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Review – Testis Cancer

High-Dose Chemotherapy plus Stem Cell Transplantation in Advanced Germ Cell Cancer: A Review

Roisin M. Connolly^{a,b,*}, John A. McCaffrey^b

^a Sidney Kimmel Comprehensive Cancer Centre, Johns Hopkins School of Medicine, 1650 Orleans Street, CRB 1, Room 186, Baltimore, MD 21231-1000, USA

^b Department of Medical Oncology, Mater Misericordiae University Hospital, Eccles St, Dublin 7, Ireland

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Abstract

Context: High-dose chemotherapy (HDCT) with stem cell transplantation (SCT) has been investigated as a treatment strategy for advanced germ cell cancer (GCC) for >2 decades. In an effort to improve on the overall cure rates of 80% achievable with conventional chemotherapy, researchers have investigated this therapeutic option as a first-line therapy for those with poor-prognosis disease and as a salvage therapy for those with relapsed or refractory disease.

Objective: The primary objective of this review is to define the role of HDCT plus SCT in advanced GCC. Prognostic indicators for this group of patients are also presented.

Evidence acquisition: A Medline search of English-language literature was performed to identify studies published in the last 20 yr relating to the use of HDCT plus SCT in advanced GCC. Phase 1, phase 2, and phase 3 trials were included, as were retrospective reviews and meta-analyses.

Evidence synthesis: Phase 2 trials investigating HDCT plus SCT as a therapeutic option for advanced germ cell cancer have indicated a survival advantage over conventional chemotherapy. This has not been confirmed in the phase 3 setting. Alternative chemotherapeutic strategies and options following failure of HDCT plus SCT are discussed.

Conclusions: Studies to date have not indicated a survival advantage for the use of HDCT plus SCT in advanced germ cell cancer. Many questions, however, remain unanswered, and further research is required to identify whether optimising the strategy of HDCT plus SCT will improve outcome in this predominantly young group of patients.

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* Corresponding author. Sidney Kimmel Comprehensive Cancer Centre, Johns Hopkins School of Medicine, 1650 Orleans Street, CRB 1, Room 186, Baltimore, MD 21231-1000, USA.
Tel. +1 4109558893; Fax: +1 4109558587.
E-mail address: rconnol2@jhmi.edu (R.M. Connolly).

1. Introduction

1.1. Germ cell cancer

Testicular germ cell cancer (GCC) is a rare disease accounting for only 1% of all male malignancies [1]. It is, however, the most common solid neoplasm in the male population aged 15–34 yr [2]. Five-year survival rates in patients with metastatic GCC have reached 80% since the advent of cisplatin-based chemotherapy >30 yr ago [3]. For good-prognosis disease, three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP), followed by surgical resection of residual masses, is standard first-line therapy [4,5]. A 5-yr survival rate of 91% is achieved with this strategy, and the main aim of current research is to minimise the toxic effects of treatment [6–8].

Results are not as favourable for those with intermediate- and poor-prognosis disease; 5-yr survival rates are 75–80% and 50%, respectively [6]. Over the years, research efforts to improve survival in these groups have included double-dose cisplatin regimens [9], dose-intensification regimens [10], the incorporation of paclitaxel [11], and the use of high-dose chemotherapy (HDCT) plus autologous stem cell transplantation (SCT). For those patients who relapse after first-line therapy, standard-dose salvage chemotherapy can achieve long-term remission in 10–40% of patients [12]. Attempts to improve on these results have also included the use of HDCT plus SCT.

This article reviews the role of HDCT plus SCT in advanced germ cell tumours (GCTs), both as first-line treatment for those with poor-prognosis disease and in the salvage setting.

1.2. High-dose chemotherapy plus stem cell transplantation

Bone-marrow transplantation (BMT) has been used in the treatment of cancer since the late 1960s. It allows the administration of HDCT and radiation therapy that would cause severe or lethal myelosuppression if given alone. Peripheral SCT (PSCT) avoids a surgical procedure, and recovery after engraftment occurs earlier with PSCT [13,14].

The direct toxic effects of chemotherapy include nausea and vomiting, mucositis, and alopecia. Severe myelosuppression, resulting infectious complications, and veno-occlusive disease are early complications. Graft failure and graft-versus-host disease may also occur. Late complications of this strategy include infertility, early menopause, hypothyroidism, cataracts, and secondary malignancies. Recent studies have reported that the risk of secondary myeloid leukaemia is between 2% and 3%, similar to that expected with a salvage regimen consisting of four courses of standard-dose etoposide [15,16]. Improved supportive care and less pretreatment has reduced the morbidity and mortality associated with this procedure in recent years.

2. Evidence acquisition

A Medline search of English-language literature published between January 1988 and June 2008 was performed in

order to identify publications relating to the use of HDCT plus SCT in advanced GCC. The following key words were used as search terms: *germ cell cancer, testicular cancer, high-dose chemotherapy, stem cell transplant*. The references of the articles obtained were also reviewed for potentially relevant publications. The early phase 1 and phase 2 trials investigating the role of HDCT plus SCT in these settings are initially presented to provide historical perspective. This is followed by a detailed description of recent phase 3 trials. Retrospective studies and meta-analyses are also included.

3. Evidence synthesis

3.1. Prognostic indicators

In 1997, the International Germ Cell Cancer Collaborative Group (IGCCCG) presented a new prognostic-factor staging system for untreated metastatic GCC (Table 1). Its aim was to facilitate international collaboration and to standardise risk-based decisions on therapy. Retrospective data included 5202 patients with nonseminomatous GCT (NSGCT) and 660 patients with seminomatous tumours. Primary end points of the study were progression-free survival and overall survival. Adverse risk factors identified for NSGCT at time of diagnosis included primary mediastinal tumour, degree of elevation of alfa-fetoprotein (AFP), degree of elevation of human chorionic gonadotropin (hCG), degree of elevation of lactic dehydrogenase (LDH), and the presence of nonpulmonary visceral metastases (NPVM) including the liver, bone, and brain. Patients were divided into the following categories for prognosis: good, intermediate, and poor (Table 1). This is now the generally accepted prognostic tool used to aid treatment decisions and to determine eligibility for clinical trials [6].

Predictors of prognosis for those with relapsed or refractory GCT receiving conventional-dose salvage chemotherapy have been reported in various clinical trials, but few have suggested prognostic classifications for clinical use. Prior complete response to chemotherapy, good-prognosis group at initial diagnosis and primary tumour of the testis were found by multivariate analysis to be statistically significantly associated with increased likelihood of favourable response to vinblastine, ifosfamide, and cisplatin (VeIP) salvage therapy ($n = 135$). This study included 32 patients with extragonadal GCC, none of whom survived [17]. In a cohort of patients treated with VeIP or etoposide, ifosfamide, and cisplatin (VIP) as salvage therapy, survival and durable complete remission was also found to be superior for those with both primary tumour of the testis and complete response to first-line therapy versus those with extragonadal primary cancer or those with primary tumour of the testis and incomplete response to first-line therapy [18]. Fossa et al identified prognostic factors for 164 patients with progressive GCC after cisplatin-based chemotherapy and suggested categorisation of patients with good prognoses and poor prognoses based on multivariate analysis. A progression-free interval <2 yr from the beginning of first-line therapy, less than a complete response to induction chemotherapy, and high markers at

Table 1 – International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic classification

Prognosis	Patients, % (NSGCT, SGCT)	5-yr survival (NSGCT, SGCT)	NSGCT	SGCT
Good	56%, 90%	92%, 86%	Testes/retroperitoneal primary <i>and</i> no NPVM <i>and</i> all of the following: AFP <1000 ng/ml, hCG <5000 IU/l, <i>and</i> LDH <1.5 normal	Any primary site <i>and</i> no NPVM <i>and</i> normal AFP, any hCG, any LDH
Intermediate	28%, 10%	80%, 72%	Testes/retroperitoneal primary <i>and</i> no NPVM <i>and</i> any of the following: AFP ≥1000–≤10 000 hCG ≥5000–≤50 000 IU/l LDH ≥1.5 normal to ≤10 times normal	Any primary site <i>and</i> NPVM <i>and</i> normal AFP, any hCG, any LDH
Poor	16%, NA	48%, NA	Mediastinal primary or NPVM <i>or</i> any of the following: AFP >10 000, hCG >50 000 IU/l, <i>or</i> LDH >10 times normal	NA

NSGCT = nonseminomatous germ cell tumour; SGCT = seminomatous germ cell tumour; NA = not applicable; NPVM = nonpulmonary visceral metastases; AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; LDH = lactic dehydrogenase.

progression (AFP >100 kU/l and/or hCG >100 IU/l) predicted a poor prognosis. Patients with all three factors had a 3-yr survival rate of 0%, whereas those with (at most) two of these risk factors had a 5-yr survival rate of 47%. Complete data, however, were available for only 102 patients; only 15 patients received an ifosfamide-containing regimen, so the clinical significance of this prognostic classification is questionable [19].

Prognostic variables relating to treatment outcome after HDCT in patients with relapsed or refractory GCC have also been identified. A retrospective multivariate analysis was performed by Beyer et al to identify those patients who would benefit from treatment intensification, in an effort to avoid exposing others to a futile and toxic treatment regimen ($n = 283$). The vast majority of patients reviewed had failed to respond to a cisplatin-based first-line regimen and at least one conventional-dose salvage regimen prior to HDCT. Five variables were identified at the time of commencement of HDCT as independent predictors associated with treatment failure:

- Progressive disease before HDCT (an increase of any radiologically measurable tumour by >25% or a >10% increase of elevated tumour markers)
- Primary mediastinal tumour

- Refractory disease before HDCT (when at least stable disease or better was achieved but evidence of tumour progression within 4 wk of the last cisplatin-based chemotherapy)
- Absolute refractory disease before HDCT (when not even stable disease was achieved, despite cisplatin-based chemotherapy)
- hCG >1000 IU/l.

Patients were stratified into categories of prognosis: good (score of 0), intermediate (score of 2), and poor (score of >2). These categories were associated with 51%, 27%, and 5% failure-free survival rates, respectively [20]. The majority of patients investigated during this treatment period (1984–1993) received a single cycle of HDCT (Table 2).

Einhorn et al more recently conducted a review of 184 consecutive cases of HDCT administration in the setting of progressive GCC after cisplatin-based chemotherapy between 1996 and 2004 [21]. Patients had received varying numbers of chemotherapy regimens prior to administration of HDCT; 73% of patients had received only one regimen. Those with primary mediastinal GCT or late relapse had not been offered HDCT during this period. The following variables were significantly associated with worse progression-free survival:

Table 2 – Factors with multivariate significance for failure-free survival (FFS) after high-dose chemotherapy (HDCT) [20]

Factors with multivariate significance for FFS after HDCT	HR	95% CI of HR	<i>p</i> value	Score
Progressive disease before HDCT	1.51	1.06–2.06	0.024	1
Primary mediastinal tumour	1.69	1.06–2.69	0.029	1
Refractory disease before HDCT	1.71	1.19–2.46	0.004	1
Absolute refractory disease before HDCT	1.98	1.28–3.06	<0.002	2
Pre-HDCT HCG >1000 IU/l	2.38	1.61–3.52	<0.001	2

CI = confidence interval; HCG = human chorionic gonadotropin; HR = hazard ratio.

Table 3 – Multivariate Cox proportional hazards analysis and prognostic score [21]

Prognostic variable	HR (95% CI)	p value	Prognostic score
Third-line or subsequent chemotherapy	2.19 (1.35–3.56)	0.002	3
Platinum-refractory disease	1.74 (1.01–3.00)	0.05	2
IGCCCG high-risk stage	1.67 (1.00–2.78)	0.05	2

HR = hazard ratio; CI = confidence interval; IGCCCG = International Germ Cell Cancer Collaborative Group.

- Third-line or subsequent chemotherapy (3 points)
- Platinum-refractory disease (2 points; tumour progression within 4 wk after the most recent cisplatin-based chemotherapy)
- IGCCCG poor-prognosis category (2 points).

A score of 4–7 (high risk) indicated a low probability of disease-free survival and zero points indicated a high probability of disease-free survival (Table 3).

3.2. High-dose chemotherapy plus stem cell transplant as first-line treatment of poor-prognosis disease

HDCT plus SCT has been used as a first-line treatment option in poor-prognosis patients whose disease is cisplatin resistant. Standard cisplatin-based chemotherapy is initially administered, and patients with a delayed or unfavourable response have proceeded to dose-intensive therapy. Until recently, due to small patient numbers, there was a lack of phase 3 randomised data in this area. Evidence had previously been derived from small phase 2 studies, and the only randomised study among these had failed to show a benefit of HDCT over conventional treatment [22]. Long-term results of this trial at a median follow-up of 9.7 yr confirmed this earlier conclusion. The results, however, are difficult to interpret because the dose-intensity in the high-dose arm was low, and the four-drug regimen used (vinblastine, etoposide, cisplatin, and bleomycin) was not standard [23].

In 1993, the German Testicular Cancer Study Group began a single-arm, multicentre, phase 1/2 trial with stepwise dose escalation of first-line chemotherapy followed by sequential cycles of high-dose VIP plus autologous SCT. The aim of the study was to improve on the 45–50% long-term survival rates achieved with standard chemotherapy. Dose-finding trials had previously only been undertaken in the salvage setting. There were 239 patients with “Indiana” advanced disease or poor-prognosis disease enrolled. Stem cells were collected after one cycle of standard VIP. Three to four cycles of high-dose VIP were then administered. The doses of the high-dose regimen were escalated, with dose levels 3–8 receiving stem cell support. Dose level 7 (cisplatin 20 mg/m², etoposide 300 mg/m², and ifosfamide 2400 mg/m² administered day 1–5) was the maximum tolerable dose. Progression-free survival rates for those with poor-prognosis disease ($n = 182$) were 69% and 68% at 2 yr and at 5 yr, respectively. Acute myeloid leukaemia developed in 1% of patients, and 4% of patients died of treatment-related toxicities [24].

The German Study Group also published a matched-pair analysis in 1999. Patients who had received sequential

high-dose VIP and stem cell support were matched to a group who received standard treatment with BEP or VIP ($n = 423$). The progression-free survival rate at 2 yr was 75% in the high-dose group; this rate was 59% in the standard-treatment group. The figures for overall survival rate were 82% in the high-dose group and 71% in the standard-treatment group, suggesting an advantage of HDCT plus SCT over standard treatment [25].

The European Bone Marrow Transplant Solid Tumours Working Party reported that 22 patients with extragonadal GCC were treated with HDCT; 12 of these patients were treated with the Carbo-PEC regimen (high-dose carboplatin, etoposide, and cyclophosphamide). At a median follow-up of 50 mo, 68% of these patients were alive and disease free [26]. These survival rates were higher than those expected according to the IGCCCG classification.

Motzer et al identified a group of patients predicted to have <50% chance of achieving complete response and treated them with VAB-6 (cisplatin, vinblastine, bleomycin, cyclophosphamide, and dactinomycin). Delayed reduction in markers was observed in 22 patients, and these patients proceeded to high-dose carboplatin and etoposide followed by SCT. A complete response to HDCT was reported in 55% of patients, and 57% of patients were disease free at a median follow-up of 31 mo [27].

A subsequent trial with a cohort of 30 patients used VIP as standard chemotherapy. Failure to respond resulted in the use of high-dose carboplatin, etoposide, and cyclophosphamide (CEC). Overall, 57% of patients achieved a complete response, including 7 out of 14 of those who proceeded to high-dose treatment. At a median follow-up of 30 mo, 50% of all patients were disease free. A survival advantage versus standard treatment was suggested when patients were compared with historical controls [28].

The final analysis of a cooperative group, phase 3 trial in the United States comparing first-line conventional-dose chemotherapy alone or with HDCT for those with poor- or intermediate-prognosis GCC was recently reported. Patients were randomised to either four cycles of BEP ($n = 111$) or two cycles of BEP followed by two cycles of high-dose CEC plus SCT ($n = 108$). The declines in AFP and hCG during cycle 1 and cycle 2 were monitored to evaluate whether there was a correlation with long-term outcome. The trial was originally designed to target those with poor-prognosis features and aimed to detect an improvement in durable complete response at 1 yr from 30% to 50%. The eligibility criteria were later expanded to include those in the intermediate-prognosis group. Nevertheless, patient accrual was not achieved, and the trial was closed early in August 2003. No significant difference in complete response

at 1 yr was detected between the treatment groups. Durable complete response at 1 yr for the standard-dose arm was 48%; this rate was 52% for the high-dose arm ($p = 0.53$). The progression-free survival rate and the overall survival rate were worse for those patients who had slow marker decline during the first two cycles of chemotherapy ($p = 0.02$). Of these patients ($n = 67$), complete response at 1 yr was higher for those who received HDCT (61%) compared with those who received four cycles of BEP (31%) ($p = 0.03$) [29]. These results indicate that only a certain subgroup of patients may benefit from dose intensification. Further studies are required to examine this relationship before HDCT in this subgroup can be recommended.

Despite the promising results observed in many of the small phase 2 trials previously published in this area, routine use of HDCT as first-line treatment of patients with advanced GCC is not recommended. Four cycles of BEP remains the standard of care for those with intermediate- or poor-prognosis disease.

3.3. Salvage high-dose chemotherapy plus stem cell transplantation

Approximately 20–30% of patients receiving primary therapy for advanced GCC will relapse or will have an incomplete response [4,30]. Two treatment regimens show curative potential in these settings: conventional chemotherapy and HDCT plus SCT.

Conventional-dose chemotherapy can achieve a 10–40% long-term remission [12]. A 25% overall complete response is seen with use of VIP as first-line salvage treatment [31,32]. The use of paclitaxel, ifosfamide, and cisplatin (TIP) chemotherapy in a selected patient population ($n = 46$) with favourable prognostic factors resulted in a complete response rate of 63% and a 2-yr progression-free survival rate of 65% (95% CI: 51–79%) [33]. Despite this, many young patients ultimately die from their disease.

HDCT has been investigated since the 1980s as a salvage treatment. Early studies at Indiana University reported long-term survival rates of 15–20% in heavily pretreated patients but with significant morbidity and mortality [34]. This strategy is currently a recognised treatment option for patients with a second relapse because there are virtually no long-term survivors among those treated with conventional chemotherapy [34,35]. Controversy remains, however, in relation to optimal treatment in the first-line salvage setting.

A number of phase 1 and phase 2 trials have suggested the superiority of HDCT over conventional chemotherapy as an initial salvage treatment. Motzer et al focused on those with unfavourable prognostic features and used paclitaxel as part of a sequential dose-intensive regimen [36]. The Norton-Simon model was followed, which states that multiple, rapidly recycled applications of chemotherapy are more likely to eradicate residual cancer cells [37]. Paclitaxel was found to have antitumour activity as a single agent in previously treated patients, and also synergy against cisplatin resistance has been suggested in vitro [38,39]. Therefore rapid recycling of paclitaxel and ifosfa-

mid was followed by high-dose carboplatin and etoposide (TICE) in 37 patients between 1994 and 1997. A complete response was achieved in 57% of patients, and 41% of patients remained disease-free at a median follow-up of 30 mo.

A subsequent phase 1/2 trial at this centre investigated the efficacy and toxicity of a similar TICE regimen plus PSCT. Patients with an incomplete response to initial conventional chemotherapy that were believed to have a low likelihood of responding to conventional salvage chemotherapy were enrolled ($n = 47$). A complete response to chemotherapy alone was achieved in 49% of patients, and this rate rose 6% with the addition of surgical resection to dose-dense chemotherapy. At median follow-up of 40 mo, 51% of patients remained continuously disease free. Combined data from these two trials reveal a complete response in 47 of 84 patients (56%), supporting a strategy of HDCT plus SCT in this patient group [40].

A German, single-institution study reported a 66% 2-yr survival rate with initial salvage therapy in 1998 [41]. Of those patients with good prognostic variables 68% were continuously disease free, compared to 40% in the intermediate- and poor-prognosis groups. Results overall were noted to be superior to previous studies involving heavily pretreated patients, suggesting that early treatment with HDCT is beneficial [42].

Rick et al subsequently entered 80 patients who had relapsed or who had refractory GCC into an intention-to-treat trial [43]. All prognostic categories were included. Conventional-dose chemotherapy was carried out using TIP, and 78% of patients proceeded to HDCT with carboplatin, etoposide, and thiotepa (CET). Median follow-up at 3 yr revealed an overall survival rate of 30% and an event-free survival rate of 25%. This compared favourably with results of other trials and also supported the use of paclitaxel [44]. Thiotepa was used in an effort to reduce renal toxicity; however, unacceptable skin toxicity occurred, and dose reduction was required. Neurotoxicity, a significant drawback of this study, was related to the use of paclitaxel and the subsequent high-dose CET regimen. Survival rates again depended largely on prognostic variables, and there were no long-term survivors in the poor-prognosis group.

Because of the ongoing controversy over optimal treatment, a German group performed a retrospective analysis of 193 patients treated with or without HDCT as part of first-salvage treatment [20]. Hazard ratios in favour of HDCT were between 0.72 and 0.84 for event-free survival and between 0.77 and 0.83 for overall survival. The benefit of HDCT was slightly more pronounced in the poor-prognosis patients, but the sample size was small. Estimated absolute improvement in event-free survival was 6–12% for HDCT. This benefit was lower than in previous phase 1 and phase 2 studies. Those receiving conventional dose chemotherapy, however, were from a different treatment period and may not have received optimal salvage therapy.

Bhatia et al published a retrospective analysis of 65 patients treated with HDCT as initial salvage therapy [45]. Because of previous experience with patients with primary

mediastinal NSGCT whose outcome was extremely poor, these patients were excluded [46]. Patients were treated with one or two cycles of standard-dose chemotherapy, such as VeIP, for cytoreduction and to assess chemosensitivity. Two cycles of HDCT were then administered to 89.2% of patients, followed by autologous BMT or PSCT. Complete response was reported in 43% of patients, and 57% of patients were continuously disease free at a median follow-up of 39 mo.

Einhorn et al also conducted a retrospective review of 184 patients with advanced GCC who had progressed after cisplatin-based chemotherapy. Those with primary mediastinal NSGCT and those experiencing late relapse were excluded from the study. The percentage of patients being treated in the first-, second-, and third-line salvage setting were 73.4%, 24.4%, and 2.2%, respectively. VeIP was administered for cytoreduction prior to HDCT in 110 patients. Two cycles of HDCT (carboplatin 700 mg/m² and etoposide 750 mg/m² each for 3 d consecutively) followed by PSCT were administered to 173 patients. Those with a partial or complete remission after HDCT and who had normal tumour markers received maintenance doses of etoposide 50 mg/m² orally for 21 d every 4 wk for three cycles. A two-drug HDCT regimen was employed due to concerns that using a three-drug regimen would result in dose reductions of the two most active drugs in this setting, namely carboplatin and etoposide. Complete remission was observed in 116 patients (63%) at median follow-up of 48 mo. At 2 yr, 90% of these 116 patients remained free of disease. Variables significantly associated with progression-free survival were identified as described previously [21].

The only phase 3 trial comparing standard versus HDCT in the salvage setting was undertaken in Europe. This large prospective randomised trial consisted of 280 patients and compared four cycles of VIP/VeIP with three cycles of VIP/VeIP followed by one cycle of high-dose Carbo-PEC. The trial failed to show a significant benefit of HDCT over conventional-dose chemotherapy; the overall complete response rates were 43% for the VIP/VeIP group and 42% for the VIP/VeIP/Carbo-PEC group. In an unplanned subgroup analysis based on prognostic indicators, however, the 3-yr disease-free survival rates were 75% for the VIP/VeIP group and 55% for the VIP/VeIP/Carbo-PEC group for those with favourable prognoses. Significant differences were observed in event-free and overall survival based on the Indiana prognostic classification, suggesting that those with poor prognostic indicators should be spared the toxicities of HDCT [47].

The strategy used in this phase 3 trial of single HDCT after several cycles of conventional-dose therapy has been predominantly employed by European researchers. As a component of this strategy, a third chemotherapeutic agent has been added to high-dose carboplatin and etoposide such as cyclophosphamide, ifosfamide, or thiotepa at maximum tolerated doses. Use of two or more high-dose cycles has been more widely investigated in the United States (carboplatin and etoposide alone). The rationale for this approach is an assumption that upfront use of multiple high-dose chemotherapy cycles may induce cell death in a higher fraction of sensitive and intermediately sensitive

tumour cells before drug resistance develops. This assumption stems from the observation that administration of chemotherapy with a higher dose intensity can lead to improved outcome in a number of tumour types, including lymphoma [48].

In an effort to establish the most appropriate mode of administration of HDCT in patients with advanced GCC, results of a phase 3 trial comparing single versus sequential HDCT in relapsed or refractory disease were recently presented. This was a prospective, randomised, multicentre trial in which 216 patients were randomised to arm A or arm B. Arm A consisted of one cycle of VIP (cisplatin 20 mg/m², etoposide 75 mg/m², and ifosfamide 1.2 g/m² for 5 d) followed by three cycles of high-dose carboplatin 1500 mg/m² and etoposide 1500 mg/m² administered in three divided doses over 3 d followed by PSCT 2 d later. Arm B consisted of three cycles of conventional VIP followed by one high-dose cycle of carboplatin 2200 mg/m², etoposide 1800 mg/m², and cyclophosphamide 6400 mg/m² administered in four divided doses over 4 d followed by PSCT 2 d later. Recruitment was ended early due to excess treatment-related mortality in the single high-dose arm. Severe renal and unexpected cardiac toxicity and infectious complications were more common in the single HDCT arm. The 1-yr event-free survival rate was 55% in arm A; this rate was 37% in arm B. It was concluded that sequential high-dose therapy is at least as effective as single high-dose therapy, with less toxicity [49].

3.4. Options following failure of high-dose chemotherapy plus stem cell transplantation

For those patients who relapse after HDCT plus SCT, long-term, disease-free survival appears to be achievable with surgical salvage and with novel regimens incorporating gemcitabine, paclitaxel, and oxaliplatin [50–52]. In a phase 2 trial investigating the combination of paclitaxel and gemcitabine for 32 patients progressing following HDCT plus SCT, 31% of patients achieved an objective response. Four of six patients who achieved a complete response remained disease free at up to 57 mo from the start of treatment with chemotherapy alone. One patient with complete response remained disease free at 63 mo after chemotherapy and two subsequent resections of carcinoma [53]. The combination of gemcitabine and oxaliplatin has resulted in an overall response rate of 46% (95% CI: 30–64%) [54]. Management of this small group of patients should take place in cancer centres with expertise in managing GCC.

4. Conclusions

Phase 2 trials investigating the role of HDCT plus SCT as first-line therapy for patients with poor-prognosis GCC suggested a survival advantage over conventional chemotherapy. These encouraging results were not reproduced in the only phase 3 trial to date in this patient cohort. The suggestion that patients with slow marker decline may in fact benefit from this treatment strategy requires further

investigation prior to routine use of HDCT plus SCT in this subgroup.

HDCT plus SCT has been more widely investigated as a salvage therapy for those with an incomplete response to initial chemotherapy or for those with relapsed GCC. The only phase 3 trial conducted in this patient group has failed to show superiority of a single HDCT regimen over a conventional salvage regimen. Interestingly, those with favourable-prognosis disease appeared to gain benefit from this approach based on an unplanned subgroup analysis. Investigation of strategies that incorporate two or more high-dose cycles of chemotherapy may yield more promising results in future trials. This strategy, however, remains the preferred treatment option for those with a second relapse.

Despite decades of work in this area and the excellent overall cure rates for metastatic GCC, many young men unfortunately continue to die from their disease. Research remains challenging in this patient group because numbers are small and optimal accrual to large phase 3 trials has proven difficult. Issues that remain unresolved include optimum timing of therapy, choice and dose of chemotherapeutic agents, and the number of high-dose cycles used. Patients should be treated wherever possible in experienced centres and should be entered into multicentre randomised trials.

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Study concept and design: McCaffrey, Connolly.

Acquisition of data: Connolly.

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