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The status of high-dose chemotherapy with hematopoietic stem cell transplantation in patients with germ cell tumor

UGO DE GIORGI,* GIOVANNI ROSTI,*° GIORGIO PAPIANI,* MAURIZIO MARANGOLO*

*Department of Oncology and Hematology, Santa Maria delle Croci Hospital, Ravenna, Italy; °European Group for Blood and Marrow Transplantation (EBMT) Solid Tumors Working Party

Correspondence: Dr. Ugo De Giorgi, MD, Department of Oncology and Hematology, Santa Maria delle Croci Hospital, viale Randi 5, 48100 Ravenna, Italy. Phone: international +39.0544 285247. Fax: international +39.0544.285330. E-mail: ugo.degiorgi@ra.nettuno.it

Background and Objectives. Germ cell tumors (GCTs) are very chemosensitive cancers, in which high-dose chemotherapy (HDCT) has been investigated as salvage therapy or as first-line treatment in poor prognosis patients. This paper presents an update of available information in order to define the status of HDCT in GCT patients.

Information sources. The authors have been working in this field, contributing to international clinical trials and to peer-reviewed journals with original papers. The material examined in this review includes articles published in journals covered by MedLine®, reviews from journals with high impact factor, and unpublished data from the European Group for Blood and Marrow Transplantation (EBMT) registry.

State of the Art and Perspectives. The delineation of prognostic factors associated with a poor probability of survival after HDCT contributed to the selection of patients who are likely to get an advantage from HDCT and those who should be spared from dose-intensive treatment. HDCT as first-line therapy for poor prognosis GCT (IGCCCG classification), and in a salvage setting in good risk GCT (prognostic index from Beyer *et al.*[77]), has been associated with a very high rate of complete remissions and long-term disease-free survivors. However, it is important to wait for the results of ongoing randomized trials for the validation of these findings. Other strategies are required for patients with refractory GCTs. Several new treatment options are currently emerging for this subset of patients.

Key words: germ cell tumor, high-dose chemotherapy, hematopoietic stem cell transplantation, review.

Germ cell tumors (GCTs) are rare neoplasms, accounting for only 1% of male cancers, but are the most common solid tumor type in men between the ages of 20 and 35 years.[1] Thanks to the development of effective cisplatin-based chemotherapy, disseminated GCT has become a model of a highly curable malignant disease.[2,3] Out of the 20-30% of patients who do not achieve a durable remission after first-line cisplatin-based chemotherapy, nearly 25% will be cured with a standard salvage chemotherapy regimen.[4] In the late 1970s and early 1980s, the success of high-dose chemotherapy (HDCT) in other very chemosensitive neoplasms, such as lymphomas, induced some investigators to employ HDCT in relapsing or resistant GCTs. The first experiences with HDCT supported by autologous bone marrow transplantation (ABMT) used regimens containing high-dose cyclophosphamide, etoposide, both of them, or melphalan plus etoposide .[5-9] After introducing cisplatin in combination chemotherapy regimens, a substantial improvement of the cure rate for advanced disease was achieved; it was followed by the initial evidence of dose-response and dose-survival advantage for high- versus low-dose cisplatin.[10] Although in a subsequent study a further dose escalation of cisplatin did not translate into an improved survival rate,[11] these findings induced some investigators to include cisplatin in some salvage HDCT regimen trials in refractory GCT,[12-15] and, successively, in the first-line treatment of poor-risk disease.[16,17] Because of its nephrotoxicity, cisplatin is not suitable for very HDCT;[18] moreover the observation that carboplatin is active in GCT with a more favorable spectrum of side effects than cisplatin, induced some investigators to include carboplatin in HDCT regimens.[19] In 1989, Nichols *et al.* reported the results of the first phase I/II study of high-dose combination chemothera-

py including carboplatin at increasing doses, and a fixed high-dose of etoposide.[20] Following this trial, several phase I studies investigated HDCT combination regimens with either carboplatin, etoposide and cyclophosphamide,[21-23] or carboplatin, etoposide and ifosfamide.[24-26] In the 1990s, these HDCT regimens with the support of peripheral blood stem cells (PBSCs) were included in clinical trials for patients with GCT either in salvage therapy or in first-line treatment of poor-risk disease. In the last years, HDCT has become a therapeutic option with more than 300 GCT patients being treated in Europe each year.[27]

This paper will present an overview of the available data, and try to define the status and the perspectives of HDCT in patients with GCT.

Toxicity

All HDCT regimens employed for GCT patients have significant acute and late toxicities. The side effects related to HDCT regimens are directly correlated with the three classes of drugs employed, platinum complexes (cisplatin or carboplatin), epipodophyllotoxins (etoposide), and oxazaphosphorines (cyclophosphamide or ifosfamide), and also their application schedule.

Mortality

The *European Group for Blood and Marrow Transplantation* (EBMT) Solid Tumors Registry has recently reported an update of the data concerning the mortality rate related to GCT patients treated in Europe in the period 1990-1999.[28] The rate of toxic death, defined as any death occurring within 100 days from grafting and not directly related to the disease itself, declined progressively from 8% in 1990 to 3% in 1999 (between 1990 to 1999, less than 5% altogether) (Figure 1).[28] The toxic death rate of 3% is not higher than that reported for major conventional-dose regimens.[2]

An unpublished analysis of the EBMT Solid Tumors Registry, related to over 1,400 GCT patients treated with HDCT, revealed that the main risk factor for toxic death is a poor performance status before the treatment, whereas no statistically significant role was found regarding the type of support with either ABMT or PBSC.

Hematologic toxicity

Severe leukocytopenia, thrombocytopenia and anemia are major causes of treatment-related complications following HDCT with autologous stem cell support, and are directly related to the time required for hematologic reconstitution.[29] PBSC support plus granulocyte colony-stimulating factor (G-CSF) resulted in a significantly shorter

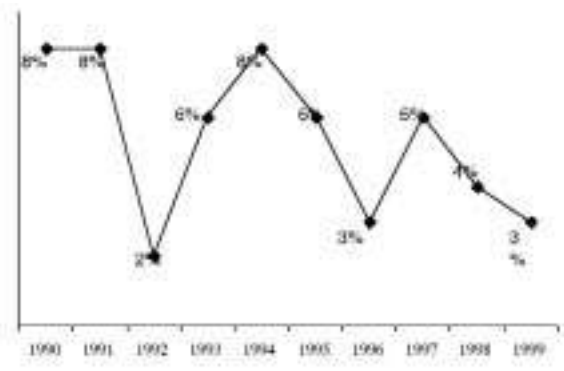

Figure 1. EBMT Registry: total toxic deaths in germ cell tumors in Europe (1990-1999).

time for hematologic reconstitution after HDCT for GCT than did ABMT plus G-CSF.[30] A rapid hematopoietic engraftment, in a median of 9 to 11 days after HDCT for GCT, can be achieved by a PBSC dose greater than 2.5×10^6 $CD34^+$ cells/kg,[31] even if the optimal cell dose for every PBSC transplantation is $>8\times10^6$ $CD34^+$ cells/kg.[32] Sustained hematopoietic reconstitution can be obtained by a PBSC product collected by a single leukapheresis even in heavily pretreated GCT patients.[31,33] GCT cells can be detected in 28% to 50% of PBSC harvests, but whether the presence of contaminating tumor cells in PBSC products reinfused to patients with GCT affect long-term outcome is still controversial.[34,35]

Non-hematologic toxicity

HDCT regimens used for the treatment of patients with GCT induce significant side effects in addition to myelosuppression. Severe acute organ failure is uncommon, although it may be life-threatening.[36] Veno-occlusive disease of the liver has been rarely reported with HDCT regimens for GCTs.[37,38] Acute toxicities frequently include nausea, vomiting, diarrhea, fatigue, and mucositis.[36] All HDCT regimens are cisplatin or carboplatin-based, and thus may be associated with long-lasting or irreversible sensory peripheral neuropathy, ototoxicity, and renal function impairment.[39-42] High-dose etoposide may induce hepatic injury, besides mucositis.[43,44] The administration of oxazaphosphorines (cyclophosphamide or ifosfamide) as part of a HDCT regimen may be associated with mild and transient hemorrhagic cystitis, despite concomitant administration of mesna.[45] An excessive renal toxicity was reported in two series with high doses of ifosfamide administered concurrent-

ly with carboplatin and etoposide.[46,47] Other studies have included ifosfamide in HDCT regimens without severe renal toxicity.[24-26,37,48] Such variations could be due to patient selection, to the application schedule as well as to the definitions of renal dysfunction that vary widely between studies.[49] A pruritic maculopapular rash was observed in nearly 20-25% of GCT patients usually starting on the last day of HDCT.[50-51] Other chronic toxicities include infertility (nearly 100% of patients), chronic fatigue syndrome, and neuropsychological sequelae.[52-54]

Second tumors

Apart from a recognized association between primary mediastinal GCT and the development of hematologic malignancies,[55-57] the risk of developing second non-germinal malignant neoplasms after treatment is well-known and related both to radiotherapy and to cisplatin-based chemotherapy.[58-60] Previous treatments for testicular cancer are associated with an increased risk of leukemia, with evidence for dose-incidence relationships for both radiotherapy and chemotherapy.[60] An elevated risk of gastrointestinal tumors is associated mainly with irradiation of the para-aortic lymph nodes in seminoma GCT.[58,61] A recent retrospective study reported an incremental occurrence of skin malignancies in extragonadal GCT patients treated with chemotherapy.[59] Moreover, chemotherapy, when compared to radiotherapy or surgery alone, seems to decrease the risk of a controlateral testicular cancer, likely expression of an eradicating effect of chemotherapy on carcinoma *in situ* or subclinical cancer.[61] Studies investigating the risk of secondary leukemia following standard-dose regimens described an incidence of 0.4% to 0.6% at a median follow-up of 5 years after etoposide-containing chemotherapy,[62-66] whereas no increase in risk was observed following conventional chemotherapy regimens without etoposide.[61,63,67] The cumulative incidence of secondary leukemia in patients treated with etoposide at cumulative doses higher than 2 g/m^2 was approximately 2% at a median follow-up of 5 years.[62,64,68,69] Eleven of the twelve reported cases of secondary leukemias were acute myeloid leukemia.[62,64,68,69] HDCT regimens including etoposide are associated with an acceptably low number of therapy-related leukemias, and the risk-benefit analysis clearly favors the use of HDCT.[70]

Indications and outcome

Over the last years, HDCT has been increasingly investigated as salvage therapy for patients with refractory or relapsed GCT and as first-line treatment for patients with poor prognosis GCT. The delineation of prognostic factors associated with a poor probability of survival after HDCT contributed to the selection of patients who are likely to take advantage from HDCT and those who should be spared from such dose-intensive treatment.

Salvage treatment

The activity of HDCT in the salvage setting of GCT patients has been well established in the past years. The first studies with HDCT supported by ABMT in heavily pretreated GCT patients showed a long-term survival rate of 15% to 20%.[20,24,37,71] In 1996, a comprehensive literature review of HDCT in the salvage treatment of GCT involved 436 patients, 96 (22%) of whom were continuously disease-free.[36] The modest results obtained with conventional-dose salvage treatments, associated with the better patient selection for HDCT and improved supportive care, induced the investigators to advance HDCT from third-line or subsequent therapy to treatment of patients at initial relapse.[72-74] In the early 1990s, some authors analyzed the prognostic factors for long-term remission following HDCT,[75,76] and in 1996, a large multivariate analysis from four institutions produced a prognostic index for GCT patients receiving HDCT as salvage therapy.[77] Independent adverse variables for failure-free survival after HDCT were identified to be non-seminomatous mediastinal primary site, progressive disease before HDCT, refractory or absolute refractory disease to standard-dose cisplatin, and high serum levels of β-human chorionic gonadotropin (β-HCG). These prognostic factors were used to stratify patients into good, intermediate, and poor risk categories; patients in the good risk category had a significantly higher probability of overall survival at 2 years (61%), than those in either the intermediate risk (34%) or poor risk (8%) group.[77] Results of two retrospective analyses and one phase II study have recently shown similar overall survival rates according to the prognostic risk categories.[78-80] It rarely happens that patients in the poor risk category can be cured with HDCT, but impressive results can be achieved with HDCT in patients in the good risk group. This validated prognostic index might represent a useful tool for designing new trials with salvage HDCT for selected GCT patients in the salvage setting.

Conventional salvage chemotherapy appears to produce an inferior survival rate in extragonadal non-seminomatous GCT, in particular those in which the primary site is mediastinal rather than testicular.[81] In this subset of patients, overall survival rates after HDCT did not appear to differ from

the results of standard-dose salvage chemotherapy.[82] Thus, the role of HDCT as salvage therapy for patients with extragonadal GCT, in particular with primary mediastinal disease, is controversial. An analysis of the EBMT registry on HDCT in extragonadal GCT patients is underway to provide reliable information on this subject.

Current approaches to the improvement of the results of salvage HDCT in GCT patients include: intensive conventional-dose chemotherapy for remission induction before HDCT, the introduction of new drugs (mainly paclitaxel) which are not cross-resistant with those conventionally used in HDCT schedules, the repetitive administration of HDCT cycles, and up-front multiple HDCT.

The Norton-Simon model predicts that multiple, rapidly recycled applications of chemotherapy are more likely to eradicate residual cancer cells than either single applications or multiple applications with long intervals between cycles.[83] Therefore, in order to increase the dose-intensity of chemotherapy, Motzer *et al.* designed a new 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 given at 14- to 21-day intervals. Out of 37 enrolled patients, 15 (41%) remained alive and relapse-free at a median follow-up of 30 months.[84] Two other recent studies included paclitaxel in the induction regimen for relapsed or refractory GCT patients.[80,85] Rick *et al.* included paclitaxel with ifosfamide and cisplatin in a conventional-dose induction regimen; patients received three courses followed by a single shot of high-dose carboplatin, etoposide and thiotepa supported by PBSC. The event-free survival rate was 32% (20 out of 62 patients) at a median follow-up of 3 years.[80] After three courses of an induction chemotherapy with paclitaxel, cisplatin and ifosfamide, Shamash *et al.* administered an HDCT schedule containing high-dose carboplatin, etoposide, cyclophosphamide and paclitaxel with PBSC support. Only 13 patients were enrolled, and 6 of them (46%) are continuously disease-free at a median follow-up of 40 months.[85]

Two studies determined the efficacy of two repeated courses of HDCT, after two courses of conventional-dose induction chemotherapy, for initial relapse of GCT.[38,86] Rodenhuis *et al.* gave two courses of high-dose carboplatin, cyclophosphamide and thiotepa with PBSC support, achieving an event-free survival rate of 54% (19 out of 35 patients) at a median follow-up of 26 months.[38] Broun *et al.* reported a tandem HDCT schedule (carboplatin and etoposide) supported by ABMT: this produced an event-free survival rate of 52% (13 out of 25 patients) at a median follow-up of 26 months.[86]

Three studies investigated two up-front courses of salvage HDCT.[49,77,87] Bhatia *et al.* scheduled two courses of initial salvage HDCT with high-dose carboplatin and etoposide supported by PBSC. Thirty-seven (57%) out of the 65 enrolled patients resulted continuously disease-free at a median follow-up of 39 months.[77] Ayash *et al.* reported on 29 patients treated for primary refractory GCT or for first, second or third relapse of GCT, with two courses of high-dose carboplatin and etoposide with ABMT support. Eight (28%) patients resulted continuously relapse-free at a median follow-up of 60 months.[87] Margolin *et al.* evaluated the activity of two courses of high-dose carboplatin, etoposide and ifosfamide in 20 relapsed patients. Eight (40%) of them remained continuously disease-free at a median follow-up of 45 months.[49]

Finally, a recent international matched-pair analysis has shown that there might be a survival improvement of nearly 10% when HDCT is compared to standard treatment in relapsing patients.[88]

Based on all these data, there are chances of inducing long-term survival with HDCT in a subgroup of patients. But the question remains whether this subgroup is larger than the one achieving long-term disease-free survival after standard-dose chemotherapy.

In order to clarify the exact role of HDCT in patients with incomplete response or in those relapsing after complete remission, an EBMT randomized study (IT-94) was carried out: it closed in September 2001 (Table 1). This trial compares four courses of VIP (etoposide, ifosfamide, cisplatin) or VeIP (vinblastine, ifosfamide, cispltin) as the standard arm, with three courses of VIP or VeIP followed by a single shot of HDCT with CarboPEC (carboplatin, etoposide, cyclophosphamide) as the experimental arm. Preliminary results will be presented at the American Society of Clinical Oncology Annual Meeting in May 2002.

First-line treatment of poor-prognosis patients

The *International Germ Cell Cancer Collaborative Group* (IGCCCG) provided a prognostic classification for advanced GCT patients, at the time of their diagnosis.[89] Poor-prognosis GCT patients have been defined as those with non-seminomatous GCT and any of the following characteristics: mediastinal

Table 1. Ongoing and unreported randomized studies of standard-dose chemotherapy versus high-dose chemotherapy in germ cell tumors.

Country	*Group*	*Patient selection*	*Standard arm*	*High-dose arm*	*Accrual*
Europe	EBMT STWP	salvage therapy	4 VeIP or VIP	3 VeIP or VIP + CARBOPEC	280/280
USA	SWOG ECOG CALGB	first-line therapy in poor-prognosis patients	4 PEB	2 PEB + 2 CARBOPEC	170/220
Europe	EORTC GUG German TCSG Spanish GCCSG	first-line therapy in poor-prognosis patients	4 PEB	1 VIP + 3 HD VIP	34/222
Italy	NCI Milan	first-line therapy in poor-prognosis patients	4 PEB	2 PEB + 1 HDS	30/100

primary tumor or non-pulmonary visceral metastases or any of β-HCG > 50,000 U/L or α-fetoprotein > 10,000 ng/mL or lactate dehydrogenase (LDH) > 10 × upper limit of normal.[89] The long-term survival rate of such patients after standard-dose chemotherapy and surgery, when necessary, is approximately 50%, and thus the optimum treatment for GCT patients with poor prognosis at diagnosis still needs improvement.[89-91] Furthermore, a recent analysis identified subsets of GCT patients with different outcomes within the poor-prognosis group.[92] If this finding is confirmed in other studies, new treatment strategies might be evaluated in more selected subgroups of the poor-prognosis GCT patients.

The first experiences with HDCT as primary treatment for poor-prognosis GCT were performed at the Memorial Sloan Kettering Cancer Center. Significantly improved overall survival and event-free survival were observed for patients treated with HDCT compared with those treated in prior studies based on standard-dose chemotherapy.[93,94] Two phase II studies have recently determined the efficacy of one or more courses of HDCT as intensification after one or more courses of conventional-dose induction chemotherapy for poor-prognosis GCT patients, as strictly defined by the IGCCCG criteria.[95,96] Bokemeyer *et al.* employed one course of standard-dose VIP followed by 3-4 courses of high-dose VIP supported by PBSCs, obtaining a two-year survival rate of 70% for poor-prognosis patients as defined by the IGCCCG classification.[95] Twenty-two patients with metastatic GCT, including brain metastases at the time of initial diagnosis, were identified within this HDCT study group. Seventeen (77%) patients resulted continuously disease-free at a median follow-up of 23 months.[97] Decatris *et al.* reported the results of a series of twenty GCT patients treated with three or four courses of PEB followed by HDCT (CarboPEC) with PBSC support. Twelve (60%) patients are disease-free at a median follow-up of 27 months.[96]

The only randomized study published so far which used HDCT as consolidation treatment during first-line therapy for advanced metastatic disease, failed to demonstrate an advantage from the high-dose arm.[17] Patients in this study were treated with a four-drug regimen consisting of cisplatin, etoposide, vinblastine, and bleomycin, given for either four courses (standard-dose arm) or for three courses, followed by HDCT with cisplatin, etoposide, and cyclophosphamide (high-dose arm). The results of this trial should, however, be interpreted with care. The study had a number of relevant limitations: the number of randomized patients was rather small (114), the four-drug regimen used cannot be considered a true conventional treatment, the dose-intensity in the high-dose arm was low and approximately 30% of the patients initially randomized to the high-dose arm did not complete HDCT because of early death or toxicity. Indeed, the results of a matched-pair analysis point out that HDCT (high-dose cisplatin, etoposide, and ifosfamide) may induce a significant prolongation of progression-free and overall survival as compared to conventional cisplatin-based chemotherapy.[98]

Patients presenting with poor-prognosis disease at the time of initial diagnosis are still being accrued in three ongoing randomized studies (Table 1). A US Intergroup trial by SWOG (*Southwest Oncology Group*), ECOG (*Eastern Cooperative Oncology Group*), and CALGB (*Cancer and Leukemia Group B*) is comparing four courses of PEB (cisplatin, etoposide, bleomycin) with two courses of PEB followed by two courses of HDCT with CarboPEC. At the time of writing, 170 patients out of the 220 required are being randomized; final results will be available in 2003. Two other randomized trials have recently been activated. A study by the *European Organization for Research and Treatment of Cancer* (EORTC), *Genito-Urinary Tract Cancer Group* (GUG), the *German Testicular Cancer Study Group* (German TCG), and the *Spanish Germ Cell Cancer Study Group* (Spanish GCCG)

is comparing four courses of PEB with one course of standard-dose VIP followed by three courses of high-dose VIP. A study by the *National Cancer Institute* (NCI) of Milan is comparing four courses of PEB with 2 courses of PEB followed by high-dose sequential (HDS) chemotherapy consisting of one course of high-dose cyclophosphamide, one course of a particular schedule of PEB containing high-dose etoposide, and two courses of high-dose carboplatin. Results of the said three randomized trials are required to define the role of HDCT as first-line treatment for poor-prognosis GCT patients.

Perspectives

In the past few years, with advances in the understanding of HDCT for GCTs, it has become possible to select patients better, improving their outcome and quality of life. Developments in the use of cytoprotectors in patients undergoing HDCT might further improve their quality of life. In a recent clinical trial, recombinant human keratinocyte growth factor effectively reduced the duration of grade III-IV oral mucositis after HDCT.[99] The use of amifostine as a chemoprotectant during HDCT in GCT patients showed no unequivocal advantage in protection from treatment-related toxicities.[100,101] The use of PBSCs is associated with faster hematologic recovery than is ABMT, and, furthermore, global costs are lower and cost-effectiveness ratios are better with PBSCs.[102] The costs of using PBSCs have significantly decreased in many countries over the years and the cost of HDCT is approximately three times more expensive than that standard-dose chemotherapy; moreover, most centers are evaluating new strategies to reduce the overall cost of HDCT.[103]

HDCT in first-line therapy in poor-prognosis GCT patients and in the salvage setting in good-risk GCT patients has been associated with a very high rate of complete remissions and long-term disease-free survivors.[77-80,98] The planning of new and more intensive treatments is justified for chemosensitive patients, in whom the ability to achieve cytoreduction by HDCT may prove to be an essential component of a multistep approach together with surgical resection of post-chemotherapy residual masses. However, it is important to complete ongoing randomized trials rapidly in order to validate the hypothesis of improvement in survival in first-line treatment in poor-prognosis patients and/or in the first salvage therapy in incomplete responding or relapsing patients. These ongoing studies are based on the assumption of an at least 20% improvement in overall survival, but this does not exclude that an overall improvement of treatment results in the range of 10-15% (data resulting from available matched-pair analyses) may nevertheless still be very valid in young patients with 50% or only 30% long-term survival. The cost-effectiveness of HDCT depends largely on the magnitude of the difference in survival produced by it and that achieved by standard-dose chemotherapy, and economic analyses will be an important issue in the decision for or against HDCT. Therefore, HDCT for GCT should be still considered an investigational therapy.

Several new treatment options are emerging which raise hope that cisplatin-refractory GCT can be successfully treated. New drugs, such as oxaliplatin, gemcitabine and paclitaxel, showed interesting activity.[104-109] In a recent report, the expression of epidermal growth factor receptor (EGFR) was documented in β-HCG-positive components of GCTs, this being a negative prognostic factor in mixed GCTs; this finding might suggest the utility of specific EGFR inhibitor drugs.[110] However, clinical data are needed to evaluate whether the expression of EGFR in a specific subcomponent of GCTs can be used therapeutically. HER-2/neu resulted only rarely overexpressed or amplified in GCTs, and its potential role in cisplatin-refractory GCT patients is more controversial.[110,111] Non-myeloablative allogeneic transplantation might also represent a new approach in GCT patients;[79] this strategy has so far been used in only three patients and results are not yet available (*Gratwohl A: personal communication*). All-trans-retinoic acid failed as a differentiating agent in two patients with malignant teratoma.[112]

The use of prognostic classifications has led to the performance of studies with HDCT in more selected patient categories,[77,89] but in the near future, using gene-expression profiling with DNA micro-array, a sophisticated genetic classification of GCTs will be attainable by exemplifying how variations in the transcript levels of particular genes relate to mechanisms of drug sensitivity and molecular pharmacology; this may be helpful for designing clinical trials with HDCT for selected subsets of chemosensitive GCT patients.[113-115] Further on, improved understanding of the biology and the genetics of GCTs may lead to new therapeutic targets and approaches.

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