

High dose chemotherapy with stem cell support in the treatment of testicular cancer

Lazar Popovic, Gorana Matovina-Brko, Milica Popovic, Dragana Petrovic, Ana Cvetanovic, Jelena Vukojevic, Darjana Jovanovic

Lazar Popovic, Gorana Matovina-Brko, Milica Popovic, Jelena Vukojevic, Darjana Jovanovic, Medical School, University of Novi Sad, 21000 Novi Sad, Serbia

Lazar Popovic, Gorana Matovina-Brko, Dragana Petrovic, Jelena Vukojevic, Darjana Jovanovic, Department for Medical Oncology, Oncology Institute of Vojvodina, 21204 Sremska Kamenica, Serbia

Milica Popovic, Department for Internal Medicine, Clinical Center of Vojvodina, 21000 Novi Sad, Serbia

Ana Cvetanovic, Department for Oncology, Clinical Center Nis, 18000 Nis, Serbia

Author contributions: Popovic L wrote core of the manuscript, collected the data; Matovina-Brko G, Petrovic D and Vukojevic J collected the data; Popovic M collected the data and tables; Cvetanovic A collected the data, finalized the manuscript writing; Jovanovic D wrote parts of the manuscript.

Conflict-of-interest statement: Authors declare no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Lazar Popovic, MD, PhD, Department for Medical Oncology, Oncology Institute of Vojvodina, Put Dr Goldmana 4, 21204 Sremska Kamenica, Serbia. lazar.popovic@yahoo.com
Telephone: +381-21-4805569

Received: December 31, 2014
Peer-review started: January 1, 2015
First decision: February 7, 2015
Revised: September 18, 2015

Accepted: November 13, 2015
Article in press: November 17, 2015
Published online: December 26, 2015

Abstract

Testicular germ cell cancer (TGCC) is rare form of malignant disease that occurs mostly in young man between age 15 and 40. The worldwide incidence of TGCC is 1.5 per 100000 man with the highest rates in North Europe. After discovery of cisplatin cure rates of TGCC are very favorable between 90%-95% and unlike most solid tumors, cure rate for metastatic TGCC is around 80%. Metastatic TGCC is usually treated with 3-4 cycles of bleomycin, etoposide, cisplatin chemotherapy with or without retroperitoneal surgery and cure rates with this approach are between 41% in poor risk group and 92% in good risk group of patients. Cure rates are lower in relapsed and refractory patients and many of them will die from the disease if not cured with first line chemotherapy. High dose chemotherapy (HDCT) approach was used for the first time during the 1980s. Progress in hematology allowed the possibility to keep autologous haematopoietic stem cells alive *ex-vivo* at very low temperatures and use them to repopulate the bone marrow after sub-lethal dose of intensive myeloablative chemotherapy. Despite the fact that there is no positive randomized study to prove HDCT concept, cure rates in relapsed TGCC are higher after high dose therapy than in historical controls in studies with conventional treatment. Here we review clinical studies in HDCT for TGCC, possibilities of mobilising sufficient number of stem cells and future directions in the treatment of this disease.

Key words: High dose chemotherapy; Germ-cell cancer; Stem cell transplantation; Plerixafor

© The Author(s) 2015. Published by Baishideng Publishing

Group Inc. All rights reserved.

Core tip: High dose chemotherapy with autologous haematopoietic stem cell transplantation is effective option in treating relapsed metastatic germ-cell cancer. We reviewed this topic in regard of clinical studies, optimal mobilising and conditioning regimens, with special review on plerixafor in this indication. We also analysed risk adapted approach in those patients and future directions in field.

Popovic L, Matovina-Brko G, Popovic M, Petrovic D, Cvetanovic A, Vukojevic J, Jovanovic D. High dose chemotherapy with stem cell support in the treatment of testicular cancer. *World J Stem Cells* 2015; 7(11): 1222-1232 Available from: URL: <http://www.wjgnet.com/1948-0210/full/v7/i11/1222.htm> DOI: <http://dx.doi.org/10.4252/wjsc.v7.i11.1222>

INTRODUCTION

Testicular germ cell cancer (TGCC) is a rare form of malignant disease that occurs mostly in young man between age 15 and 40. The worldwide incidence of TGCC is 1.5 per 100000 man with the highest rates in Northern Europe^[1]. One half of all TGCC are seminomas and other half are non-seminomas. The majority of TGCC arise from the gonads while around 5% arise from extragonadal sites in the body's mid-line: retroperitoneum, mediastinum or brain^[2]. After discovery of cisplatin TGCC cure rates have become very favorable ranging between 90%-95% and unlike most solid tumors, cure rate for metastatic TGCC is around 80%^[1,2]. Metastatic TGCC is usually treated with 3-4 cycles of bleomycin, etoposide, cisplatin (BEP) chemotherapy with or without retroperitoneal surgery and cure rates with this approach are between 41% in poor risk group and 92% in favourable risk group of patients^[3] (Table 1). Cure rates are lower in relapsed and refractory patients and many of them will die from the disease if not cured with first line chemotherapy^[3]. High dose chemotherapy (HDCT) approach was first used during the 1980s. Progress in hematology allowed the possibility to keep autologous haematopoietic stem cells alive *ex-vivo* in very low temperatures and using them to repopulate the bone marrow after sub-lethal dose of intensive myeloablative chemotherapy^[4].

RATIONALE FOR HIGH DOSE CHEMOTHERAPY

Resistance to chemotherapy is a major problem in the treatment of patients with malignant diseases. Large number of studies are directed towards finding and overcoming resistance mechanisms. One of the simplest and most logical way is to increase the dose of cytotoxic drugs^[5]. The evidence that higher doses

Table 1 Prognostic criteria for metastatic germ cell tumors^[3]

	Good prognosis group	Intermediate prognosis group	Poor prognosis group
Seminoma	90% of cases 5 yr PFS 82% 5 yr OS 86% All of the following criteria: Any primary site No non-pulmonary visceral metastases Normal AFP Any hCG Any LDH	10% of cases 5 yr PFS 67% 5 yr OS 72% Any of the following criteria: Any primary site Non-pulmonary visceral metastases Normal AFP Any hCG Any LDH	-
Non-seminoma	56% of cases 5 yr PFS 89% 5 yr OS 92% All of the following criteria: Testis/ retroperitoneal primary Non non-pulmonary visceral metastases AFP < 1000 ng/mL hCG < 5000 IU/L (1000 ng/mL) LDH < 1.5 × ULN	28% of cases 5 yr PFS 75% 5 yr OS 80% Testis/ retroperitoneal primary Non non-pulmonary visceral metastases AFP 1000-10000 ng/mL hCG 5000-50000 IU/L (1000 ng/mL) LDH 1.5-10 × ULN	28% of cases 5 yr PFS 75% 5 yr OS 80% Any of the following criteria: Mediastinal primary Non-pulmonary visceral metastases AFP > 10000 ng/mL hCG > 50000 IU/L (1000 ng/mL) LDH > 10 × ULN

AFP: Alpha-fetoprotein; hCG: Human chorionic gonadotrophin; LDH: Lactate dehydrogenase; PFS: Progression free survival; OS: Overall survival.

of cytotoxic drug kill more malignant cells has been well known for decades. Back in 1964, Skipper *et al*^[6] demonstrated that the curve showing the dose dependency of the treatments with cytotoxic drugs is very steep, indicating that even a small increase of the cytotoxic drug dose will kill more malignant cells. Also, this curve for cytotoxic drugs, unlike the curves from other drugs, has no plateau, which means that a constant increase of the dose of cytotoxic drugs leads to a steady increase in numbers of destroyed malignant cells^[6]. During the 1980s, Frei *et al*^[7] showed a dose-dependent killing of malignant cells in AKR and L1210 cell lines. Frei *et al*^[8] demonstrated the same on MCF7 breast cancer cells treated with alkylating agents BCNU, melphalan and nitrogen mustard. However, it was not possible to administer the 5 to 10-fold higher dose of chemotherapy *in vivo* due to the high toxicity and virtually lethal toxicity on bone marrow. Therefore, the researchers started to scrutinize bone marrow transplantation as a method for overcoming this high toxicity after chemotherapy^[9]. Afterwards, numerous studies of high dose chemotherapy and autologous stem cell transplantation in a large number of solid tumor cases were completed, however, this form of treatment

has remained standard practice only for TGCC^[10-13].

CLINICAL TRIALS WITH HDCT TGCC

As already mentioned, the majority of patients with metastatic TGCC are cured with standard chemotherapy: 3-4 cycles of BEP protocols^[3]. However, in patients with a poor prognosis, cure rate is below 50%. In these patients, and in patients with relapsed testicular cancer, unsatisfactory performance standard chemotherapy has directed researchers to search for new forms of treatment. The rationale of using high dose chemotherapy in chemo-sensitive cancer lead on investigators to start clinical trials with high dose chemotherapy and stem cell support^[3,14].

HDCT AS THE INITIAL TREATMENT IN PATIENTS WITH POOR PROGNOSIS

The initial studies of high dose chemotherapy for patients with poor prognosis in the first line setting were completed in the nineties. Motzer *et al.*^[15,16] from Memorial Sloan-Kettering Cancer Center in phase II studies demonstrated slightly better response to HDCT compared to a historical control with the standard dose chemotherapy (SDCT). In a study from 1993, 15 of 27 patients (56%) achieved a complete remission, 46% were free of disease, and 57% alive after a median of 31.2-mo follow-up^[15]. In another study by the same authors 30 patients were treated, 16 with etoposide, ifosfamide, cisplatin (VIP) chemotherapy, while 14 patients after VIP therapy, received HDCT, combination carboplatin, etoposide, cyclophosphamide (CEC). Patients selected for HDCT included those in whom tumour markers did not normalise after two cycles of chemotherapy. After a median follow-up of 30 mo, 15 (50%) patients remained progression-free. Patients treated with marker-dependent, early-intervention HDCT experienced longer survival^[16]. Bokemeyer *et al.*^[17] published in 1999 a match-paired multivariate analysis which compared the outcomes of patients with poor prognosis metastatic TGCC treated sequentially with standard VIP protocol and HDCT in a multicentric study including patients from German group studies and patients treated in two studies from Indiana University, with BEP or VIP conventional chemotherapy. High dose chemotherapy group included 147 patients, while 309 patients were in the SDCT group. Patients treated with HDCT had a longer progression free survival (PFS) 75% vs 59% ($P = 0.0056$) and a longer overall survival (OS) 82% vs 71% ($P = 0.0184$)^[17]. After that, Schmoll *et al.*^[18] from German Testicular Cancer Study Group (GTCSG) published a phase I/IIa study where they treated poor prognosis TGCC patients with a VIP-escalated protocol. After one cycle of standard VIP protocol, they applied dose escalated VIP with autologous stem cell transplantation, three to four cycles. Five-year PFS in this group of patients was 68%,

which is longer than the historical control with SDCT. After the advent of paclitaxel, and proven effectiveness of this drug in cisplatin-resistant TGCC, GTCSG announced the study of addition of a paclitaxel to dose-escalated VIP protocol^[19]. Addition of paclitaxel to high dose-VIP (HD-VIP) protocol resulted in higher response rate of 79%, and five-year PFS and OS of 64.1% and 75.2% respectively.

The only completed randomized phase III study is the one of Motzer *et al.*^[20]. This study included 219 untreated patients with metastatic TGCC intermediate and poor prognosis. One group of patients was treated with standard therapy, four cycles of BEP, while the experimental group received two cycles of BEP and afterwards two cycles high dose CEC (HD-CEC) protocol. Proportion of one year complete remission was not different in the two groups of patients (52% PEB + HD-CEC vs 48% BEP, $P = 0.53$). Benefit of a high dose chemotherapy, in this clinical trial, was observed only in those patients with unsatisfactory tumor markers decline. The study concludes that there is no benefit of adding a HDCT in this group of patients. Two other studies have started the third phase, but due to poor recruiting of patients they are not fully completed^[21-23]. The analysis of the included patients from high dose chemotherapy did not show the expected benefit in first-line treatment of metastatic TGCC with a poor prognosis. A review of studies of the first line is given in Table 2.

HDCT IN SECOND-LINE THERAPY

Therapeutic options of SDCT in patients with relapsed/refractory testicular cancer can achieve long-term remission of 25% of the cases with vinblastine, etoposide, ifosfamide (VeIP) protocol^[24], to about 65% of patients treated with paclitaxel, ifosfamide, cisplatin (TIP)^[25]. Considering the chemosensitivity of TGCC and relative modest results of conventional chemotherapy protocols, a large number of researchers have designed a variety of studies which applied HDCT with the support of haematopoietic autologous stem cell transplantation (Table 3).

Rodenhuis *et al.*^[26] have demonstrated a 54% PFS after a median follow-up of 37 mo in a phase II study on 35 patients. In this study they used two cycles of a HDCT after the induction with conventional chemotherapy. Similar design study was published in 2000^[27]. Two cycles of intensification were used and the results were almost the same as in the previous study. The same year, Motzer *et al.*^[28] demonstrated overall survival of 54% after a median of nearly three years of follow-up. They used the induction regimen with paclitaxel and ifosfamide, and three cycles of high dose protocol carboplatin/etoposide (TI-CE). A slightly worse result was achieved in the study by Rick *et al.*^[29] which included only one cycle of high dose protocol after the induction with three cycles of TIP. Three-year survival in this study was 30%. The explanation for the slightly

Table 2 Studies of first line high dose chemotherapy for poor prognosis patients

Ref.	Type of study	Number of patients	Protocol	OS (%)	PFS (%)	Median follow-up (mo)
Motzer <i>et al</i> ^[15]	Phase II, prospective	28	VAB-6 × 2 + HD-CE × 2	57	46	31
Motzer <i>et al</i> ^[16]	Phase II, prospective	30	VIP × 2 + HD-CEC × 2	48 (5 yr)	48 (5 yr)	60
Bokemeyer <i>et al</i> ^[17]	Comparative, retrospective	147 (HDCT) vs 309 (SDCT)	VIP × 2 + HD-VIP × 2 vs BEP/VIP × 4	82 vs 72 (2 yr) P = 0.0184	75 vs 59 (2 yr) P = 0.0056	21
Schmoll <i>et al</i> ^[18]	Phase I/II, prospective	221	VIP + HD-VIP × 3-4	73 (5 yr)	68 (5 yr)	48
Hartmann <i>et al</i> ^[19]	Phase I/II, prospective	52	VIP + T-HD-VIP	75 (5 yr)	64 (5 yr)	41
Motzer <i>et al</i> ^[20]	Phase III, prospective	108 (HDCT) vs 111 (SDCT)	BEP × 2 + HD-CEC × 2 vs BEP × 4	71 vs 72 (2 yr)	60 vs 57 (2 yr)	33
Daugaard <i>et al</i> ^[23]	Phase III, prospective	65 (HDCT) vs 66 (SDCT)	VIP + HD-VIP × 3 vs BEP × 4	86.1 vs 83 (2 yr)	66.1 vs 48 (1 yr)	NR
Necchi <i>et al</i> ^[22]	Phase II, prospective	43 (HDCT) vs 42 (SDCT)	BEP × 2 + HD-CpE + HD-Carbo vs BEP × 4	54.8 vs 55.8 (5 yr)	59.3 vs 62.8 (5 yr)	114

BEP: Bleomycin, etoposide, cisplatin; HD: High dose; HD-CE: High dose carboplatin, etoposide; HD-CEC: High dose carboplatin, etoposide, cyclophosphamide; HDCT: High dose chemotherapy; HD-VIP: High dose, etoposide, ifosfamide, cisplatin; NR: Not reported; OS: Overall survival; PFS: Progression free survival; SDCT: Standard-dose chemotherapy; VAB: Actinomycin D, vinblastine, cyclophosphamide, bleomycin, cisplatin.

Table 3 High dose chemotherapy as second line treatment

Ref.	Type of study	Number of patients	Protocol	OS (%)	PFS (%)	Median follow-up (mo)
Rodenhuis <i>et al</i> ^[26]	Phase II, prospective	35	Conventional chemotherapy + HD-CTC × 2	NR	54	37
Bhatia <i>et al</i> ^[27]	Phase II, prospective	65	VeIP × 1-2 + HD-CE × 2	NR	57	39
Motzer <i>et al</i> ^[28]	Phase II, prospective	37	TI × 2 + HD-CE × 3	54	49	31
Rick <i>et al</i> ^[29]	Phase II, prospective	62	TIP × 3 + HD-CET × 1	30 (3 yr)	25 (2 yr)	36
Pico <i>et al</i> ^[30]	Phase III, prospective, randomized	135 (HDCT) vs 128 (SDCT)	VIP/VeIP × 3 + HD-CE × 1 vs VIP/VeIP × 4	53 vs 53 (3 yr)	42 vs 35 (3 yr)	45
Einhorn <i>et al</i> ^[31]	Retrospective	135	HD-CE × 2	NR	70	48
Lorch <i>et al</i> ^[32]	Phase II, prospective, randomized	111 (sequential HDCT) vs 105 (single HDCT)	VIP × 1 + HD-CE × 3 vs VIP × 3 + HD-CE × 1	47 vs 45 (5 yr) P = 0.057	49 vs 39 (5 yr) P = 0.057	90
Feldman <i>et al</i> ^[33]	Phase I/II, prospective	107	TI × 2 + HD-CE × 3	52 (5 yr)	48 (5 yr)	61
Lorch <i>et al</i> ^[34]	Comparative, retrospective	821 (HDCT) vs 773 (SDCT)		53.2 vs 40.8 (5 yr) P < 0.001	49.6 vs 27.8 (2 yr) P < 0.001	NR
Selle <i>et al</i> ^[36]	Phase II, prospective	45	Epi-Tax × 2 + HD Thio-Tax + HD-ICE × 2	66% (2 yr)	50% (2 yr)	26
Berger <i>et al</i> ^[37]	Comparative, retrospective	95 (HDCT) vs 48 (SDCT)	HDCT vs SDCT	P = 0.931	Median 8 vs 42 mo P < 0.001	NR
Nieto <i>et al</i> ^[64]	Phase II, prospective	42	BEC-GDMC + BEV + HD-ICE	65% (2 yr)	63% (2 yr)	NR

BEV: Bevacizumab; Epi-Tax: Epirubicine, paclitaxel; GDMC: Gemcitabine, docetaxel, melphalan, carboplatin; HD: High dose; HD-CE: High dose carboplatin, etoposide; HD-CET: High dose carboplatin, etoposide, thiotepa; HDCT: High dose chemotherapy; HD-CTC: High dose carboplatin, thiotepa, cyclophosphamide; HD-ICE: High dose ifosfamide, carboplatin, etoposide; NR: Not reported; OS: Overall survival; PFS: Progression free survival; SDCT: Standard-dose chemotherapy; Thio-Tax: Thiotepa, paclitaxel; TI: Paclitaxel, ifosfamide; TIP: Paclitaxel, ifosfamide, cisplatin; VeIP: Vinorelbine, ifosfamid, cisplatin; VIP: Etoposide, ifosfamide, cisplatin.

worse result in this study could be the application of only one cycle of high dose protocol.

The only prospective, randomized phase III study by Pico *et al*^[30] compared four cycles of conventional chemotherapy VeIP or VIP with three cycles of SDCT with the addition of one cycle of high dose carboplatin/etoposide (HD-CE) protocol. This study included a total of 263 patients. It did not demonstrate the superiority of the addition of one cycle of HDCT. Based on that study and study by Rick *et al*^[29], it was concluded that one cycle of HDCT was not sufficient to achieve better results in treatment compared to conventional chemotherapy, so further studies had two or even three cycles of HDCT.

The study which probably had the greatest impact on the practice of treating relapsed TGCC and utilization of HDCT was that by Einhorn *et al*^[31].

One hundred and eighty-four patients were retrospectively analysed, and 135 of 184 patients received two cycles of HD-CE protocol in the first relapse, while the other 49 were treated in second and subsequent relapses with the same protocol. After a median follow-up of four years, progression free survival in patients treated in the first relapse was 70%. Lorch *et al*^[32] compared one cycle of high dose therapy with three cycles of to HD-CE. After long-term follow-up PFS was 49% vs 39% in favor of the sequential approach while overall survival did not differ between these two groups.

Table 4 High dose chemotherapy for third or subsequent lines, refractory/absolute refractory

Ref.	Type of study	Number of patients	Setting	Protocol	OS (%)	PFS (%)	Median follow-up (mo)
Vaena <i>et al</i> ^[38]	Retrospective	80	Second and subsequent lines, refractory	HD-CE × 2	40 (2 yr)	32 (2 yr)	24
Lotz <i>et al</i> ^[39]	Prospective	45	Second and subsequent lines, refractory/absolute refractory	Epi-Tax × 2 + HD Thio-Tax × 1 + HD-ICE × 2	23.5 (3 yr)	23.5 (3 yr)	36
Kondagunta <i>et al</i> ^[40]	Prospective	47	Second and third line, refractory/absolute refractory	TI × 2 + HD-CE × 3	NR	51	40
Einhorn <i>et al</i> ^[31]	Retrospective	49	Third or subsequent	HD-CE × 2	55	45	48
Lorch <i>et al</i> ^[41]	Retrospective	49	Third or subsequent, refractory	Various	17 (5 yr)	26 (5 yr)	48
Popovic <i>et al</i> ^[42]	Prospective	8	Fourth or fifth line, refractory	Epi-Tax × 2-3 + HD-CE × 1-2	Median 11 mo	NR	NR

Epi-Tax: Epirubicin, paclitaxel; HD: High dose; HD-CE: High dose carboplatin, etoposide; HDCT: High dose chemotherapy; HD-ICE: High dose ifosfamide, carboplatin, etoposide; NR: Not reported; OS: Overall survival; PFS: Progression free survival; SDCT: Standard-dose chemotherapy; Thio-Tax: Thiotepa, paclitaxel; TI: Paclitaxel, ifosfamide.

Feldman *et al*^[33] demonstrated in a prospective study of 107 patients a five-year PFS of 48% using the TI-CE protocol with three cycles of high dose chemotherapy.

A multicenter retrospective analysis of 1984 patients by Lorch *et al*^[34] compared the standard and high dose chemotherapy in patients with metastatic TGCC after progression on first-line chemotherapy. Patients were divided into five prognostic groups according to previously established criteria: Very low risk, low risk, intermediate risk, high and very high risk^[35]. Total of 1594 patients had all the data necessary for analysis, 773 of which received conventional chemotherapy, while 821 patients received HDCT. Two-year PFS and five-year OS was longer in the group with HDCT: 49.6% vs 27.8% (HR = 0.44; $P < 0.001$), 53.2% vs 40.8% (HR = 0.65; $P < 0.001$). This difference was seen in all prognostic groups except in low-risk group^[34].

Selle *et al*^[36] in the study TAXIF II demonstrated efficiency of a complex protocol which included several high dose cycles of paclitaxel, thiotepa, ifosfamide, carboplatin and etoposide, after induction with a combination of paclitaxel/epirubicin. The median PFS was 22 mo and OS was 32 mo. Two-year PFS was 50%, with Kaplan-Meier curve that showed a plateau at that value, and two-year OS of 66%^[36]. German Testicular Cancer Study Group retrospectively analyzed 143 patients and compared the HDCT ($n = 95$) with CDCT ($n = 48$). They showed a significantly longer median PFS 8 mo vs 42 mo ($P < 0.001$) with HDCT, but this difference was not seen when they analyzed overall survival^[37].

HDCT FOR REFRACTORY AND HEAVILY PRETREATED PATIENTS

Patients who progressed during standard cisplatin based chemotherapy have the worst prognosis. This group of patients also includes those who have not been cured after two lines cisplatin protocol. For this group of patients there have been several studies that, despite the very poor prognostic characteristics, showed some benefit from HDCT (Table 4).

Vaena *et al*^[38] retrospectively analyzed the results of HDCT in platinum-refractory patients. Two-year PFS was 32%, while two-year OS was 40%. Lotz *et al*^[39] applied a different concept in refractory patients. In TAXIF study they prospectively treated 45 patients with absolutely refractory metastatic TGCC. After mobilization therapy with paclitaxel/epirubicin, they gave two cycles of high dose ifosfamide, carboplatin, etoposide (ICE) protocol. Three-year PFS and OS were 23.5%^[39]. Kondagunta *et al*^[40] prospectively treated 47 refractory patients with high dose chemotherapy. After a median of 40 mo of observation the PFS was 51%. The Study by Einhorn *et al*^[31] treated 49 patients with HDCT in third and subsequent lines of chemotherapy. Time to disease progression and OS in these patients was 45% and 55% respectively. In patients with third and subsequent lines of therapy, Lorch *et al*^[41] reached five-year OS of 17% at five-year PFS 27%. In a pilot study, we have treated 8 heavily pretreated patients with HDCT. We used a modified TAXIF protocol^[39]. All patients had previously received four lines of different therapies. The median OS was 11 mo, with no long-term survival^[42,43].

HDCT FOR EXTRAGONADAL GCC

Extragenital GCC tumors occur most often in retroperitoneum and mediastinum and have worse prognosis compared to TGCC^[2]. Several studies with high dose chemotherapy administration has addressed this subgroup of patients (Table 5). Bokemeyer *et al*^[44] have treated patients with primary mediastinal germ cell tumors (PMNSGCT) initially with high dose chemotherapy. They included 28 patients and achieved 56% and 64% PFS and OS, respectively. Banna *et al*^[45] also used HDCT in the first line of treatment PMNSGCT and reached a three-year OS 41%. Rosti *et al*^[46] retrospectively analyzed 22 patients who had primary extragonadal non-seminomatous germ cell tumor (EGNSGCT) and received HDCT. Five-year survival in this group of patients was 75%. Hartmann *et al*^[47] and De Giorgi *et al*^[48] in two studies published in 1999 showed retrospective results of a treatment of

Table 5 High dose chemotherapy for extragonadal germ cell cancer

Ref.	Type of study	Number of patients	Setting	Protocol	OS (%)	PFS (%)	Median follow-up (mo)
Bokemeyer <i>et al</i> ^[44]	Phase I/II, prospective	28	PMNSGCT, first line	VIPx 1 + HD-VIP × 3	64 (5 yr)	56 (5 yr)	43
Banna <i>et al</i> ^[45]	Prospective	21	PMNSGCT, first line	BEP or VIP × 4 + HD-CEC × 1	41 (3 yr)	43 (5 yr)	52
Rosti <i>et al</i> ^[46]	Retrospective	22	EGCT, poor prognosis, first line	Various	75 (5 yr)	67 (5 yr)	50
Hartmann <i>et al</i> ^[47]	Retrospective	142	EGNSGCT, salvage	Various	12 (3 yr)	11 (3 yr)	45
De Giorgi <i>et al</i> ^[48]	Retrospective	59	EGNSGCT, salvage	Various	14 (PMNSGCT only)	14 (PMNSGCT only)	58

EGCT: Extragonadal germ cell tumor; EGNSGCT: Extragonadal non-seminomatous germ cell tumor; HD: High dose; HD-CEC: High dose carboplatin, etoposide, cyclophosphamide; HDCT: High dose chemotherapy; HD-ICE: High dose ifosfamide, carboplatin, etoposide; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; PMNSGCT: Primary mediastinal non-seminomatous germ cell tumor.

Table 6 International Germ Cell Cancer Collaborative Group-2 prognostic criteria for relapsed germ cell cancer patients

Parameter	Score points			
	0	1	2	3
Primary site	Gonadal	Extragenadal	-	Mediastinal non-seminoma
Prior response	CR/PRm-	PRm+/SD	PD	-
PFI, mo	> 3	≥ 3	-	-
AFP salvage	Normal	≤ 1000	> 1000	-
HCG salvage	≤ 1000	> 1000	-	-
LBB	No	Yes	-	-
Score sum (0-10)				
Regroup into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3				
Add histology points: Seminoma = -1; Non-seminoma or mixed = 1				
Final prognostic score: -1 = Very low risk; 0 = Low risk; 1 = Intermediate risk; 2 = High risk; 3 = Very high risk				

AFP: Alpha-fetoprotein; CR: Complete remission; HCG: Human chorionic gonadotrophin; LBB: Liver, brain, bone; PD: Progressive disease; PFI: Progression free interval; PRm-: Partial remission, markers negative; PRm+: Partial remission, markers positive; SD: Stable disease.

EGNSGCT after progression on first-line therapy. Results were rather modest with 12%-14% long term survival.

RISK ADAPTED APPROACH FOR USING HDCT

The first prognostic score related to the outcome of a HDCT was developed Beyer *et al*^[49]. They have analyzed a series of 310 patients treated with HDCT in four centers in Europe and the United States and by multivariate analysis of prognostic factors determined the data which had influenced the outcome. Progressive disease before HDCT, primary mediastinal localization, refractory or absolute refractory disease to cisplatin therapy and the value of human chorionic gonadotropin (HCG) over 1000 were independent factors for failure-free survival (FFS) after HDCT. These parameters separated patients into groups with good, intermediate and poor prognosis. Patients with good, intermediate

and poor prognosis had 51% FFS after HDCT, 27%, and 5% ($P < 0.001$) respectively. The International Prognostic Factors Study Group (Table 6) analyzed data of 1984 patients with TGCC, who have progressed after at least three cycles of cisplatin based chemotherapy. Patients' data were collected from 38 centers worldwide and 1594 patients had sufficient data for analysis. Patients were treated with SDCT or HDCT based on carboplatin. Factors that influenced the outcome were: Site of primary tumor, previous response to therapy, progression free survival on previously applied therapy, alpha-fetoprotein and HCG above 1000 and the presence of metastases in the liver, bone and/or bone^[35].

Based on these factors, patients were divided into five categories: Very low risk with a two-year PFS of 72%, low risk with PFS 51%, medium risk with 40%, high risk with 26% and very high risk with 6%. This is followed by the already mentioned retrospective analysis by Lorch *et al*^[34] which showed benefits in all prognostic categories, except in the low risk group. Given that the benefit was demonstrated even in the category of very low risk, there is a question in which prognostic groups, in patients with relapsed GCC, HDCT should be applied and which groups should receive conventional chemotherapy. Opinions differ greatly, and certain groups of authors believe that high dose chemotherapy should be applied in all patients with relapsed GCC, while some groups believe that patients with a low risk should be treated with the conventional chemotherapy in the second line, and HDCT should be applied in patients with medium and higher risk as well as in those with a low risk who relapse after second-line of conventional chemotherapy^[50]. Our position is closer to the second opinion.

STEM CELLS MOBILISATION AND OPTIMAL PROTOCOL OF CONDITIONING

Collection of sufficient numbers of hematopoietic stem cells is a key step in the further implementation of

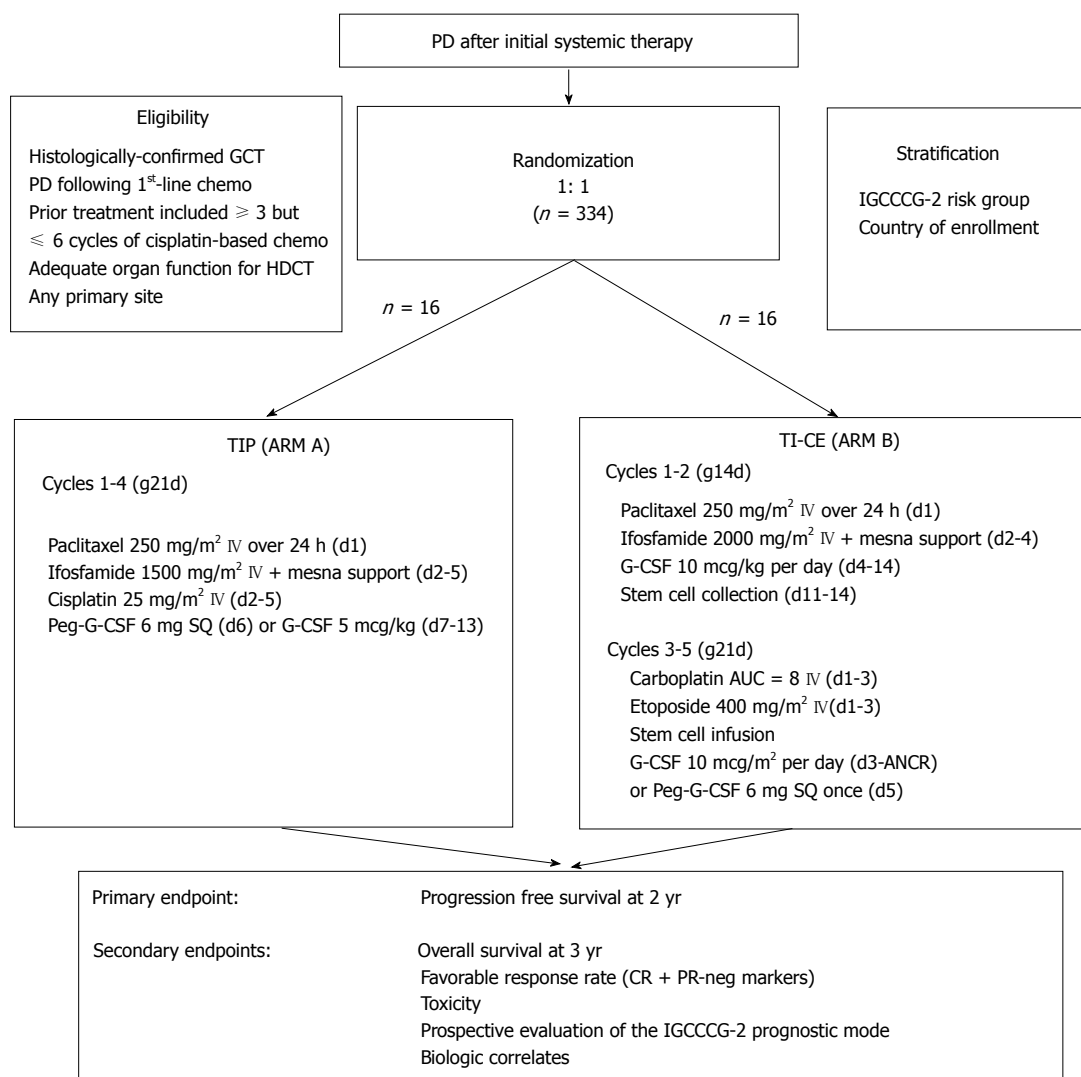


Figure 1 Training intervention and genetics of exercise response study design^[62]. PD: Progressive disease; GCT: Germ cell tumors; HDCT: High dose chemotherapy; G-CSF: Granulocyte colony-stimulating factor.

a HDCT, and the possibility of treating patient with multiple cycles of HDCT. Combination of chemotherapy with granulocyte growth factor (G-CSF) is a standard for the mobilization of hematopoietic stem cells. However, in heavily pretreated patients, this method of mobilization is not enough to collect a sufficient number of stem cells. In our cohort of heavily pretreated patients median collected hematopoietic stem cells was 3.6×10^6 cells/kg of BW. Consequently, it was not possible for us to apply tandem transplantation in some patients^[43]. Some other authors as well conclude that the mobilization with chemotherapy + G-CSF was inadequate for obtaining a sufficient number of stem cells, especially in cases of highly pretreated patients^[4,51-53].

Plerixafor is the CXCR4 receptor antagonists which separate hematopoietic stem cells from bone marrow stroma and can lead to better mobilization of these cells into peripheral blood^[54]. After the positive outcome in poor-mobilisers with lymphoma and multiple myeloma increased enthusiasm for using plerixafor to mobilize hematopoietic stem cells in patients with TGCC. The four

smaller cohorts and three case studies^[52-60] showed the efficiency of plerixafor in heavily pretreated patients with TGCC. Worel *et al.*^[55] showed the efficiency of plerixafor in 33 patients with non-hematologic diseases, of which 11 were metastatic GCC. A total of 28 (85%) patients gathered a sufficient number of stem cells. Kobold *et al.*^[57] showed a series of 6 patients who had previously received chemotherapy for 3.5 lines metastatic GCC and were not able to mobilize a sufficient number of stem cells for transplantation. After the use of plerixafor, five of these six patients mobilized an adequate number of cells for a minimum one transplant. Kosmas *et al.*^[52], in a pilot study, showed stem cells mobilization in pretreated patients with GCC, in which 7 out of 10 patients could yield an adequate number of hematopoietic stem cells for transplantation. The remaining three, poor-mobilisers, have amassed an adequate number of stem cells after applying plerixafor. In all these publications, engraftment of stem cells obtained after the mobilization with plerixafor was adequate.

Despite attempts with different drugs that would

supplement carboplatin, such as thiotepa and ifosfamide, panelists of the third European consensus conference on the treatment of GCC, agreed that a combination of carboplatin and etoposide is a standard high dose protocol^[50].

FUTURE DIRECTIONS

Although HDCT is considered standard treatment option for relapsed GCC in most major cancer centers, there are still no level IA evidence for applying HDCT in the current recommendations for the treatment of GCC^[2,3,61]. The reason for this is the series of negative results of the randomized phase III studies by Motzer *et al.*^[20] in the first line, and Pico *et al.*^[30] in metastatic relapsed GCC, therefore TIGER (randomized phase III trial of initial salvage chemotherapy for patients with germ cell tumors) has been initiated^[62]. The study design is shown in Figure 1. The plan is to include 390 patients, a group of which will receive four cycles of TIP protocol, while the second group will receive TI-CE protocol with three cycles of a HDCT. The hypothesis is that the overall survival of patients should be 13% higher after the treatment with the HDCT.

The second concept is target therapy in addition to the treatment of relapsed GCC, for conventional, as well as for high dose chemotherapy. Vascular endothelial growth factor over-expression is an independent factor of poor prognosis for non-seminomatous germ cell tumor (NSGCT), especially for teratoma NSGCT which is the most refractory to chemotherapy^[4]. Voigt *et al.*^[63] showed a case of successful treatment of patients absolutely refractory to cisplatin with bevacizumab and HD-ICE protocol. At the last ASCO meeting, Nieto *et al.*^[64] presented a phase II study for the first and the second relapse of intermediate and high risk metastatic GCC. They combined bevacizumab with tandem HDCT. In the first cycle of HDCT they combined bevacizumab with gemcitabine, docetaxel, melphalan and carboplatin, while in the second cycle they combined bevacizumab with HD-ICE protocol. One-year and 2 year-OS were 72% and 65% respectively^[64]. In addition to these studies, there is an ongoing study TAXIF III, of the French group, with the addition of bevacizumab to HD-ICE protocol^[65]. Approximately 70% of embryonic GCT express CD30 receptor on cell surface^[66]. Brentuximab-vedotin is an anti-CD30 conjugated to a monoclonal antibody that has shown significant results in the treatment of Hodgkin's and peripheral T-cell lymphomas^[67]. The Italian group has started a phase II clinical study of efficiency brentuximab vedotin in refractory CD30-positive metastatic testicular cancer^[68].

CONCLUSION

Although there are no randomized phase III trials that support HDCT as an effective treatment option for patients with metastatic GCT, the majority of centres use this type of therapy in patients with intermediate

and high risk according International Germ Cell Cancer Collaborative Group-2 score^[35]. TIGER study might give a definitive answer whether HDCT should be a standard treatment for these patients, and a better understanding of tumor biology, detection of markers of resistance to cisplatin, as well as if adding target therapy such as bevacizumab should improve the treatment of GCT, especially in the group of patients with a poor prognosis.

REFERENCES

- 1 **McGlynn KA**, Cook MB. Male Reproductive Cancers: Epidemiology, Pathology and Genetics. Cancer Genetics. Foulkes WD, Cooney KA, editors. New York, United States: LLC, 2010
- 2 **Oldenburg J**, Fossa SD, Nuver J, Heidenreich A, Schmoll HJ, Bokemeyer C, Horwich A, Beyer J, Kataja V. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** Suppl 6: vi125-vi132 [PMID: 24078656 DOI: 10.1093/annonc/mdt304]
- 3 **Albers P**, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, Horwich A, Laguna MP. EAU guidelines on testicular cancer: 2011 update. *Eur Urol* 2011; **60**: 304-319 [PMID: 21632173 DOI: 10.1016/j.eururo.2011.05.038]
- 4 **Selle F**, Gligorov J, Richard S, Khalil A, Alexandre I, Avenin D, Provent S, Soares DG, Lotz JP. Intensive chemotherapy as salvage treatment for solid tumors: focus on germ cell cancer. *Braz J Med Biol Res* 2015; **48**: 13-24 [PMID: 25493378 DOI: 10.1590/1414-431X20144214]
- 5 **Porrata LF**, Adjei AA. The pharmacologic basis of high dose chemotherapy with haematopoietic stem cell support for solid tumours. *Br J Cancer* 2001; **85**: 484-489 [PMID: 11506483 DOI: 10.1054/bjoc.2001.1970]
- 6 **Skipper HE**, Schabel FM, Wilcox WS. Experimental evaluation of potential anticancer agents. xiii. on the criteria and kinetics associated with "curability" of experimental leukemia. *Cancer Chemother Rep* 1964; **35**: 1-111 [PMID: 14117037]
- 7 **Frei E**, Canellous GP. Dose: a critical factor in cancer chemotherapy. *Am J Med* 1980; **69**: 585-594 [PMID: 6999898 DOI: 10.1016/0002-9343(80)90472-6]
- 8 **Frei E**, Teicher BA, Holden SA, Cathcart KN, Wang YY. Preclinical studies and clinical correlation of the effect of alkylating dose. *Cancer Res* 1988; **48**: 6417-6423 [PMID: 3180059]
- 9 **Little MT**, Storb R. History of haematopoietic stem-cell transplantation. *Nat Rev Cancer* 2002; **2**: 231-238 [PMID: 11990860 DOI: 10.1038/nrc748]
- 10 **Lotz JP**, Gligorov J, Selle F, Lefèvre G, Pautier P, Lhomme C. [High dose chemotherapy in ovarian and breast adenocarcinoma with poor prognosis]. *Gynecol Obstet Fertil* 2000; **28**: 620-631 [PMID: 11075500]
- 11 **Berry DA**, Ueno NT, Johnson MM, Lei X, Caputo J, Rodenhuis S, Peters WP, Leonard RC, Barlow WE, Tallman MS, Bergh J, Nitz UA, Gianni AM, Basser RL, Zander AR, Coombes RC, Roché H, Tokuda Y, de Vries EG, Hortobagyi GN, Crown JP, Pedrazzoli P, Bregni M, Demirer T. High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials. *J Clin Oncol* 2011; **29**: 3214-3223 [PMID: 21768471 DOI: 10.1200/JCO.2010.32.5910]
- 12 **Berry DA**, Ueno NT, Johnson MM, Lei X, Caputo J, Smith DA, Yancey LJ, Crump M, Stadtmayer EA, Biron P, Crown JP, Schmid P, Lotz JP, Rosti G, Bregni M, Demirer T. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. *J Clin Oncol* 2011; **29**: 3224-3231 [PMID: 21768454 DOI: 10.1200/JCO.2010.32.5936]
- 13 **Bui-Nguyen B**, Ray-Coquard I, Chevreau C, Penel N, Bay JO, Coindre JM, Cupissol D, Italiano A, Bonichon F, Lotz JP, Thyss A, Jimenez M, Mathoulin-Pélissier S, Blay JY. High-dose chemotherapy consolidation for chemosensitive advanced soft

- tissue sarcoma patients: an open-label, randomized controlled trial. *Ann Oncol* 2012; **23**: 777-784 [PMID: 21652583 DOI: 10.1093/annonc/mdr282]
- 14 **Necchi A**, Lanza F, Rosti G, Martino M, Farè E, Pedrazzoli P. High-dose chemotherapy for germ cell tumors: do we have a model? *Expert Opin Biol Ther* 2015; **15**: 33-44 [PMID: 25243977 DOI: 10.1517/14712598.2015.963051]
- 15 **Motzer RJ**, Mazumdar M, Gulati SC, Bajorin DF, Lyn P, Vlamis V, Bosl GJ. Phase II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. *J Natl Cancer Inst* 1993; **85**: 1828-1835 [PMID: 7693955 DOI: 10.1093/jnci/85.22.1828]
- 16 **Motzer RJ**, Mazumdar M, Bajorin DF, Bosl GJ, Lyn P, Vlamis V. High-dose carboplatin, etoposide, and cyclophosphamide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. *J Clin Oncol* 1997; **15**: 2546-2552 [PMID: 9215823]
- 17 **Bokemeyer C**, Kollmannsberger C, Meisner C, Harstrick A, Beyer J, Metzner B, Hartmann JT, Schmoll HJ, Einhorn L, Kanz L, Nichols C. First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: A multivariate and matched-pair analysis. *J Clin Oncol* 1999; **17**: 3450-3456 [PMID: 10550141]
- 18 **Schmoll HJ**, Kollmannsberger C, Metzner B, Hartmann JT, Schleucher N, Schöffski P, Schleicher J, Rick O, Beyer J, Hossfeld D, Kanz L, Berdel WE, Andreessen R, Bokemeyer C. Long-term results of first-line sequential high-dose etoposide, ifosfamide, and cisplatin chemotherapy plus autologous stem cell support for patients with advanced metastatic germ cell cancer: an extended phase I/II study of the German Testicular Cancer Study Group. *J Clin Oncol* 2003; **21**: 4083-4091 [PMID: 14568987 DOI: 10.1200/JCO.2003.09.035]
- 19 **Hartmann JT**, Gauler T, Metzner B, Gerl A, Casper J, Rick O, Horger M, Schleicher J, Derigs G, Mayer-Steinacker R, Beyer J, Kuczyk MA, Bokemeyer C. Phase I/II study of sequential dose-intensified ifosfamide, cisplatin, and etoposide plus paclitaxel as induction chemotherapy for poor prognosis germ cell tumors by the German Testicular Cancer Study Group. *J Clin Oncol* 2007; **25**: 5742-5747 [PMID: 18089869 DOI: 10.1200/JCO.2007.11.9099]
- 20 **Motzer RJ**, Nichols CJ, Margolin KA, Bacik J, Richardson PG, Vogelzang NJ, Bajorin DF, Lara PN, Einhorn L, Mazumdar M, Bosl GJ. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol* 2007; **25**: 247-256 [PMID: 17235042 DOI: 10.1200/JCO.2005.05.4528]
- 21 **Di Nicola M**, Necchi A, Nicolai N, Bengala C, Siena S, Novarino A, Carlo-Stella C, Piva L, Gianni AM, Salvioni R. High-dose sequential chemotherapy versus conventional-dose chemotherapy as first-line treatment for advanced poor prognosis germ-cell tumors: a multicenter Phase III Italian trial. *EJC Supplements* 2009; **7**: 422 [DOI: 10.1016/S1359-6349(09)71433-8]
- 22 **Necchi A**, Mariani L, Di Nicola M, Lo Vullo S, Nicolai N, Giannatempo P, Raggi D, Farè E, Magni M, Piva L, Matteucci P, Catanzaro M, Biasoni D, Torelli T, Stagni S, Bengala C, Barone C, Schiavetto I, Siena S, Carlo-Stella C, Pizzocaro G, Salvioni R, Gianni AM. High-dose sequential chemotherapy (HDS) versus PEB chemotherapy as first-line treatment of patients with poor prognosis germ-cell tumors: mature results of an Italian randomized phase II study. *Ann Oncol* 2015; **26**: 167-172 [PMID: 25344361 DOI: 10.1093/annonc/mdu485]
- 23 **Daugaard G**, Skoneczna I, Aass N, De Wit R, De Santis M, Dumez H, Marreud S, Collette L, Lluch JR, Bokemeyer C, Schmoll HJ. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSCG, and Grupo Germinal (EORTC 30974). *Ann Oncol* 2011; **22**: 1054-1061 [PMID: 21059637 DOI: 10.1093/annonc/mdq575]
- 24 **Loehrer PJ**, Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. *J Clin Oncol* 1998; **16**: 2500-2504 [PMID: 9667270]
- 25 **Kondagunta GV**, Bacik J, Donadio A, Bajorin D, Marion S, Sheinfeld J, Bosl GJ, Motzer RJ. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol* 2005; **23**: 6549-6555 [PMID: 16170162 DOI: 10.1200/JCO.2005.19.638]
- 26 **Rodenhuis S**, Westermann A, Holtkamp MJ, Nooijen WJ, Baars JW, van der Wall E, Slaper-Cortenbach IC, Schornagel JH. Feasibility of multiple courses of high-dose cyclophosphamide, thiopeta, and carboplatin for breast cancer or germ cell cancer. *J Clin Oncol* 1996; **14**: 1473-1483 [PMID: 8622061]
- 27 **Bhatia S**, Abonour R, Porcu P, Seshadri R, Nichols CR, Cornetta K, Einhorn LH. High-dose chemotherapy as initial salvage chemotherapy in patients with relapsed testicular cancer. *J Clin Oncol* 2000; **18**: 3346-3351 [PMID: 11013274]
- 28 **Motzer RJ**, Mazumdar M, Sheinfeld J, Bajorin DF, Macapinlac HA, Bains M, Reich L, Flombaum C, Mariani T, Tong WP, Bosl GJ. Sequential dose-intensive paclitaxel, ifosfamide, carboplatin, and etoposide salvage therapy for germ cell tumor patients. *J Clin Oncol* 2000; **18**: 1173-1180 [PMID: 10715285]
- 29 **Rick O**, Bokemeyer C, Beyer J, Hartmann JT, Schwella N, Kingreen D, Neureither S, Metzner B, Casper J, Wandt H, Hartmann F, Schmoll HJ, Derigs G, Gerl A, Berdel WE, Kanz L, Siegert W. Salvage treatment with paclitaxel, ifosfamide, and cisplatin plus high-dose carboplatin, etoposide, and thiopeta followed by autologous stem-cell rescue in patients with relapsed or refractory germ cell cancer. *J Clin Oncol* 2001; **19**: 81-88 [PMID: 11134198]
- 30 **Pico JL**, Rosti G, Kramar A, Wandt H, Koza V, Salvioni R, Theodore C, Lelli G, Siegert W, Horwich A, Marangolo M, Linkesch W, Pizzocaro G, Schmoll HJ, Bouzy J, Droz JP, Biron P. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. *Ann Oncol* 2005; **16**: 1152-1159 [PMID: 15928070 DOI: 10.1093/annonc/mdi228]
- 31 **Einhorn LH**, Williams SD, Chamness A, Brames MJ, Perkins SM, Abonour R. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med* 2007; **357**: 340-348 [PMID: 17652649 DOI: 10.1056/NEJMoa067749]
- 32 **Lorch A**, Kleinhans A, Kramar A, Hartmann JT, Bokemeyer C, Rick O, Bayer R. Superior survival after sequential high-dose chemotherapy (HDCT) as compared to single HDCT in patients with relapsed or refractory germ cell tumors (GCT): Six-year long-term follow-up of a prospective, randomized phase II trial. *J Clin Oncol* 2011; **29** (suppl): abstr 4507
- 33 **Feldman DR**, Sheinfeld J, Bajorin DF, Fischer P, Turkula S, Ishill N, Patil S, Bains M, Reich LM, Bosl GJ, Motzer RJ. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. *J Clin Oncol* 2010; **28**: 1706-1713 [PMID: 20194867 DOI: 10.1200/JCO.2009.25]
- 34 **Lorch A**, Bascoul-Mollevis C, Kramar A, Einhorn L, Necchi A, Massard C, De Giorgi U, Fléchon A, Margolin K, Lotz JP, Germà-Lluch JR, Powles T, Kollmannsberger C, Beyer J. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. *J Clin Oncol* 2011; **29**: 2178-2184 [PMID: 21444870 DOI: 10.1200/JCO.2010.32.6678]
- 35 **Lorch A**, Beyer J, Bascoul-Mollevis C, Kramar A, Einhorn LH, Necchi A, Massard C, De Giorgi U, Fléchon A, Margolin KA, Lotz JP, Germà-Lluch JR, Powles T, Kollmannsberger CK. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. *J Clin Oncol* 2010; **28**: 4906-4911 [PMID: 20956623 DOI: 10.1200/JCO.2009.26.8128]
- 36 **Selle F**, Wittnebel S, Biron P, Gravis G, Roubaud G, Bui BN, Delva R, Bay JO, Fléchon A, Geoffrois L, Caty A, Soares DG, de Revel T, Fizazi K, Gligorov J, Micléa JM, Dubot C, Provent S, Temby I, Gaulet M, Horn E, Brindel I, Lotz JP. A phase II trial of high-

- dose chemotherapy (HDCT) supported by hematopoietic stem-cell transplantation (HSCT) in germ-cell tumors (GCTs) patients failing cisplatin-based chemotherapy: the Multicentric TAXIF II study. *Ann Oncol* 2014; **25**: 1775-1782 [PMID: 24894084 DOI: 10.1093/annonc/mdl198]
- 37 **Berger LA**, Bokemeyer C, Lorch A, Hentrich M, Kopp HG, Gauler TC, Beyer J, de Wit M, Mayer F, Boehlke I, Oing C, Honecker F, Oechsle K. First salvage treatment in patients with advanced germ cell cancer after cisplatin-based chemotherapy: analysis of a registry of the German Testicular Cancer Study Group (GTCSG). *J Cancer Res Clin Oncol* 2014; **140**: 1211-1220 [PMID: 24696231 DOI: 10.1007/s00432-014-1661-z]
 - 38 **Vaena DA**, Abonour R, Einhorn LH. Long-term survival after high-dose salvage chemotherapy for germ cell malignancies with adverse prognostic variables. *J Clin Oncol* 2003; **21**: 4100-4104 [PMID: 14615439]
 - 39 **Lotz JP**, Bui B, Gomez F, Théodore C, Caty A, Fizazi K, Gravis G, Delva R, Peny J, Viens P, Duclos B, De Revel T, Curé H, Gligorov J, Guillemaut S, Ségura C, Provent S, Droz JP, Culine S, Biron P. Sequential high-dose chemotherapy protocol for relapsed poor prognosis germ cell tumors combining two mobilization and cytoreductive treatments followed by three high-dose chemotherapy regimens supported by autologous stem cell transplantation. Results of the phase II multicentric TAXIF trial. *Ann Oncol* 2005; **16**: 411-418 [PMID: 15659420]
 - 40 **Kondagunta GV**, Bacik J, Sheinfeld J, Bajorin D, Bains M, Reich L, Deluca J, Budnick A, Ishill N, Mazumdar M, Bosl GJ, Motzer RJ. Paclitaxel plus Ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. *J Clin Oncol* 2007; **25**: 85-90 [PMID: 17194908]
 - 41 **Lorch A**, Neubauer A, Hackenthal M, Dieing A, Hartmann JT, Rick O, Bokemeyer C, Beyer J. High-dose chemotherapy (HDCT) as second-salvage treatment in patients with multiple relapsed or refractory germ-cell tumors. *Ann Oncol* 2010; **21**: 820-825 [PMID: 19822531 DOI: 10.1093/annonc/mdl366]
 - 42 **Popovic L**, Jovanovic D, Donat D, Petrovic D, Roganovic T, Lotz JP. High-dose chemotherapy with autologous stem cell support for the heavily pretreated patients with germ cell tumours: a Serbian single-centre first-experience report. *Bone Marrow Transpl* 2011; **46** (Supp 1): 385 [DOI: 10.1038/bmt.2011.48]
 - 43 **Popovic L**, Jovanovic D, Donat D, Petrovic D, Roganovic T, Lotz JP. High dose chemotherapy with autologous stem cell transplantation for patients with germ-cell cancer. *J BUON* 2013; **18**: 290-291 [PMID: 23613419]
 - 44 **Bokemeyer C**, Nichols CR, Droz JP, Schmoll HJ, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Kanz L, Einhorn L, Hartmann JT. Extragenital germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol* 2002; **20**: 1864-1873 [PMID: 11919246 DOI: 10.1200/JCO.2002.07.062]
 - 45 **Banna GL**, De Giorgi U, Ferrari B, Castagna L, Alloisio M, Marangolo M, Rosti G, Santoro A. Is high-dose chemotherapy after primary chemotherapy a therapeutic option for patients with primary mediastinal nonseminomatous germ cell tumor? *Biol Blood Marrow Transplant* 2006; **12**: 1085-1091 [PMID: 17084372 DOI: 10.1016/j.bbmt.2006.06.008]
 - 46 **Rosti G**, De Giorgi U, Wandt H, Lioure B, Leyvraz S, Kolbe K, Papiani G, Ballardini M, Kulecki A, Demirel T. First-line high-dose chemotherapy for patients with poor prognosis extragonadal germ cell tumors: the experience of the European Bone Marrow Transplantation (EBMT) Solid Tumors Working Party. *Bone Marrow Transplant* 2004; **34**: 1033-1037 [PMID: 15516940 DOI: 10.1038/sj.bmt.1704704]
 - 47 **Hartmann JT**, Einhorn L, Nichols CR, Droz JP, Horwich A, Gerl A, Fossa SD, Beyer J, Pont J, Schmoll HJ, Kanz L, Bokemeyer C. Second-line chemotherapy in patients with relapsed extragonadal nonseminomatous germ cell tumors: results of an international multicenter analysis. *J Clin Oncol* 2001; **19**: 1641-1648 [PMID: 11250992]
 - 48 **De Giorgi U**, Demirel T, Wandt H, Taverna C, Siegert W, Bornhauser M, Kozak T, Papiani G, Ballardini M, Rosti G. Second-line high-dose chemotherapy in patients with mediastinal and retroperitoneal primary non-seminomatous germ cell tumors: the EBMT experience. *Ann Oncol* 2005; **16**: 146-151 [PMID: 15598952 DOI: 10.1093/annonc/mdl017]
 - 49 **Beyer J**, Kramar A, Mandanas R, Linkesch W, Greinix A, Droz JP, Pico JL, Diehl A, Bokemeyer C, Schmoll HJ, Nichols CR, Einhorn LH, Siegert W. High-dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variables. *J Clin Oncol* 1996; **14**: 2638-2645 [PMID: 8874322]
 - 50 **Beyer J**, Albers P, Altena R, Aparicio J, Bokemeyer C, Busch J, Cathomas R, Cavallin-Stahl E, Clarke NW, Claßen J, Cohn-Cedermark G, Dahl AA, Daugaard G, De Giorgi U, De Santis M, De Wit M, De Wit R, Dieckmann KP, Fenner M, Fizazi K, Flechon A, Fossa SD, Germá Lluch JR, Gietema JA, Gillessen S, Giwercman A, Hartmann JT, Heidenreich A, Hentrich M, Honecker F, Horwich A, Huddart RA, Kliesch S, Kollmannsberger C, Krege S, Laguna MP, Looijenga LH, Lorch A, Lotz JP, Mayer F, Necchi A, Nicolai N, Nuver J, Oechsle K, Oldenburg J, Oosterhuis JW, Powles T, Rajpert-De Meyts E, Rick O, Rosti G, Salvioni R, Schrader M, Schwyer S, Sedlmayer F, Sohaib A, Souchon R, Tandstad T, Winter C, Wittekind C. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. *Ann Oncol* 2013; **24**: 878-888 [PMID: 23152360 DOI: 10.1093/annonc/mdl579]
 - 51 **Simonelli M**, Rosti G, Banna GL, Pedrazzoli P. Intensified chemotherapy with stem-cell rescue in germ-cell tumors. *Ann Oncol* 2012; **23**: 815-822 [PMID: 21948814 DOI: 10.1093/annonc/mdl403]
 - 52 **Kosmas C**, Athanasopoulos A, Dimitriadis G, Miltioudou C, Zilakos M, Lydakis D, Magiorkinis E, Gekas C, Daladinos T, Mylonakis N, Ziras N. Plerixafor added to G-CSF-supported paclitaxel-ifosfamide-cisplatin salvage chemotherapy enhances mobilization of adequate numbers of hematopoietic stem cells for subsequent autografting in hard-to-mobilize patients with relapsed/refractory germ-cell tumors: a single-center experience. *Anticancer Drugs* 2014; **25**: 841-847 [PMID: 24625457 DOI: 10.1097/CAD.000000000000100]
 - 53 **Daphne O'Hara VJ**, Karr AH, Srivastava S, Kiel PJ. Experience with plerixafor for hematopoietic cell mobilization in nine patients with germ cell tumors. *Pharmacotherapy* 2014; **34**: 85-88 [PMID: 23864559 DOI: 10.1002/phar.1332]
 - 54 **Goterris R**, Hernández-Boluda JC, Teruel A, Gómez C, Lis MJ, Terol MJ, Tormo M, Solano C, Arbona C. Impact of different strategies of second-line stem cell harvest on the outcome of autologous transplantation in poor peripheral blood stem cell mobilizers. *Bone Marrow Transplant* 2005; **36**: 847-853 [PMID: 16113660]
 - 55 **Worel N**, Apperley JF, Basak GW, Douglas KW, Gabriel IH, Gaudes C, Hübel K, Jakšic O, Koristik E, Lanza F, Lemoli R, Mikala G, Selleslag D, Duarte RF, Mohty M. European data on stem cell mobilization with plerixafor in patients with nonhematologic diseases: an analysis of the European consortium of stem cell mobilization. *Transfusion* 2012; **52**: 2395-2400 [PMID: 22414093 DOI: 10.1111/j.1537-2995.2012.03603.x]
 - 56 **De Blasio A**, Rossi L, Zappone E, Ortu La Barbera E, Salvatori R, Pacilli M, Carbone A, Zaccarelli E, Papa A, Tomao S. Plerixafor and autologous stem cell transplantation: impressive result in a chemoresistant testicular cancer patient treated with high-dose chemotherapy. *Anticancer Drugs* 2013; **24**: 653-657 [PMID: 23698254 DOI: 10.1097/CAD.0b013e328360cd8c]
 - 57 **Kobold S**, Isernhagen J, Hübel K, Kilic N, Bogner C, Frickhofen N, Bokemeyer C, Fiedler W. Plerixafor is effective and safe for stem cell mobilization in heavily pretreated germ cell tumor patients. *Bone Marrow Transplant* 2011; **46**: 1053-1056 [PMID: 21102500 DOI: 10.1038/bmt.2010.264]
 - 58 **Tuffaha H**, Abdel-Rahman FA. Successful stem-cell mobilization and transplantation using plerixafor in a patient with a germ cell tumor. *Hematol Oncol Stem Cell Ther* 2010; **3**: 203-205 [PMID: 21150242]
 - 59 **Saure C**, Weigelt C, Schroeder T, Klärner V, Galonska L, Haas

- R, Kobbe G. Plerixafor enables successful hematopoietic stem cell collection in an extensively pretreated patient with testicular cancer. *Acta Haematol* 2010; **124**: 235-238 [PMID: 21099212 DOI: 10.1159/000321509]
- 60 **García-Escobar I**, Parrilla L, Ortega LM, Castellanos D, Pallarés MA, Cortés-Funés H. Clinical experience with plerixafor as a mobilization regimen for autologous peripheral blood stem cell transplantation in patients with refractory germ cell tumors. *Mol Clin Oncol* 2014; **2**: 923-926 [PMID: 25279175]
- 61 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Testicular Cancer Version 1 2015. Available from: URL: http://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf
- 62 **Feldman DR**, Huddart R, Hall E, Beyer J, Powles T. Is high dose therapy superior to conventional dose therapy as initial treatment for relapsed germ cell tumors? The TIGER Trial. *J Cancer* 2011; **2**: 374-377 [PMID: 21750688]
- 63 **Voigt W**, Kegel T, Maher G, Jordan K, Müller L, Schmoll HJ. Bevacizumab plus high-dose ifosfamide, etoposide and carboplatin (HD-ICE) as third-line salvage chemotherapy induced an unexpected dramatic response in highly platinum refractory germ-cell cancer. *Ann Oncol* 2006; **17**: 531-533 [PMID: 16234294]
- 64 **Nieto Y**, Tu SM, Jones R, Tannir N, Bassett R, Margolin KM, Holmberg L, Champlin R, Pagliaro L. Phase 2 trial of bevacizumab (BEV)/high-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) for refractory germ-cell tumors (GCT). *J Clin Oncol* 2014; **32**: 5s
- 65 **Assistance Publique - Hôpitaux de Paris**. Salvage Chemotherapy for Poor Prognosis Germ Cell Tumors (TAXIF III). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: <https://clinicaltrials.gov/ct2/show/NCT01966913>
- 66 **Giannatempo P**, Paolini B, Miceli R, Raggi D, Nicolai N, Farè E, Catanzaro M, Biasoni D, Torelli T, Stagni S, Piva L, Mariani L, Salvioni R, Colecchia M, Gianni AM, Necchi A. Persistent CD30 expression by embryonal carcinoma in the treatment time course: prognostic significance of a worthwhile target for personalized treatment. *J Urol* 2013; **190**: 1919-1924 [PMID: 23624209 DOI: 10.1016/j.juro.2013.04.057]
- 67 **Popovic L**, Jovanovic D, Popovic DJ. CD30-the head of the TNF family or the successful story of brentuximab-vedotin. *Arch Oncol* 2013; **21**: 17-19 [DOI: 10.2298/AOO1301017P]
- 68 **Fondazione Michelangelo**. Brentuximab Vedotin (SGN-35) as Salvage Treatment for CD30-positive Germ Cell Tumors. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: <https://clinicaltrials.gov/ct2/show/NCT01851200>

P- Reviewer: Aponte PM, Desai DJ, Yao CL **S- Editor:** Gong XM
L- Editor: A **E- Editor:** Wu HL





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

