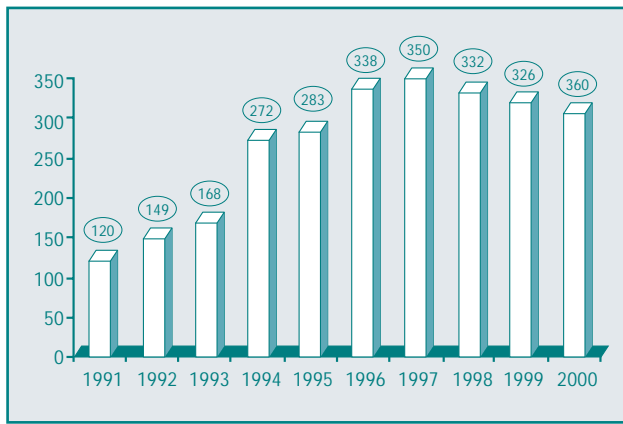


Fig 1. — Number of patients with germ cell tumors treated with high-dose chemotherapy in Europe during 1991-2000. Data from the European Group for Blood and Marrow Transplantation Solid Tumors Registry.

platin, due mainly to its primary toxicity of myelosuppression with minor nephrotoxicity and neurotoxicity, led to the substitution of carboplatin for cisplatin in HDC regimens.²⁰⁻²²

In 1989, a phase I-II study investigated the high-dose combination of carboplatin and etoposide, supported by ABMT.²³ In the early 1990s, phase I trials added either high-dose cyclophosphamide or ifosfamide.²⁴⁻²⁹ Thus, these HDC regimens were initially studied within phase II trials as third-line or subsequent therapy. Later, due to better patient selection and improved supportive care, patients underwent transplantation earlier (ie, at initial relapse or as late intensification of first-line therapy for poor prognosis disease).³⁰⁻³³ Moreover, hematopoietic support improved with the use of peripheral blood stem cells (PBSCs) replacing ABMT³⁴ and the addition of hematopoietic growth factor such as GM-CSF and G-CSF.^{35,36} The number of patients with GCTs receiving HDC in Europe during the last decade (1991-2000) increased, but in the last few years a plateau emerged with 300-350 cases treated per year (Fig 1).³⁷ The toxic death rate progressively declined to 3% to 4% so that now HDC can be considered a relatively safe procedure.³⁷ Moreover, HDC regimens that include etoposide have been associated with a low risk of secondary acute myeloid leukemias, and a recent risk-benefit analysis clearly supports the use of these regimens.³⁸ The role of HDC is currently being investigated as salvage treatment and in a first-line setting for poor prognosis disease.

First-Line High-Dose Chemotherapy

Nearly 50% of patients with poor prognosis GCTs, in accordance with the IGCCCG classification, achieve long-term remissions after first-line SDC.^{8,9,39} Furthermore, a recent analysis identified subsets of GCT

patients with a different outcome among the poor prognosis group. In particular, the analysis suggested that the presence of additional lung metastases in patients with a primary mediastinal site significantly worsened the prognosis, and it demonstrated that the presence of visceral metastases is more important in the hierarchy of prognostic factors for survival than the mediastinal primary site.⁴⁰ If this finding is validated, new treatment modalities (eg. HDC, use of new active drugs) might be evaluated in more selected subgroups among poor prognosis GCT patients.

Early studies with first-line HDC in poor prognosis GCT patients showed a significant improvement in event-free and overall survival compared with historical controls of previous studies of SDC.^{41,42} Two recent phase II studies investigated schedules that included one or more cycles of HDC as intensification after one or more courses of induction SDC in patients with poor prognosis GCTs (IGCCCG classification).^{43,44} Bokemeyer et al⁴³ employed one cycle of standard-dose etoposide, ifosfamide, and cisplatin (VIP) followed by 3 to 4 courses of high-dose VIP supported by PBSCs. The 2-year survival rate was 70%. Moreover, of 22 patients with brain metastases at the time of initial diagnosis, 17 (77%) remained continuously relapse-free with a median follow-up of 23 months.⁴⁵ Decatris and colleagues⁴⁴ administered three or four courses of cisplatin, etoposide, and bleomycin (PEB) followed by HDC carboplatin, etoposide, and cyclophosphamide (CARBOPEC) with PBSC support; 12 (60%) of 20 patients remained continuously disease-free with a median follow-up of 27 months. Recently, Hartmann and colleagues⁴⁶ presented the results of first-line HDC consisting of one course of VIP followed by three courses of high-dose VIP (sequential high-dose VIP chemotherapy) supported by PBSCs in 28 patients with primary nonseminomatous mediastinal GCT. The 2-year progression-free and overall survival rates were 54% and 64%, respectively. In the largest analysis of primary mediastinal GCT patients receiving first-line, cisplatin-based SDC, the 2-year progression-free and overall survival rates were 47% and 55%, respectively.⁴⁷ This represents approximately a 10% improvement in survival in mediastinal GCT patients treated with first-line HDC compared with historical controls.

A matched-pair analysis including 292 poor prognosis GCT patients compared sequential high-dose VIP chemotherapy with cisplatin-based SDC. The estimated 2-year disease-free survival rate was 75% for the HDC group and 59% for the SDC group ($P=.0056$). The estimated 2-year overall survival rate was 82% and 71%, respectively ($P=.0184$). The results showed significant 16% and 11% improvements in the 2-year disease-free and overall survival rates for patients treated with HDC

Table 2. — First-Line High-Dose Chemotherapy in Patients With Germ Cell Tumor: Summary of Ongoing Phase III Randomized Trials

	Group	Patient Selection	Standard Arm	High-Dose Arm	Accrual
United States	SWOG ECOG CALGB	Poor and intermediate prognosis	4 PEB	2 PEB + 2 CARBOPEC	210 of 280
Europe	EORTC GUG German TCSG Spanish GCCSG	Poor prognosis	4 PEB	1 VIP + 3 HD VIP	57 of 222
Italy	NCI Milan	Poor prognosis	4 PEB	2 PEB + 1 HDS	47 of 100

PEB = cisplatin, etoposide, and bleomycin
 CARBOPEC = carboplatin, etoposide, and cyclophosphamide
 VIP = etoposide, ifosfamide, and cisplatin
 HDS = high-dose sequential chemotherapy

compared with patients who received SDC. Despite the limitations of a matched-pair analysis, the results suggest that first-line HDC may induce a significant prolongation of disease-free and overall survival in comparison with SDC.⁴⁸ In a phase III randomized study published as an extended abstract only, four courses of a four-drug regimen consisting of cisplatin, etoposide, vinblastine, and bleomycin (SDC arm) were compared to three courses of the same regimen followed by HDC with cisplatin, etoposide, and cyclophosphamide and autologous stem cell rescue (HDC arm). No advantage for the HDC arm was observed, but some possible biases should be considered: Only 114 patients have been randomized; the four-drug regimen used cannot be considered a true conventional treatment; the dose-intensity in the HDC arm was low; and approximately 30% of the patients initially randomized to the HDC arm did not receive HDC because of early death or toxicity during the standard dose induction phase.⁴⁹

Three phase III randomized studies are ongoing in patients presenting with poor prognosis disease (Table 2). A US Intergroup phase III randomized trial of the Southwest Oncology Group, the Eastern Cooperative Oncology Group, and the Cancer and Leukemia Group B is comparing four courses of PEB with two courses of PEB followed by two courses of HDC with CARBOPEC supported by hematopoietic stem cells. In April 1999, the European Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, in cooperation with the German Testicular Cancer Study Group and the Spanish Germ Cell Cancer Study Group opened a phase III randomized study comparing four courses of PEB with one course of standard-dose VIP followed by three courses of high-dose VIP and hematopoietic stem cell rescue. In December 1996, a phase III randomized study supported by the National Cancer Institute of Milan comparing four courses of PEB with two courses of PEB followed by high-dose sequential (HDS) chemotherapy consisting of one course of high-dose

cyclophosphamide, two cycles of a super-PEB (containing high-dose etoposide), and one final course of high-dose carboplatin was launched. All courses of high-dose therapy are supported by hematopoietic stem cell infusion. Preliminary results have been reported, noting that no toxic deaths have occurred among the 28 evaluable patients enrolled between December 1996 and April 2001. Complete responses rates were 46% (7 of 15 patients) in the SDC arm and 61% (8 of 13 patients) in the HDS arm. Seven of 15 patients in the SDC arm and 8 of 13 patients in the HDS arm remain continuously disease-free at a median follow-up of 18 months. This study is ongoing to verify whether the preliminary trend in favor of HDS will be confirmed.⁵⁰ Final results of the three above-mentioned randomized trials are needed to define the role of HDC as part of initial management of poor prognosis GCT patients.

Salvage High-Dose Chemotherapy

The optimal salvage treatment for patients with relapsed or refractory GCT is controversial.^{51,52} In earlier series with HDC supported by ABMT in previously

Table 3. — Prognostic Index for Patients With Germ Cell Tumors Receiving High-Dose Chemotherapy (HDC) as Salvage Therapy

Independent Adverse Prognostic Variables for DFS After HDC	Score
Progressive disease before HDC	1
Mediastinal primary site	1
Refractory disease before HDC*	1
Absolute refractory disease before HDC**	2
hCG before HDC >1000 IU/L	2

* Refractory disease was considered when at least stable disease or better was achieved, but there was evidence of tumor progression within 4 weeks of the last cisplatin-based chemotherapy before HDC.
 ** Absolute refractory disease was considered when not even stable disease was achieved, despite cisplatin-based chemotherapy before HDC.

incurable, heavily pretreated and multiple-relapsed patients, 15% to 25% achieved durable complete remissions.^{21,25,28,53-55} These modest results have been attributed to the combination of platinum-refractory disease, poor performance status, and limited tolerance of HDC.^{56,57} Thus, investigators have selected patients with relapse earlier in their clinical course to undergo HDC, and this has resulted in improved outcomes.⁵⁸⁻⁶¹

In 1996, a multivariate analysis of 283 patients produced a prognostic index for GCT patients receiving salvage HDC.⁶² Patients were stratified into good-, intermediate-, and poor-risk categories on the basis of a cumulative score scale (Table 3). One point was given for the presence of each of the following conditions: nonseminomatous mediastinal primary site, progressive disease, or cisplatin-refractory disease before HDC. Two points were given for absolute refractory disease and for serum levels of β hCG >1,000 IU/L. Patients in the good-risk category with a cumulative score of 0 had a significantly higher probability for overall survival rate at 2 years (61%) compared with the patients in the intermediate-risk category with a cumulative score of 1 to 2 (34%) or with patients in the poor-risk category with a cumulative score of greater than 2 (8%) (Table 4). Within each prognostic category, the different HDC regimens or higher dosages of carboplatin or etoposide did not have a significant influence on treatment outcome. Other variables, such as the maximal response durations to conventional-dose treatment, number of salvage regimens used, or minimal marker elevations before HDC, were also found to be of no prognostic significance for disease-free survival.⁶² Three further retrospective analyses and one phase II study have recently validated these results according to the prognostic risk groups.⁶³⁻⁶⁶ In the good-risk category, HDC resulted in a high overall survival rate, whereas in the poor-risk group, HDC was rarely associated with prolonged survival. Therefore, other treatment options should be investigated in this patient category. The prognostic index might be helpful for designing clinical trials with salvage HDC for selected groups of GCT patients.

The optimal strategy for the minority of patients with pure seminoma who require salvage chemotherapy is unknown. Salvage therapy with vinblastine, ifos-

Table 4. — Treatment Outcome After High-Dose Chemotherapy According to Prognostic Categories

Prognostic Categories	2-Year Disease-Free Survival	2-Year Overall Survival
Good (score 0)	51%	61%
Intermediate (score 1 and 2)	27%	34%
Poor (score >2)	5%	8%

Data from Beyer et al.⁶²

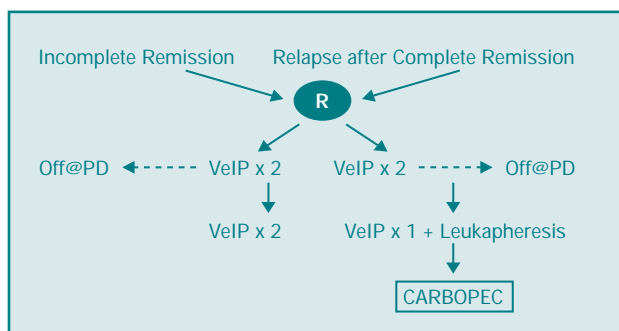


Fig 2. — Trial design of the EBMT Randomized Study (IT-94). Off@PD = off study if progressive disease.

famide, and cisplatin (VeIP) resulted in more long-term survivors in seminomatous GCT patients (nearly 50%) than in nonseminomatous GCT patients (nearly 25%) in two different series.^{4,67} Response rates and long-term survival did not differ significantly whether or not HDC was used as first or subsequent salvage treatment.^{68,69} The role of salvage HDC in patients with extragonadal nonseminomatous GCTs, in particular with primary mediastinal site, is controversial.^{70,71} To clarify this issue, the European Group for Blood and Marrow Transplantation (EBMT) is performing a retrospective analysis of the role of HDC in extragonadal GCT patients. Moreover, a recent matched-pair analysis has demonstrated that there may be a survival advantage of nearly 10% when comparing salvage HDC to SDC in relapsed patients.⁷²

The first results of the prospective, randomized EBMT IT-94 study were presented at the 2002 annual meeting of the American Society of Clinical Oncology.⁷³ In this trial, 280 advanced gonadal or extragonadal patients, relapsing after previous complete remission or achieving an incomplete remission after first-line cisplatin-based chemotherapy, were randomized to four courses of SDC with VIP or VeIP vs three courses of these regimes followed by a single dose of HDC with CARBOPEC (Fig 2). Toxic deaths occurred in 2 patients in the SDC arm and in 9 patients in the HDC arm. Overall complete and partial response marker negative rates were 41% and 17% in the SDC arm and 44% and 18% in the HDC arm, respectively. Median follow-up was in excess of 3 years. The 1-year event-free survival rates were 48% and 52%, respectively ($P=NS$). Three-year overall survival rates were 53% in both arms. Thus, the trial showed that a single cycle of HDC did not affect outcomes. Some limitations should be considered: patient selection included those who relapsed after complete remission or achieved an incomplete remission after first-line chemotherapy; results are preliminary and longer follow-up is required; and strategies in terms of postchemotherapy residual tumor resection and treatment at progression or relapse were not defined.

Currently, several new treatment options are emerging as salvage HDC in GCT patients. In Germany, a randomized phase III trial is comparing one cycle of VIP plus three courses of HDC with carboplatin and etoposide to three courses of VIP plus one course of CARBOPEC in patients with relapsed or refractory GCT. At the time of writing, 160 patients out of the 230 required are being randomized. The repetitive administration of HDC courses, an intensive chemotherapy for remission induction before HDC, the incorporation of paclitaxel in the induction chemotherapy and/or in the HDC schedule, and upfront multiple HDC courses are the most investigated strategies. The results of the pivotal studies exploring these issues are briefly described in Table 5. Two trials determined the efficacy of two repeated courses of HDC, after conventional-drug induction chemotherapy.^{64,74} Bhatia et al⁶⁴ described a salvage HDC regimen consisting of one to two courses of SDC followed by two courses of high-dose carboplatin and etoposide supported by PBSCs. Rodenhuis and colleagues⁷⁴ performed two courses of high-dose carboplatin, cyclophosphamide, and thiotepa with PBSC support following two cycles of induction chemotherapy. In order to increase dose intensity, Motzer et al⁷⁵ scheduled a salvage therapy regimen consisting of two courses of paclitaxel plus ifosfamide given 14 days apart followed by three courses of high-

dose carboplatin and etoposide with PBSC support. Rick et al⁶⁵ designed a schedule of induction SDC with three courses of paclitaxel, ifosfamide, and cisplatin followed by a single course of high-dose carboplatin, etoposide, and thiotepa supported by PBSCs. Shamash and colleagues⁷⁶ evaluated a regimen consisting of high-dose carboplatin, etoposide, cyclophosphamide, and paclitaxel with PBSC support in patients previously treated with three courses of an induction chemotherapy with paclitaxel, cisplatin, and ifosfamide. In this study, deferring HDC to consolidate third-line rather than second-line therapy did not appear to influence survival. Lotz et al⁷⁷ evaluated the activity of the Taxif protocol, a new regimen consisting of two cycles of epirubicin plus paclitaxel given 14 days apart followed by one course of high-dose cyclophosphamide and thiotepa and then two courses of high-dose carboplatin, etoposide, and thiotepa.

Four studies have investigated the use of salvage therapy consisting of two cycles of HDC for induction failures.^{64,78-80} Margolin et al⁷⁸ evaluated the activity of two courses of high-dose carboplatin, etoposide, and ifosfamide. Ayash and colleagues⁷⁹ reported the results of a phase II study in patients treated for primary refractory disease or GCT in the first, second or third relapse administering two courses of high-dose carboplatin and

Table 5. — Salvage High-Dose Chemotherapy (HDC) in Germ Cell Tumor Patients: Novel Approaches

Approach	Study	No. of Patients	Treatment (mg/m ² q 3 wk)	Relapse-Free Rate at Median Follow-up
Conventional induction chemotherapy followed by 2 courses of HDC	Bhatia et al ⁶⁴ (first relapse)	65	VeIP (12/6000/100) × 1 or 2, JV (2100/2250) × 2	57% at 39 months
	Rodenhuis et al ⁷⁴ (first relapse)	35	VI (300/4000) × 1, JV (AUC 10/1500) × 1, JThC (AUC 20/480/6000) × 2	54% at 37 months
Intensive induction chemotherapy containing paclitaxel followed by 1 to 3 courses of HDC	Motzer et al ⁷⁵ (first relapse)	37	IT (6000/200) q 2 wk × 2, HD-JV (AUC 12-32/1200) × 3	41% at 30 months
	Rick et al ⁶⁵ (relapsed or refractory)	62	TIP (175/6000/100) × 3, HD-JVTh (1500/2400/150-250) × 1	34% at 36 months
	Shamash et al ⁷⁶ (relapsed or refractory)	13	TIP (210/4500/100) × 3, HD-JVC + T (AUC 20/1500/6000 + 210) × 1	46% at 40 months
	Lotz et al ⁷⁷ (relapsed or refractory)	42	ET (100/250) × 2, HD-CTh (3000/400) × 1, HD-JVI (AUC 20/1500/10 g) × 2	24% at 6 months
Upfront multiple HDC	Margolin et al ⁷⁸ (relapsed or refractory)	20	JVI (1200/60 mg × Kg/6000) × 1, JVI (1200/60 mg × Kg/9000) × 1	45% at 45 months
	Ayash et al ⁷⁹ (relapsed or refractory)	29	JV (1500-2100/1200-2250) × 2	28% at 60 months
	Doroshov et al ⁸⁰ (first relapse)	29	HD-TJV (425/AUC 21/60mg × Kg) × 1, HD-TJI (425/AUC 21/9000)	41% at 42 months
C = cyclophosphamide E = epirubicin I = ifosfamide J = carboplatin P = cisplatin T = paclitaxel Th = thiotepa V = etoposide Ve = vinblastine AUC = area under the curve				

etoposide with ABMT support. Doroshow and colleagues⁸⁰ evaluated a regimen consisting of one cycle of high-dose carboplatin, etoposide, and paclitaxel, followed by one cycle of high-dose carboplatin, ifosfamide, and paclitaxel in GCT patients with first relapse.

It appears clear that one cycle of HDC is ineffective, and studies should include the tandem approach. On the basis of the results of the new HDC approaches in patients with relapsed GCT, the Department of Oncology and Hematology in Ravenna, Italy, plans to undertake a new study of high-dose dense chemotherapy (HDC with reduced intercycle intervals) with paclitaxel, carboplatin, and ifosfamide consisting of a stem-cell mobilizing course, followed by two courses of HDC.

Discussion and Conclusions

In recent years, HDC has become a safer treatment due to better patient selection, improved supportive care, and the use of PBSCs and hematopoietic growth factors resulting in more rapid hematopoietic recovery than ABMT.³⁴⁻³⁶ In the future, the development of new and more effective mobilizing regimens, the use of ex vivo stem-cell expansion, and the potential of cytoprotectors might further improve the safety of the procedure and the quality of life of GCT patients undergoing HDC.^{81,82} While HDC remains more expensive and toxic than SDC, these differences are justified if concomitant increases in the cure rate are demonstrated.^{83,84}

The first results of the EBMT IT-94 study show that the addition of an HDC course after three cycles of second-line chemotherapy does not add any benefit in terms of survival for patients with relapse following standard therapy or for those achieving only an incomplete response to standard therapy.⁷³ The late-intensification HDC strategy is based on the assumption that a final course of chemotherapy with higher doses may eradicate residual disease. In solid tumors, late-intensification HDC has been variously investigated with interesting results derived from phase II studies but with no significant advantages for HDC demonstrated in randomized studies so far. The EBMT IT-94 study was planned in early 1990, and the late-intensification strategy was applied. In recent studies, HDC regimens have been applied earlier in the treatment of chemosensitive disease. Since minimal residual disease is not considered chemosensitive, complete resection of all residual masses is recommended. Complete residual tumor resection after salvage HDC has resulted in good treatment outcomes in the main studies.^{31,59,64} New strategies based on administration schedules or new drugs are warranted when complete surgical resection of postchemotherapy residual masses is not feasible.

Thus, early HDC can be used as a platform on which to add novel therapies aimed at treating residual tumor. Although clinicians await more effective biologically based treatments, few studies have been reported regarding the expression of epidermal growth factor receptor, *HER2/neu*, and c-KIT in GCTs; early results are controversial.⁸⁵⁻⁸⁹

The delineation of prognostic factors associated with a high probability of survival after HDC will contribute to the selection of a subgroup of patients who are more likely to derive an advantage from HDC.⁹² Moreover, new HDC regimens, including drugs (eg, paclitaxel) that show potential activity in GCTs, need to be established.^{90,92} Finally, a recent report showed that [¹⁸F]fluorodeoxyglucose positron emission tomography imaging can be used to assess response to HDC in relapsed GCT patients early in the course of treatment and may help to identify patients most likely to achieve a favorable response to subsequent HDC.⁹³ The planning of new and more intensive treatments is justified for chemosensitive patients, but the question remains whether this subgroup is larger than the group achieving long-term disease-free survival after SDC. Mature data resulting from prospective randomized studies are needed to better define the role of HDC in GCTs.

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