Review Article

Standard versus high-dose chemotherapy in mediastinal germ cell tumors: a narrative review

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Objective: The aim of this review is to analyze feasibility and toxicities of high-dose chemotherapy (HDCT) in comparison to standard dose chemotherapy (SDCT) in patients affected by mediastinal germ cell tumors (MGCTs), discussing factors that may affect therapeutic choices, such as: management of residual disease, early response predictors for chemotherapeutic efficacy and determinants of chemotherapeutic resistance. In this review, we discuss the main clinical experiences with HDCT and SDCT in germ cell tumor (GCT) patients specifically in those affected by MGCT.

Background: MGCTs represent a very small subset characterized by a poor prognosis, despite improvements in their clinical management and in understanding their biology. From early 1970s, HDCT has become an alternative to SDCT for both first-line and salvage therapeutic settings in advanced GCT patients. Several HDCT schedules—either cisplatin or carboplatin-based—have been tested so far, both in clinical randomized trial and in single-center experiences, with divergent results in terms of clinical outcomes and tolerability. Moreover, the majority of these studies included, but were not exclusively designed for, advanced MGCT patients, making difficult to infer data for this specific subset.

Methods: an extended review of literature through PubMed was conducted using the keywords "mediastinal germinal cell tumors", "standard dose chemotherapy" and "high dose chemotherapy".

Conclusions: HDCT regimens could not be considered to date a standard option as first-line therapy in advanced MGCT patients, whilst they could be an alternative to SDCT regimens in relapsed tumors after proper patient selection.

Keywords: Mediastinal germ cell tumors (MGCTs); standard dose chemotherapy (SDCT); high-dose chemotherapy (HDCT)

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Introduction

Germ cell tumors (GCTs) are neoplasms originating from stem cells of the germ line, usually developing in the gonads (1). Concerning male gender, testicular GCTs are globally rare; however, they represent the most common cancer diagnosed in young adult men (<40 years) (2). In females, ovarian GCT are definitely infrequent (3).

Extragonadal germ cell tumors (EGGCTs) are rare entities, with a similar incidence among males and females (1.9–3.4/1,000,000) as reported in a large U.S. series, being mediastinum, retroperitoneum, and brain in males and mediastinum and placenta the most frequently involved extragonadal sites in males and females, respectively (4). Etiopathogenesis of EGGTCs is still debated: a widely accepted hypothesis poses in the prematurely stop of germ cell precursors during midline embryogenetic migration the origin of EGGTCs; but new theories, such as the gonadal origin with regression of the primary tumor (5), or an origin *in situ* from common precursor stem cells (6), have emerged in the latest decades.

Compared to their gonadal counterpart, mediastinal germ cell tumors (MGCTs) display different histological characteristics. In fact, 60–70% of them are teratomas—both mature and immature, while seminoma and non-seminoma histologies are less frequently diagnosed (7). Among them, immature teratoma and non-seminoma express the most aggressive behavior. MGCTs usually manifest with an anterior mediastinal mass—possibly along with elevated serum marker levels—chest pain, dyspnea, and cough in a young male patient (8), since MGCTs are almost exclusively diagnosed in male patients, with a male:female ratio of 9:1 (9). It is worthy to note that the only ascertained risk factor for MGCTs development is the Klinefelter syndrome to date (10).

Clinical management of MGCTs is similar to that of the gonadal counterpart. The International Germ Cell Cancer Collaborative Group (IGCCCG) Consensus Classification in 1997 identified mediastinal location as a negative prognostic factor for non-seminoma, so that all mediastinal non-seminoma patients are automatically included in the poor prognostic risk category (11), whilst both mediastinal teratoma and seminoma are included in good and intermediate risk categories depending on other prognostic factors, or the presence of non-pulmonary visceral metastases and high serum markers values.

Surgery, performed through a complete *en-bloc* excision, is a curative approach for teratoma, whilst for seminoma and non-seminoma could be an alternative to observation only [or to second-line high-dose chemotherapy (HDCT) or to radiation therapy] in selected cases of residual masses after chemotherapy (8). It should be mentioned also that non-seminomatous MGCTs patients who underwent resection of primary tumor could still have a good outcome despite the presence of rising serum tumor markers (STMs) (12). Moreover, non-seminomatous MGCTs could transdifferentiate into non-GCTs (i.e., sarcomatous histotype), which furtherly support the surgical approach—whenever feasible—in order to avoid metastatic spread of these aggressive variants (13).

In this review we discuss current treatment modalities adopting either standard dose or high-dose chemotherapeutic regimens in advanced MGCT patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-21-29/rc).

Methods

An extended review of literature through PubMed was conducted, using the keywords “mediastinal germinal cell tumors”, “standard dose chemotherapy” and “high dose chemotherapy”, including also studies relating to “germinal cell tumors” in which a subset of MGCT patients was included. Data collection has been evaluated in order to delineate differences between HDCT and standard dose chemotherapy (SDCT).

First-line SDCT in MGCTs

Given the rarity of primary MGCTs, currently used chemotherapeutic regimens are the same used for all other GCT patients, even without level 1 evidence available from randomized clinical trials, as pointed out in the 2018 edition of European Society for Medical Oncology (ESMO) consensus conference on testicular cancer (14). Therefore, MGCT patients should receive chemotherapy accordingly to their IGCCCG risk categories.

An old retrospective series of 38 MGCT patients—all of which diagnosed with non-seminomatous histology—treated at the Institute Gustave-Roussy is the first work describing efficacy of cisplatin-based regimen in this specific population. However, the chemotherapeutic regimens adopted are anachronistic, with outdated and particularly toxic drugs that have been abandoned over time (15).

Current first-line standard chemotherapy consists of PEB

Table 1 Standard dose chemotherapeutic regimens tested in GCT patients—including MGCT ones—as first-line therapy

Authors and year	Type of study	Chemotherapeutic regimen	No. of enrolled pts	MGCT pts enrolled, n (%)	Main investigated outcome(s)	Ref.
Fizazi *et al.*, 1998	Retrospective analysis	Cisplatin-based CT	38	38 (100.0)	CR rate: 66%	(15)
Daugaard *et al.*, 1992	Retrospective analysis	Cisplatin-based CT	49	8 (16.3)	CR rate: 79.6%	(16)
Ranganath *et al.*, 2016	Retrospective analysis	VIP (75%), PEB (25%)	221	221 (100.0)	Postoperative complications: 24%; postoperative deaths: 5%	(17)
Hinton *et al.*, 2003	Randomized clinical trial	VIP	304	NR	PFS: 64%; OS: 69% (median follow-up of 7.3 months)	(18)
		PEB			PFS: 58%; OS: 67% (median follow-up of 7.3 months)	

CT, chemotherapy; CR, complete response; GCT, germ cell tumor; NR, not reported; MGCT, mediastinal germ cell tumor; OS, overall survival; PEB, cisplatin, etoposide and bleomycin; PFS, progression-free survival; pts, patients; VIP, cisplatin + etoposide + ifosfamide.

regimen (cisplatin + etoposide + bleomycin) administered for 3 or 4 cycles, being the number of cycles influenced by the IGCCCG risk category (8).

Standard dose PEB regimen—with cisplatin 20 mg/m^2 + etoposide 100 mg/m^2 daily for 5 days and bleomycin 15 mg/m^2 once a week—demonstrated efficacy in EGGCTs and, most importantly, similar outcomes compared to gonadal GCTs of the same IGCCCG risk category (16).

Concerns about the bleomycin-induced lung injury—and the consequent postoperative pulmonary failure in patients undergoing surgery of persistent disease—have led clinicians to use alternative regimens such as VIP (cisplatin + etoposide + ifosfamide) in MGCT patients (17). In fact, the VIP regimen had already been tested in disseminated GCT patients, showing similar efficacy compared to PEB but with a different safety profile (more hematologic but less pulmonary toxicities) (18). Primary prophylactic granulocyte colony-stimulating factor (G-CSF) is recommended when the VIP regimen is chosen given the high risk of severe neutropenia (14).

SDCT regimens contain cisplatin as their main anticancer agent despite short- and long-term toxicities associated with it (19). Given the high percentage of long survivors, replacing cisplatin with carboplatin in PEB regimen could have been an intriguing alternative at lower renal, neuro- and ototoxicity. However, a higher relapse rate was found with carboplatin than cisplatin in a randomized clinical trial on good risk metastatic non-seminomatous GCT patients (20) (*Table 1*).

First-line HDCT in MGCTs

The clinical need of testing HDCT in GCT patients is founded on two main assumptions: the chemosensitivity of tumoral germ cells (21) and the possibility to achieve a higher proportion of long-term remissions also in poor prognostic patients, like those with MGCT, compared to the SDCT.

From early 1970s, HDCT regimens have been tested in advanced GCT patients, being single-agent high-dose cyclophosphamide the first used (22). Only in 1981, it became clear that bone marrow transplantation was necessary to support patients receiving these intensive schedules (23). Following first reports of high mortality due to neutropenic fever (24), also carboplatin, was safely delivered through autologous bone marrow transplantation (ABMT) at elevated doses (1,650–2,100 mg/m^2) together with etoposide (1,200–2,250 mg/m^2) in metastatic GCT patients (25). On the other hand, it was not possible to increase the dose of cisplatin in the same way due to its non-hematological related toxicity. Doubling the daily dose of cisplatin, from 20 to 40 mg/m^2 for 5 days—as a part of the PEB regimen, despite lower myelotoxicity compared to carboplatin, did not translate in survival benefit in poor prognosis patients, as showed in a large randomized clinical trial (26).

For poor prognosis advanced GCT patients, first-line HDCT based on high-dose VIP regimen followed by peripheral blood stem cell (PBSC) support resulted as a

feasible approach, as shown in a phase I/II trial, taking also into account a high but acceptable acute toxicity (27). A multivariate matched-pair analysis between patients who received high-dose VIP schedule with autologous PBSC transplantation and patients treated with standard dose PEB or VIP regimens showed a statistically significant improvement in both progression-free survival (PFS) and overall survival (OS) in poor prognostic advanced GCT patients (28). However, not all HDCT regimens did translate in survival improvement, as happened with the modified PVeBV (cisplatin, etoposide, bleomycin, and vinblastine) regimen with ABMT as first-line treatment of high-volume metastatic non-seminomatous GCT patients (29).

EGGCT patients, particularly those with MGCT, have been selectively treated with first-line HDCT to investigate its efficacy and feasibility.

A German single arm multicenter trial investigated the efficacy of 3–4 cycles of high-dose VIP regimen supported by PBSC transplantation in 28 MGCT patients, comparing results to those obtained from patients of the International Extragonadal Germ Cell Tumour Study Group who received cisplatin-based conventional dose regimens. Concerning the safety, no toxic deaths were recorded, being mucositis and infections the most frequent adverse events; with regards to the efficacy, estimated 5-year OS was 64%, higher than what reported for standard-dose cisplatin protocols (30).

An Italian case series of 22 EGGCT patients (half of whom with MGCT) treated with HDCT regimens—the most frequent being a combination of carboplatin, etoposide and cyclophosphamide—together with PBSC support, reported acceptable safety and efficacy for those regimens (31).

Another approach to intensify the delivered chemotherapeutic dose was to administer repeat high-dose cycles after one—or more—standard dose one(s) (namely, "consolidation" approach). In a phase III trial, poor prognosis GCT patients were randomized between 4 cycles of PEB and 1 cycle of VIP followed by 3 cycles of high-dose VIP and PBSC support (32), but no benefit in either response rate or OS was demonstrated. Similarly, a phase II trial in an analogue population of patients failed to demonstrate PFS advantages for the high-dose sequence comprising of high-dose cyclophosphamide, cisplatin, etoposide with PBSC support followed by high-dose carboplatin—after 2 cycles of PEB, compared to 4 cycles of standard PEB (33). These results were confirmed by a phase III clinical trial that failed to demonstrate survival improvement with 2 cycles of BEP followed by 2 cycles of high-dose carboplatin-based regimen with PBSC support versus 4 cycles of PEB, in poor prognosis GCT patients (34).

Concerning EGGCT patients, there is a case series of 6 Japanese patients, treated with HDCT (carboplatin, etoposide, ifosfamide and paclitaxel) combined with PBSC support after 2–3 cycles of conventional-dose induction chemotherapy with PEB; safety of this approach was confirmed, but efficacy of high-dose "consolidation" therapy could not be inferred from this series (35). In another retrospective analysis, including 21 MGCT patients treated with a single cycle of HDCT consisting of carboplatin, etoposide, and cyclophosphamide after conventional induction chemotherapy and followed by PBSC infusion, 7 patients were reported to achieve complete remission with no treatment-related deaths in this study (36).

On the contrary, 2 cycles of an "induction" HDCT regimen (the CBOP, with carboplatin, bleomycin, vincristine) followed by 3 cycles of standard dose PEB has shown to improve both PFS and OS compared to the standard of PEB for 4 cycles, at the cost of increased short-term toxicities (37).

As an alternative to "classical" HDCT regimens, which aim to increase the dose-intensity of the chemotherapy by elevating the doses of chemotherapeutic agents, the use of dose-dense chemotherapy with reduced chemotherapy intervals has been investigated. In a cohort of untreated or relapsed GCT patients, dose-dense cisplatin together with etoposide, actinomycin-D, high-dose methotrexate, and G-CSF support, was administered every 15 days, rather than 21 days as per PEB schedule (38). Interestingly, MGCT patients, who were 32% of all the enrolled subjects, reached similar PFS rates compared to non-MGCT patients. However, to date, dose-dense schedules, apart from GETUG 13 phase III trial which will be discussed later (39), have not been extensively investigated in (M) GCT patients, probably due to safety concerns (*Table 2*).

Second-line HDCT in MGCTs

Metastatic GCT patients who progressed or relapsed after first-line chemotherapy have a poor prognosis. Among prognostic factors, histology, primary tumor location, response and progression-free interval after first-line treatment, serum marker levels, and site of metastases (liver, bone, or brain) were used to identify five prognostic categories—from very high to very low risk (40).

Salvage chemotherapy after failure of first-line regimen

Table 2 High-dose chemotherapeutic regimens tested in GCT patients—including MGCT ones—as first-line therapy

Authors and year	Type of study	Chemotherapeutic regimen	No of enrolled pts	MGCT pts enrolled, n (%)	Main investigated outcome(s)	Ref.
Nichols *et al.*, 1991	Randomized clinical trial	HD-PEB	159	7 (9.2)	CR: 46%; PR: 26%	(26)
		PEB		15 (19.2)	CR: 47%; PR: 18%	
Schmoll *et al.*, 2003	Phase I clinical trial	VIP → HD-VIP → ASCT	221	28 (12.7)	5-y PFS: 74%	(27)
Bokemeyer *et al.*, 1999	Multivariate analysis	HD-VIP → ASCT	147	18 (12.2)	2-y PFS: 75%; 2-y OS: 82%	(28)
		PEB or VIP	309	53 (17.2)	2-y PFS: 59%; 2-y OS: 72%	
Droz *et al.*, 2007	Randomized clinical trial	PVeBV → ASCT	115	13 (22.8)	5-y OS: 75%	(29)
		PVBV + PEC → ASCS		6 (10.5)	5-y OS: 61%	
Bokemeyer *et al.*, 2003	Clinical trial	HD-VIP → ASCT	28	28 (100.0)	5-y ePFS: 56%; 5-y eOS: 64%	(30)
Rosti *et al.*, 2004	Retrospective analysis	HDCT (various regimens)	22	11 (50.0)	DFS: 58% (median follow-up of 50 months)	(31)
Daugaard *et al.*, 2011	Randomized clinical trial	VIP → HD-VIP → ASCT	131	6 (9.2)	CR rate: 44.6%	(32)
		PEB		9 (13.6)	CR rate: 33.3%	
Necchi *et al.*, 2015	Randomized clinical trial	PEB → HDCT → ASCT	85	10 (23.8)	5-y PFS: 55.8%; 5-y OS: 62.8%	(33)
		PEB		9 (20.9)	5-y PFS: 54.8%; 5-y OS: 59.3%	
Motzer *et al.*, 2007	Randomized clinical trial	PEB → HDCT → ASCT	219	26 (24.1)	1-y dCR: 52%	(34)
		PEB		32 (28.8)	1-y dCR: 48%	
Banna *et al.*, 2006	Retrospective analysis	PEB/VIP → HDCT (9 out of 21 pts) → ASCT	21	21 (100.0)	CR rate (in 9 pts who received HDCT): 78%	(36)
Huddart *et al.*, 2015	Randomized clinical trial	CBOP → PEB	89	9 (20.9)	1-y PFS: 65%; 2-y OS: 67%	(37)
		PEB		9 (19.6)	1-y PFS: 43%; 2-y OS: 61%	
Shamash *et al.*, 2020	Retrospective analysis	DD-CT	75	24 (32.0)	2-y PFS: 61.5%; 3-y OS: 71.9%	(38)

ASCT, autologous stem cell transplant; CBOP, carboplatin, bleomycin, vincristine, cisplatin; CT, chemotherapy; CR, complete response; dCR, durable complete response; DD-CT: dose-dense chemotherapy; DFS, disease-free survival; ePFS, estimated progression-free survival; eOS, estimated overall survival; GCT, germ cell tumor; HD, high-dose; HDCT, high-dose chemotherapy; MGCT, mediastinal germ cell tumor; OS, overall survival; PEB, cisplatin, etoposide and bleomycin; PEC, high-dose cisplatin, etoposide, cyclophosphamide; PFS, progression-free survival; pts, patients; PVBV, cisplatin, vinblastine, bleomycin (continuous infusion), etoposide; PVeBV, cisplatin, vinblastine, bleomycin, etoposide; VIP, cisplatin + etoposide + ifosfamide.

could be administered at either conventional or high doses, being both acceptable options. A retrospective analysis of a large multicenter database comparing these two treatment modalities found an overall 56% decrease in the risk of progression in favor of HDCT, with an OS benefit for all previously indicated risk categories except for the low risk one (41).

Whilst most used first-salvage conventional-dose regimens are VIP and TIP (paclitaxel + ifosfamide + cisplatin) (42), several HDCT regimens have been tested in relapsed/refractory CGT patients (14). TI-CE regimen, consisting of paclitaxel and ifosfamide followed by high-dose carboplatin and etoposide plus PBSC support, was tested in 48 progressive GCT patients and unfavorable prognosis. In this study, 23 patients (48%) achieved complete responses, although with a high rate of hospitalization (67%) for neutropenic fever (43). A clinical trial of 211 relapsed or refractory GCT patients randomized patients

between arm A (1 cycle of VIP followed by 3 cycles of high-dose carboplatin plus etoposide) and arm B (3 cycles of VIP followed by 1 cycle of high-dose carboplatin plus etoposide plus cyclophosphamide), in both cases followed by PBSC support. Unfortunately, the study was prematurely interrupted because of treatment-related mortality excess in the second arm (44). A different strategy consists in administering IPO (irinotecan, paclitaxel and oxaliplatin) followed by HDCT in GCT patients who relapsed after two prior lines of cisplatin–based CT or MGCT patients who relapsed after first-line cisplatin-based treatment, as reported by a retrospective analysis (45); interestingly, among the 72 patients included in this analysis, 13 had MGCT, showing similar outcomes to the overall analyzed population.

Concerning non-seminomatous EGGCT/MGCT patients, early report of first-salvage HDCT activity were published in 1991, in which 12 second-time relapsed or cisplatin refractory MGCTs patients received high-dose carboplatin and etoposide with ABMT; however, no patient reached a complete remission (46). A retrospective analysis on 59 EGGCT patients (37 with retroperitoneal and 22 with mediastinal primary tumor) who relapsed after cisplatin-based first-line therapy and treated with HDCT—mainly carboplatin-based regimens—showed an encouraging complete remission rate of 36%, even if 3 of the 22 MGCT patients died due to treatment-related toxicity (47).

It is clear, however, that clinicians should concentrate their efforts in adopting the best treatment strategies in the first-line setting for MGCTs patients, being the relapsed or residual disease incurable.

A series of 79 patients with non-seminomatous MGCTs who underwent thoracic surgery for the resection of primary tumor after SDCT has demonstrated the prognostic role of residual disease. The pathological finding of necrosis was indeed associated with brilliant survival (mean OS 139 months) compared to the finding of teratoma (mean OS 111 months) or, worse, residual tumor (mean OS 52 months) (48). Surgery of residual disease is certainly a salvage approach in case of persistently elevated serum markers or relapsed GCT, with both curative and prognostic significance (14), but its role in MGCT patients still remains unclear in the absence of *ad hoc* data, especially after HDCT (49) and in consideration of the high surgical-related mortality after HDCT.

Discussion

Poor prognosis GCT patients have a 5-year PFS rate of 55% and OS rate of 64%, according to a wide analysis on a Danish population-based cohort of patients who received PEB as first-line regimen (50).

Results from abovementioned trials investigating the role of SDCT and HDCT as first-line therapy in poor prognosis GCT patients could easily led clinicians into considering HDCT as the favorite approach for this specific category, which includes MGCTs. However, treatment choices in this setting must also consider other factors such as management of residual disease, early response predictors for chemotherapeutic efficacy, determinants of chemotherapeutic resistance, early and late toxicities, to reach the best clinical outcome.

It is indeed clear that MGCT patients should be treated with maximal efforts in the first line setting, since primary MGCTs—especially if non-seminomatous—are generally non-curable in the salvage setting (51).

Concerning non-seminomatous GCTs, the kinetic of decline in the STMs—human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP)—has been prospectively studied as a predictor for treatment outcomes and survival in poor prognosis patients (51). The possibility of adjusting chemotherapeutic dose intensity based on STMs kinetic was therefore investigated in the GETUG 13 phase III trial, in which—after one cycle of PEB—poor prognosis GCT patients with a favorable decline in STMs received further 3 cycles of PEB, whilst patients with an unfavorable decline in STMs were randomized between continuing PEB or a dose-dense regimen with G-CSF support (39). Results from this trial support the dose intensification in patients with an unfavorable decline in STMs at the cost of acceptable toxicities, but it must be noted that this approach is similar to the "consolidation" one, which has been demonstrated to be unsuccessful in unselected poor prognosis patients.

Therefore, it would be interesting to use STMs kinetic to tailor subsequent therapy in poor prognostic GCT patients—and specifically in MGCT ones—after one cycle of HDCT, given the good premises of the "induction" approach (37), and therefore continuing HDCT solely in patients with unfavorable decline in STMs.

Toxicities from chemotherapies, in both short and long period, are a well-known issue in GCT patients, and it seems to be a no less relevant problem in MGCTs patients: in fact, in these patients, cardiac and pulmonary functions, which are already impaired by the tumour, could be undermined by chemotherapy-induced toxicities.

Hematological toxicities, as stated before, could be easily managed in GCT patients without life-threatening

consequences. However, a statistically significant increase for non-treatment-related hematological disorders—mainly acute megakaryoblastic leukemia and myelodysplastic syndrome—has been reported in MGCT patients compared with other EGGCT patients, thus highlighting a higher bone marrow frailty in this clinical subset (52). Nephrotoxicity was also studied in GCT patients receiving high-dose carboplatin-based regimens, which occurred in an acute form in 29% of 150 consecutive CGT patients who received CEI (carboplatin, etoposide and ifosfamide). The mortality rate was 3% and hemodialysis was required in 8% of patients, however nephrotoxicity was reversible in the majority of patients (53).

Cumulative incidence of secondary hematological malignancies is lower (1.37% at 20 years) than secondary solid tumors (4.17% at 20 years) in GCT patients (54) and seems to not be increased by first-line HDCT as analyzed in patients from two clinical trials, with an acceptably low risk of developing them (55).

Besides these clinical considerations on outcomes and treatment related toxicities, new data are emerging about the genomic of GCTs and platinum resistant disease. It is believed that resistance to cisplatin could be responsible for treatment failure in up to 30% of GCT patients who receive such agent in a first line regimen (53). Therefore, interest in finding genetic determinants of cisplatin-resistance has risen throughout the years, in order to improve risk stratification and identification of high-risk patients who will not respond to it. In a series of GCT patients, TP53 alterations were found exclusively in tumor samples from cisplatin-resistant patients. Moreover, TP53 alterations were more frequent among non-seminomatous MGCTs, furtherly explaining the more frequent chemoresistance of this tumor subtype (56). More efforts are needed to identify—and subsequently validate—genomic factors associated with resistance to specific drug(s) in GCT and MGCTs patients (57).

Conclusions

MGCT patients, given their poor prognosis, represent a category of patients for whom the optimization of available therapeutic tools is of paramount importance to improve survival outcome at the cost of preserving the quality of life.

HDCT—to date—should not be considered as an alternative to SDCT as first-line therapeutic approach in MGCT patients, mainly because MGCTs are highly sensitive to standard cisplatin-based chemotherapy regimens and the abovementioned studies did not show a clear benefit when upfront HDCT is adopted in this specific subset of patients.

HDCT could be therefore considered as second-line chemotherapy in inoperable patients with persistent non-seminomatous MGCTs after first-line SDCT or advanced non-seminomatous MGCTs relapsed after SDCT and surgery, given the chance to obtain a meaningful response.

It is however clear that HDCT regimens could not be administered in all GCT patients for several reasons. First of all, a high-volume center expertise is required for optimal management of high-dose related hematological toxicities and also for survivorship care. Secondly, when a HDCT scheme is adopted, regimen and sequence seem to be crucial in relation to survival outcome, possibly modulating them according to early clinical and STM responses. Thirdly, a huge percentage of patients could achieve complete remission from standard dose as well, thus sparing themselves unnecessary toxicities.

In conclusion, HDCT could be offered to MGCT patients, but only after proper selection, i.e., through better prognostic stratification or genomic profiling in the next future—and possibly, if available, in the context of randomized clinical trials.

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