Consolidative high-dose chemotherapy after conventional-dose chemotherapy as first salvage treatment for male patients with metastatic germ cell tumours

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Abstract

Introduction: Some men with metastatic germ cell tumours that have progressed after response to initial cisplatin-based combination chemotherapy are cured with conventional dose first salvage chemotherapy (CDCT) – however, many are not. High-dose chemotherapy with autologous stem cell rescue (HDCT) may be of value in these patients. Prognosis has recently been better defined by International Prognostic Factor Study Group (IPFSG) prognostic factors. HDCT after response to CDCT has been offered at our institution over the past two decades. We retrospectively assessed the validity of the IPFSG prognostic factors in our patients and evaluated the value of HDCT.

Methods: We identified eligible men with metastatic germ cell tumour progressed after at least 3 cycles of cisplatin-based chemotherapy and treated with cisplatin-based CDCT alone or with carboplatin-based HDCT. We also collected their clinical data. Patients were classified into risk groups using IPFSG factors, and progression-free and overall survival factors were analyzed and compared in patients treated with CDCT alone and with HDCT.

Results: We identified 38 eligible first salvage patients who had received a median of 4 cycles (range, 1 to 7 cycles) of CDCT. Twenty patients received CDCT alone and 18 patients received CDCT plus HDCT. The overall median progression- free survival was 24.6 months (95%CI, 7.3 to 28.7 months) and overall median overall survival was 34.6 months (95%CI, 17.2 to 51.3 months). Distribution by IPFSG category and 2-year progression- free survival and 3-year overall survival rates within each risk category were very similar to the IPFSG results. There were two toxic deaths with CDCT and none with HDCT. Overall, patients treated with CDCT plus HDCT had improved progression- free survival and overall survival.

Conclusions: The IPFSG prognostic risk factors appeared valid in our patient population. The safety of HDCT with etoposide and carboplatin was confirmed. HDCT was associated with improved progression- free survival and overall survival outcomes, consistent with observations of the IPFSG group. Ideally, the value of optimal HDCT should be determined in comparison to optimal CDCT as first salvage therapy in men with metastatic germ cell tumour with a randomized trial.

Introduction

Men with metastatic germ cell cancer are usually cured with combination cisplatin-based chemotherapy. Patients who relapse or progress despite first-line treatment are still treated curatively with second-line or "first salvage" chemotherapy treatment. The optimal first salvage approach is controversial. Impressive results have been reported using either conventional-dose chemotherapy (CDCT) or high-dose chemotherapy with stem cell rescue (HDCT).[1-4] However, these reports from single institutions are confounded by patient selection. A single randomized trial comparing CDCT to a HDCT strategy has been completed and reported as negative, but has also been subject to criticism and refuted to some degree by a large single institutional report influential in suggesting benefit of HDCT at first salvage.[5-8]

A prognostic classification for germ cell tumour patients undergoing first salvage treatment based on a large international database of patients treated with contemporary CDCT or HDCT has been developed by the International Prognostic Factor Study Group (IPFSG).[9] Using the same large multicentre population used to create the prognostic index, Lorch and colleagues compared the efficacy of treatment with CDCT and HDCT.[10] One or two courses of HDCT were given, and patients often received courses of CDCT prior to HDCT to stabilize disease and allow time for stem cell collection. The results of this nonrandomized retrospective study clearly favour the use of HDCT over CDCT in most subgroups of first salvage patients.

Since 1990, a consistent approach offering single course HDCT as consolidation after response to a full course of CDCT has been used at our institution. The rationale was

based on that results from the first salvage approach used for aggressive non-Hodgkin's lymphoma: response to CDCT demonstrated chemosensitivity, a full course of CDCT provided optimal cytoreduction prior to HDCT and opportunity to collect stem cells, and the cure rate might similarly be improved by eradication of persistent microscopic disease resistant to CDCT with HDCT.[11] We reviewed our experience to assess the validity of the IPFSG prognostic factors in our population and, by controlling for important prognostic factors, to more fairly compare our results with CDCT alone to full course CDCT plus single course HDCT consolidation.

Methods

Patients

Eligible patients received salvage chemotherapy for germ cell tumour between January 1, 1990 and December 31, 2010 at the London Health Sciences Centre, London, Ontario, Canada. Patients were identified from electronic pharmacy, HDCT and patient databases. The inclusion criteria of the IPFSG group were strictly observed.[9] To be eligible, patients had to be male with metastatic germ cell tumour defined either by histology and/or unequivocal serum tumour markers with: first-line chemotherapy after 1 January 1990, at least three cycles of cisplatin-based first-line chemotherapy in patients without refractory disease in response to first-line therapy, first-line treatment with etoposide, known response to first-line treatment, no HDCT as first-line treatment, unequivocal relapse or progression after first-line chemotherapy, no previous salvage chemotherapy, and first-salvage treatment with either cisplatin-based CDCT chemotherapy or carboplatin-based HDCT. Patients also had to have sufficient follow-up information to allow the calculation of the primary and secondary outcome variables, and may have had previous radiotherapy and/or surgery. Patient and tumour characteristics, treatment received and outcome information were extracted and entered into electronic data forms; included predictors were identified by the IPFSG. The toxicities of CDCT and HDCT in this setting are well-described, so only acute toxic deaths and late toxicities were recorded.[12] All data were checked by at least two reviewers (MB, EW).

Treatment

Men with metastatic germ cell tumour at first salvage were treated with CDCT consisting of ifosfamide 1200 mg/m^2 intravenous on days 1 to 5, cisplatin 100 mg/m^2 on days 1 to 5, and etoposide 75 to 100 mg/m^2 intravenous on days 1 to 5 (VIP) repeated every 21 days for up to four cycles with standard dose reductions.[13] A few patients received vinblastine 0.11 mg/kg on days1 to 2 instead of etoposide (VeIP).[14] Treatment was given at the hospital to insure adequate hydration and mesna administration. Other routine supportive measures included antiemetic therapy, prophylaxis with granulocyte colony-stimulating factor (G-CSF), and packed red cell and platelet transfusions as necessary. Surgical resection of persistent tumour masses was offered aggressively when most safe and feasible. Patients achieving complete or partial marker negative response (CR/PRm-) either before of after surgery were routinely offered HDCT as a consolidative option to potentially improve the chance of cure. The patient discussed HDCT with the oncologist and autologous transplant team physician. HDCT consisted of one cycle of high dose etoposide 1900 mg/m^2 intravenous over 34 to 40 hours given on day -7, followed by carboplatin 2000 mg/m^2 intravenous over 3 days (days -5 to -3) with subsequent stem cell rescue at day 0 consisting of at least 1 million CD34+ cells per kilogram of body weight. All patients were followed in a specialized surveillance clinic following first salvage treatment at regular intervals for up to 10 years with physical examination and tumour marker assays at each visit, and regularly scheduled chest radiographs and abdominopelvic computed tomography scans.

Statistical analyses

All eligible patients were classified into "very low," "low," "intermediate," "high" and "very high" risk categories using the IPFSG criteria, and then further classified by whether they received CDCT alone or followed by HDCT. Patient characteristics were compared using the Fisher's exact and Wilcoxon tests. Progression-free survival was measured from the start of first salvage chemotherapy to date of relapse, progression or last contact. Patients who died without progression were censored at the time of death. Overall survival was measured from the start of salvage chemotherapy to the date of death or censored at the date of last contact. Progression-free and overall survival was estimated using the Kaplan-Meier method with comparisons between subgroups made using the log-rank test (SAS 9.2, Cary NC). Upper 95% confidence limits (95%CI) for progression-free survival and overall survival were approximated using the largest censored value. The validity of prognostic classification was assessed by comparing the 2-year progression-free survival and 3-year overall survival point estimates and 95%CIs of the study prognostic subgroups with those of the IPFSG. Two-tailed p values less than 0.05 were considered significant.

Results

Patients

Fifty-seven patients were identified and 19 were excluded for equivocal relapse or progression (n = 10), first-line chemotherapy treatment prior to 1990 (n = 3), progression before completing 2 cycles of cisplatin-based first-line chemotherapy (n = 3), inadequate follow-up (n = 2) and identified as non-germ cell tumour (n = 1). The remaining 38 eligible first salvage patients were of median age 31 years (range: 16 to 53), had been followed for a median of 34.6 months (range: 0.2 to 190.4 months), and received a median of 4 cycles (range: 1 to 7) of CDCT with VIP/VeIP (n = 36) or other CDCT (n = 2) (Table 1). Twenty patients (53%) received CDCT without HDCT consolidation for the following reasons: cancer progression (n = 6), medically unsuitable for HDCT (n = 6), oncologist decision (n = 5), patient refused HDCT (n = 2), and CDCT-related toxic death (n = 1). Three of these patients received HDCT later as third-line or greater therapy. Eighteen patients (47%) received CDCT plus consolidative single course HDCT as first salvage treatment, a distribution similar to the IPFSG cohort (48% vs. 52%, respectively). All HDCT patients were in complete remission or partial remission with negative tumour markers, except two patients with partial remission and very slight elevation in a tumour marker. Autologous hematopoietic stem cells were obtained from bone marrow (n = 8), peripheral blood (n = 8) or both (n = 2).

Prognostic score assessment

All 38 patients could be categorized by IPSG risk score: very low (n = 5), low (n = 8), intermediate (n = 14), high

Table 1. Patient characteristics

	CDCT (n=20)		HDCT (n=18)		All (n=38)		
	No. patients	%	No. patients	%	No. patients	%	
Age, years							
Median (range)	28.5 (21-53)		32 (16-52)		31 (16-53)		$p = 0.77$
<40	16	80	13	72.22	29	76.32	$p = 0.71$
≥40	4	20	5	27.78	9	23.68	
Primary site							
Gonadal	14	70	15	83.33	29	76.32	
Mediastinal	2	10	0	0	2	5.26	$p = 0.68$
Retroperitoneal	2	10	2	11.11	4	10.53	
Unknown/extragonadal	2	10	1	5.56	3	7.89	
Histology							
Seminoma	1	5	6	33.33	7	18.42	$p = 0.038$
Non-seminoma	19	95	12	66.67	31	81.58	
Response to initial chemotherapy							
CR/PRM	11	55	16	88.89	27	71.05	
PRM+/SD	4	40	2	11.11	10	26.32	$p = 0.044$
PD	1	5	0	0	1	2.63	
PFI, months							
>3	13	65	14	77.78	27	71.05	$p = 0.48$
<3	7	35	4	22.22	11	28.95	
AFP salvage, µg/L							
Normal	13	68.42	10	55.56	23	62.16	$p = 0.51$
≤1000	6	31.58	8	44.44	14	37.84	
Missing	1		0		1		
HCG salvage, IU/L							
≤1000	13	68.42	16	88.89	29	78.38	$p = 0.23$
>1000	6	31.58	2	11.11	8	21.62	
Missing	1		0		1		
LBB							
No	14	70	14	77.78	28	73.68	$p = 0.72$
Yes	6	30	4	22.22	10	26.32	

CDCT: conventional-dose chemotherapy; HDCT: high-dose chemotherapy; CR: complete response; PRM: partial response marker; SD: stable disease; PD: partial disease; PFI: progression-free interval; AFP: alpha-fetoprotein; PFI: perinephric fat invasion; HCG: human chorionic gonadotropin; LBB: liver, bone or brain metastases.

Table 2. Outcomes by IPFSG risk category

Prognostic category	No. patients	2-year PFS rate (%)			3-year OS rate (%)		
		LHSC	95% CI	IPFSG	LHSC*	95% CI	IPSFG
Very low	5	80	45% - 100%	75.1	100	—	77
Low	8	50	15% - 85%	51	62.5	29% - 96%	65.6
Intermediate	14	57.14	31% - 83%	40.1	50	24% - 76%	58.3
High	6	20.83	0% - 57%	25.9	16.67	0% - 46%	27.1
Very high	5	25	0% - 67%	5.6	20	0% - 55%	6.1

*p = 0.001; IPFSG: International Prognostic Factor Study Group; PFS: progression-free survival; OS: overall survival; CI: confidence interval; LHSC: London Health Sciences Centre.

(n = 6) and very high (n = 5). The distribution of patients by risk category was similar to the IPFSG (Table 2). Statistically significant differences in 3-year overall survival were seen between risk categories for study patients. The overall median progression-free survival was 24.6 months (95%CI, 7.3 to 28.7 months) and overall median overall survival was 34.6 months (95% CI, 17.2 to 51.3 months). This compares to a median progression-free survival of 9.8 months (95% CI, 8.8 to 11 months) and median overall survival was 41 months (95% CI, 30 to 57 months), respectively, in the IPFSG population. Two-year progression-free survival and 3-year overall survival rates within each risk category were very similar to the IPFSG results, but less precise due to smaller numbers of patients, and 95% CIs were overlapping.

Outcomes by CDCT or CDCT plus HDCT treatment

There were two toxic deaths associated with CDCT (each due to sepsis and bleomycin-associated acute respiratory distress syndrome after retroperitoneal surgery). No deaths were seen with HDCT, and no patients developed acute leukemia or myelodysplasia. Univariable analyses identified that patients treated with HDCT more often had better responses to first-line chemotherapy and pure seminoma histology (Table 1). There were no other obvious differences in patient characteristics between those treated with CDCT alone or CDCT plus HDCT groups. Twenty percent of CDCT (4/20) and 75% of CDCT plus HDCT (12/18) patients were still alive at the time of analysis. Overall, patients treated with CDCT plus HDCT had improved progression-free survival (hazard ratio [HR]: 0.18; 95%CI, 0.07 to 0.51; p = 0.001) and overall survival (HR: 0.25; 95%CI, 0.10 to 0.65; p = 0.004) compared to CDCT alone (Table 3). Examination by IPFSG risk category showed that the 2-year progression-free survival and 3-year overall survival rates for CDCT pus HDCT treatment was higher in all prognostic groups, except for the very high risk which did not have any HDCT patients (Table 3). At 5 years, survival with HDCT in the intermediate group was 75% compared to 0% in CDCT (p = 0.001).

Discussion

The IPFSG deserves much credit for the difficult task of developing a prognostic classification system which has been desperately needed for men with metastatic germ cell tumours receiving first salvage treatment. Without this classification, it is extremely difficult to improve treatment for these uncommon, heterogeneous and potentially curable patients. In the current study we found that the IPFSG criteria accurately classified and appeared valid in our single centre first salvage germ cell tumour population. We also found that patients treated with HDCT at first salvage appeared to have higher cure rates than those treated with CDCT overall and within IPFSG prognostic categories, findings concordant with Lorch and colleagues[10] in their analysis of the IPFSG population.

Our study is limited by its retrospective nature and small sample size; however, it has the advantage of a homogeneous treatment approach. Lorch and colleagues[10] reported patients in their HDCT group received from zero to four

Table 3. Outcome by CDCT or HDCT treatment

	No. patients	2-year PFS rate (%)	5-year OS rate (%)
All			
CDCT	20	22.29	18.75
HDCT	18	77.78*	72.22†
Very low			
CDCT	1	0	—
HDCT	4	100	100
Low			
CDCT	5	40	40
HDCT	3	66.67	66.67
Intermediate			
CDCT	6	16.67	0
HDCT	8	87.5*	75†
High			
CDCT	3	0	0
HDCT	3	33.33	33.33
Very high			
CDCT	5	25	20
HDCT	0	N/A	N/A

PFS: progression-free survival; OS: overall survival; CDCT: conventional-dose chemotherapy; HDCT: high-dose chemotherapy; *p < 0.001, †p < 0.005.

CDCT treatments prior to one or two HDCT treatments. Our patients were planned to receive full course CDCT followed by a single course of carboplatin and etoposide as HDCT, using HDCT as a consolidative maneuver in patients with CR/PRm- after four cycles of CDCT. Our experience with this approach has shown that it is safe and feasible, and confirms the safety of HDCT using carboplatin and etoposide. Lorch and colleagues[10] did not report the toxic death rates associated with HDCT, but there is evidence that HDCT regimens containing cyclophosphamide may carry much higher risk of toxic death.[15]

Our data show more extreme advantages for HDCT compared to CDCT alone than reported by Lorch and colleagues.[10] This may be explained by a number of factors including: chance effects due to small patient numbers, patient selection (as response was required for HDCT consolidation), and poorer outcomes in our patients who received CDCT alone. Our conservative policy for HDCT use in patients not responding to CDCT may have contributed to the latter. Only three patients relapsing after first salvage CDCT alone were treated with HDCT and, as recent data suggest that tandem HDCT may be beneficial even in cisplatin-refractory patients, we may need to consider this in the future.[8] An important potential bias in both our study and that of Lorch and colleaugues[10] is the inclusion of patients suffering toxic death due to CDCT in the CDCT group, even if they were intended to subsequently receive HDCT. This affected only one patient in our study, and would be best addressed by an intention-to-treat analysis in a randomized trial.

Notwithstanding these limitations, an apparent benefit due to the addition of HDCT is apparent. The optimal amount and type of CDCT exposure in germ cell tumour patients treated with HDCT has not been carefully assessed, and has often been viewed as simply a temporary strategy while awaiting HDCT. The type and amount of CDCT prior to HDCT may be quite important. As standard treatment for first-line poor prognosis patients is four cycles of CDCT, it seems logical that the same might be true in patients receiving first salvage who are at even higher risk.[16] This might also in part explain the negative results of the IT-94 first salvage trial, where four cycles of VIP were compared to three cycles plus HDCT.[5] In addition to the toxicity of the HDCT regimen, the potential benefits of HDCT might have been abrogated by inferior CDCT exposure in the experimental arm; superior survival in the subgroup of patients receiving HDCT who were in remission after three cycles of CDCT supports this result. It may also explain the apparent advantage of tandem over single HDCT as reported by Lorch and colleagues;[10] it is possible that optimal cytoreductive CDCT prior to HDCT could minimize the need for tandem HDCT and the maintenance oral etoposide typically given post-HDCT in this situation.[8]

Conclusion

We found the new IPFSG prognostic system correctly classified our first salvage metastatic germ cell tumour patients. Questions remain about whether the choice of first salvage therapy should be determined by IPFSG risk group and, if so, the treatments that should be given. We also found similar results as Lorch and colleagues,[10] who showed higher cure rates in patients receiving HDCT as a component of first salvage treatment. As it is unlikely that HDCT provides much incremental benefit in the very low and low-risk subgroups, ideally the potential benefits of HDCT in intermediate-, high- and very high-risk patients should be confirmed in a prospective randomized trial. If such a trial is performed, our data suggest a fastidious approach to the use of conventional-dose chemotherapy at first salvage, with an optimal type, doses and duration of conventional-dose chemotherapy treatment whether patients are to receive HDCT or not. In the absence of such a trial, this will continue to be our local practice. For patients not responding adequately to initial CDCT, immediate HDCT as per Einhorn and colleagues[8] may be indicated.

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