

REVIEW

The predictors of the efficacy of high-dose chemotherapy and stem cell support in the management of metastatic germ cell cancer

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Abstract: *Objectives:* We aimed to analyze the predictors of outcome in metastatic germ cell cancer (MGCC) patients treated with High-dose Chemotherapy (HDC) and stem cell rescue.

Background: Various prognostic factors have been suggested in the treatment of metastatic germ cell cancer. However, there is no comprehensive evaluation of independent prognostic factors for the efficacy of HDC in published patient cohorts.

Methods: Thirty-two published patient cohorts with MGCC (encompassing 2176 patients; 510 patients treated upfront and 1666 at relapse) were identified from PUBMED and Cochrane Registry of Clinical Trials. Weighted Regression Analyses of these trials were conducted to define prognosticators.

Results: Independent correlates of overall survival (OAS) when all trials were considered were line of chemotherapy index, an indicator of line of HDC utilization (1st line: 71 % vs 2nd or higher line: 40 %, $p < 0.001$), and number of HDC cycles administered (1 cycle: 43 %, 1 to 2 cycles: 43 %, 2 or more cycles: 64 %, $p = 0.021$). In cohorts having HDC for relapsed disease, lower line of chemotherapy index again ($p = 0.004$), and higher median age ($p = 0.023$) were independently associated with better OAS. In trials utilizing upfront HDC, higher number of chemotherapeutics in the HDC regimen was marginally linked with improved OAS ($p = 0.047$).

Conclusion: The efficacy of various forms of HDC in MGCC patients with diverse prognostic factors may vary both as an initial or salvage therapy. Clinicians need to be aware of these factors for optimal patient selection for HDC in MGCC (Tab. 3, Fig. 2, Ref. 54). Full Text in free PDF www.bmj.sk.

Key words: high-dose chemotherapy, stem cell support, germ cell cancer, regression analysis.

Metastatic Germ Cell Cancer (MGCC) is a highly treatable disease, although the survival figures with conventional dose chemotherapy (CDC) in intermediate- and high-risk groups, 75 % and 40 to 50%, respectively, are considerably lower than in the low-risk group, 90 to 95 % (1). However, when the disease relapses or is refractory to standard treatment, the hope for cure drops considerably, although some patients can still have long-term durable responses or can be cured after CDC as a salvage treatment (2, 3).

To further improve the outcome after CDC in MGCC, HDC has been used since the 1980s with success both as an initial treatment and as a salvage strategy. However, randomized clinical trials comparing HDC with CDC are limited. Nevertheless, both approaches have been shown to be equivalent with increased toxicity in HDC (4, 5).

Many previous studies have evaluated prognostic factors in HDC-treated MGCC patients. However, these studies have been

in the form of retrospective reports, with sample populations not exceeding a couple of hundred patients, single centre reports, matched pair analyses from various centers, or other relatively small prognostication studies (6-9). At present, any quantitative review of all of the published literature questioning the predictors of benefit in MGCC from HDC is lacking. Therefore, in this study, we aimed to evaluate the predictors of outcome after HDC, in the form of a meta-regression analysis of data from published MGCC cohorts to specifically assess the influence of treatment, patient and disease-related factors.

Methods

Search strategy

PUBMED and Cochrane Registry of Clinical Trials were searched for all articles that employed HDC in MGCC patients. The search strategy included both randomized and non-randomized clinical trials. Likewise, usage of HDC both in upfront and relapsed disease settings was allowed. In the case of randomized clinical trials, only the relevant arms were taken into account.

Keywords of „((Germ cell) or Seminoma or Non-seminoma) and ((high dose) or (dose intensified)) and chemotherapy)“ were used. All studies published after 1966 and before 2008 and in

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English were considered. Additional searches, including use of the „Related articles“ function of PUBMED, and references of major reviews were also performed. Trial size smaller than 20 cases, absence of survival data or inability to retrieve survival data for the relevant arms, and inclusion of only pediatric patients in a trial were among the exclusion criteria. In the case of studies where results were published more than once, or were overlapping, only data from the most recent studies were considered.

Statistical methods

In order to perform Meta-regression analysis, separate Univariate Linear Regression analyses, by weighing the endpoints (survival with no evidence of disease (NED) or OAS) for trial size, were carried out to assess the association of potential prognostic factors (treatment, patient disease and trial features) with these endpoints. This approach where non-randomized evidence was gathered for the purpose of meta-regression analysis has been used with success in the literature (10). Significant factors after the Univariate analyses were subjected to Multivariate Regression analyses, utilizing a backward procedure for factor selection.

The normality of the distribution of the outcome variables was checked and any major deviation from normality was excluded before the Regression analyses. Likewise, the independence of outcome from the median follow-up times of individual studies was also secured, as otherwise usage of survival figures (survival with NED and OAS) as endpoints in the regression analysis could be misleading. The Regression analysis was carried out separately for trials utilizing upfront and salvage chemotherapy, and in all trials.

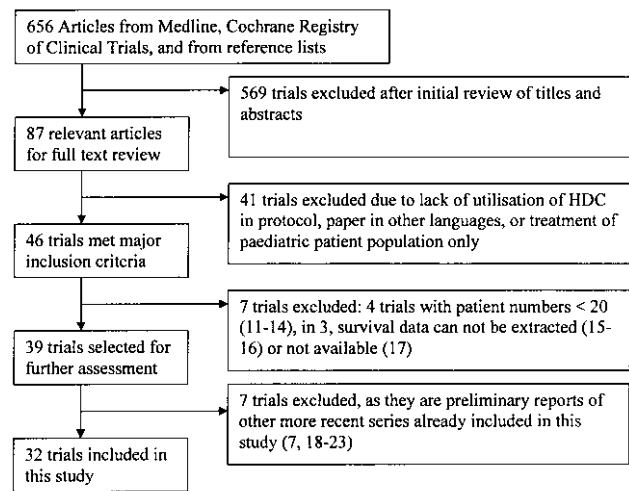
To indicate central measure for age in each trial, median or mean age was used depending on availability. Poor Risk Fraction was defined as the fraction of group with poor risk features according to the risk staging system used in that particular study. Line of Chemotherapy Index was utilized as an indicator of line of HDC administration, and was utilized as an interval variable in analyses. Line of Chemotherapy Index for each cohort was defined as the following: Line of Chemotherapy Index = ((Portion of patients having HDC 1st line (upfront)) x 1) + ((Portion of patients having HDC 2nd line) x 2) + ((Portion of patients having HDC 3rd or higher line) x 3).

Missing values for some of the variables used in the analyses (Percent Cisplatin Refractoriness and Percent Poor Risk Fraction) were replaced with the mean of that variable only in multivariate analyses. P values given are two-sided, and a value of <0.05 was considered statistically significant.

Results

Study characteristics

The search strategy yielded 656 abstracts, and 87 studies were selected for full text review after the initial elimination. At the last 2 stages of the selection process, 14 trials have been excluded for various reasons (7, 11–23). Consequently, a total of



HDC: High Dose Chemotherapy

Fig. 1. Selection of articles. Reasons for exclusion of trials from this paper.

32 cohorts encompassing 2176 patients were selected (4–6, 9, 24–51). The details of the selection progress, as well as reasons for the exclusion for individual trials, are summarized in Figure 1.

In these 32 trials, 4 were randomized, 18 were prospective non-randomized, and 10 were retrospective trials. The median trial size was 34 (min: 20, max: 221), and in most of the trials (27/32, 84 %), some form of induction chemotherapy was used. The median values for percent male, percent mediastinal primary, percent Cisplatin refractoriness, percent poor risk fraction, and line of chemotherapy were 100, 9, 22, 48 and 2.25, respectively. Table 1 presents individual study characteristics. Median follow up times were not associated with the survival outcomes. The size weighted survival with NED and OAS figures in all trials were 43 % and 48 %, respectively. Weighted survival figures are presented in Table 2. The size weighted mean toxic mortality rate for all HDC trials was 5 % (crude mean: 5 %, min: 0 %, max: 17 %).

Univariate analysis of predictors of survival

– Overall survival

Univariate correlates of weighted OAS in all trials (32 trials, 2176 patients) were line of chemotherapy index ($p < 0.001$), number of HDC cycles administered ($p = 0.010$), poor risk fraction ($p < 0.001$), Cisplatin Refractory Fraction ($p < 0.001$), type of trial ($p = 0.004$) and publication year ($p < 0.001$). In cohorts having HDC for relapsed disease (25 trials, 1666 patients), line of chemotherapy index again ($p = 0.001$), seminoma fraction ($p = 0.010$), median age ($p = 0.006$), randomization ($p = 0.042$), type of trial ($p = 0.019$) and publication year ($p = 0.013$) were associated with OAS.

In trials utilizing upfront HDC (7 trials, 510 patients), number of chemotherapeutics in the HDC regimen was marginally

Table 1. Study Characteristics																
Trial	Reference	No. of Patients	Median Age	Percent Male	Percent Seminoma Histology	Percent Medica Primary	Percent Cisplatin Refractoriness	Percent Poor Risk Fraction	Induction Chemotherapy before HDC	Percent Uplifted HDC	Line of Chemotherapy Index	HDC Regimens	Number of HDC cycles	Percent Survival Overall	Percent Toxic Mortality	
Broun 1994 [?]	24	23	30	100	n/a	0	n/a	n/a	Present	0	2	Carbo, VP-16	?2	39	50	4
Lampe 1995 ^Y	25	23	24	96	0	4	13	48	Present	0	2,57	Carbo, VP-16	1 to 2	23	52	13
Margolin 1996 ^Y	26	20	34	90	5	15	n/a	n/a	Present	25	2,3	Carbo, VP-16, I	?2	50	50	0
Motzer 1996 ^Y	27	58	29	98	7	7	57	n/a	Present	0	2,83	Carbo, VP-16, Cyc	1 to 2	21	29	12
Beyer 1996 [?]	9	283	n/a	100	n/a	9	41	48	Present	0	2,91	Carbo, VP-16 +/- I or Cyc	1 to 2	23	28	n/a
Broun 1997 ^Y	28	25	32	100	16	0	12	n/a	Present	0	2	Carbo, VP-16	?2	52	n/a	4
Beyer 1997 ^Y	29	74	27,5	100	n/a	7	32	37	Present	0	2,92	Carbo, VP-16, I	1	31	38	3
Mandanas 1998 [?]	3	21	24	86	14	0	38	n/a	Present	0	2,95	Varied, Carbo based	1	52	52	10
Rodenhuis 1999 ^Y	31	35	30,5	97	23	17	0	n/a	Present	0	2,29	Carbo, Cyc, Thio	?2	54	57	3
Decatis 2000 ^Y	32	20	28	100	0	25	0	100	Present	100	1	Carbo, VP-16, Cyc	1 to 2	60	75	0
Motzer 2000 ^Y	33	37	27	95	11	51	32	n/a	Present	0	2,22	Carbo, VP-16	?2	49	54	0
Rick 2001 ^Y	34	62	n/a	100	n/a	4	24	n/a	Present	0	2,33	Carbo, VP-16, Thio	1	26	33	2
Ayash 2001 ^Y	35	29	31	100	14	0	48	34	Absent	0	2,90	Carbo, VP-16	1 to 2	28	41	10
Beyer 2002 [?]	36	55	n/a	100	0	5	n/a	n/a	Present	0	2	Carbo, VP-16, I	1	26	32	0
Rosti 2002 [?]	37	84	29	92	4	6	n/a	21	Absent	0	2,92	Carbo, VP-16 +/- I or Cyc	1 to 2	33	37	12
Schmidl 2003 ^Y	38	221	29	100	0	13	0	82	Present	100	1	Cisp, VP-16, I	?2	66	74	4
Vaena 2003 [?]	39	78	30	97	5	16	70	28	Absent	0	2,46	Carbo, VP-16 +/- I	1 to 2	30	36	6
McNeilsh 2004 ^Y	40	36	37,4	100	28	0	33	11	Present	0	2,75	Carbo, VP-16, Cyc, Padi	1 to 2	47	50	17
Pico 2005 [*]	5	135	29	100	9	9	0	41	Present	0	2	Carbo, VP-16, Cyc	1	28	47	7
De Giorgi 2005 [?]	41	23	7	61	0	8	n/a	n/a	Present	0	2,61	Varied, Carbo based	1	43	52	0
Chaudhary 2005 ^Y	42	24	30	100	12	8	33	n/a	Present	4	2,84	Carbo, VP-16, Thio	1 to 2	38	38	7
Lotz 2005 ^Y	43	33	28	100	11	13	60	25	Present	0	2,85	Carbo, VP-16, Cyc, Thio, I	1 to 2	12	33	11
Margolin 2005 ^Y	44	33	30	97	15	9	64	33	Absent	0	2,91	Carbo, Padi, VP-16 or I	?2	36	36	3
Hera 2006 [?]	45	27	32,8	100	4	37	0	48	Present	100	1	Carbo, VP-16, I	1	68	70	0
El-Helw 2006 [?]	46	33	27	91	18	6	30	3	Present	49	1,72	Carbo, VP-16 +/- Mel or Cyc	1 to 2	55	57	6
Miki 2007 ^Y	47	25	27	100	4	0	n/a	100	Present	100	1	Carbo, VP-16, I	1 to 2	58	63	4
Droz 2007 [*]	4	57	n/a	100	0	10	0	60	Present	100	1	Cisp, VP-16	1 to 2	47	60	4
Hartmann 2007 ^Y	48	52	30	100	0	14	0	100	Present	100	1	Cisp, VP-16, I, Padi	?2	64	74	0
Motzer 2007 [*]	49	108	28	100	4	24	0	81	Present	100	1	Carbo, VP-16, Cyc	1 to 2	60	68	1
Lorch 2007 [*]	50	211	36	100	19	2	22	n/a	Present	0	2,15	Carbo, VP-16 +/- Cyc	1 to 2	47	48	9
Einhorn 2007 [?]	6	184	31	100	19	0	22	49	Absent	0	2,25	Carbo, VP-16	1 to 2	63	n/a	3
Kondeganta 2007 ^Y	51	47	32	100	11	19	81	n/a	Present	0	2,36	Carbo, VP-16	?2	51	53	0

n/a: not available or accessible, line of chemotherapy index: ((Portion of patients having HDC 1st line (upfront)) x 1) + ((Portion of patients having HDC 2nd line) x 2) + ((Portion of patients having HDC 3rd or higher line) x 3)
 ? : retrospective study, Y: non-randomised clinical trial, *: randomised clinical trial, Carbo: Carboplatin, VP-16: Etoposide, I: Ifosfamide, Cyc: Cyclophosphamide, Thio: Thiotepa, Cisp: Cisplatin, Padi: Paclitaxel, Mel: Melphalan

Table 2. Predictors of survival with High Dose Chemotherapy in Germ Cell Cancer

Features	Upfront High Dose Chemotherapy (HDC) (7 trials, 210 patients)			High Dose Chemotherapy at Relapse (25 trials, 266 patients)			All High Dose Chemotherapy Trials (22 trials, 276 patients)		
	%**	β	P	%**	β	P	%**	β	P
All Patients	62	-	-	37	-	-	43	-	-
Trial Characteristics									
Publication Year	60	0.06	0.14	30	-0.19	0.43	31	0.51	2.70
>2002	62	-0.24	-0.55	44	0.02	0.05	51	0.48	2.53
Retrospective	68	-	-	38	0.02	0.05	39	0.48	2.53
Prospective	62	-0.73	-2.41	37	-0.74	-2.46	46	0.43	2.16
Randomisation	65	-	-	37	0.08	0.40	46	0.43	2.16
Absent	56	0.06	0.14	40	-0.19	-0.43	43	0.06	0.31
Present	60	0.06	0.14	35	-0.19	-0.43	45	0.18	0.99
Single Centre	62	0.35	0.75	38	-0.13	-0.27	37	0.18	0.99
Multicentric	64	0.35	0.75	33	-0.13	-0.27	44	0.26	1.39
Patient and Disease Characteristics									
Median age	64	0.35	0.75	33	-0.13	-0.27	44	0.26	1.39
>30	68	-	-	52	0.00	-0.02	53	0.18	0.98
All Male	62	-	-	37	0.00	-0.02	45	0.18	0.98
Male and Female	-	-0.15	-0.33	37	-0.26	-1.26	37	-0.54	-3.50
Cisplatin Refractory Fraction*	62	0.32	0.74	43	-0.35	-0.83	45	-0.39	-1.92
>30%	-	0.32	0.74	30	-0.35	-0.83	30	-0.39	-1.92
Poor Risk Fraction*	62	0.32	0.74	30	-0.35	-0.83	30	-0.39	-1.92
>45%	62	0.00	-0.02	32	0.47	1.18	42	0.01	0.06
Mediastinal Germ Cell Cancer Fraction*	62	0.00	-0.02	40	0.47	1.18	47	0.01	0.06
>8%	58	0.35	0.83	43	0.35	0.83	43	-0.18	-0.83
>9%	62	0.01	0.07	31	-0.40	-0.98	43	0.50	2.67
Seminoma Fraction*	62	0.01	0.07	28	-0.40	-0.98	40	0.03	0.159
>9%	-	-	-	49	-	-	49	0.03	0.159
Treatment Characteristics									
Induction Chemotherapy before HDC	62	-	-	46	-0.35	-1.76	46	-0.08	-0.45
Absent	62	0.47	1.18	35	0.35	1.82	42	0.49	3.11
Present	68	0.47	1.18	30	0.66	1.97	33	0.49	3.11
HDC cycles administered	66	0.89	4.10	48	0.76	2.62	58	-0.30	-1.69
1 cycle	66	0.89	4.10	48	0.76	2.62	58	-0.30	-1.69
1 to 2 cycles	47	-	-	33	-0.62	-3.83	41	-0.39	-1.87
2 cycles	64	-	-	33	-0.62	-3.83	41	-0.39	-1.87
Number of chemotherapeutics in HDC	47	-	-	54	0.76	2.62	50	-0.39	-1.87
2 chemotherapeutics	64	-	-	33	-0.62	-3.83	41	-0.39	-1.87
3 chemotherapeutics	62	-	-	33	-0.62	-3.83	41	-0.39	-1.87
Line of Chemotherapy Index*	62	-	-	37	-0.50	-2.79	62	-0.64	-3.80
1st line [#]	62	-	-	37	-0.50	-2.79	62	-0.64	-3.80
2nd or higher line [#]	-	-	-	37	-0.50	-2.79	37	-0.64	-3.80

*: No evidence of disease, **: Analysed as continuous variables, #: 1st line defined as line of chemotherapy index of 1.5, and 2nd line as > 1.5, %**: mean survival weighted according to trial size, β: regression coefficient, t: t value, P: P value

Table 3. Multivariate analysis of predictors of survival with High Dose Chemotherapy in Germ Cell Cancer

Features	High Dose Chemotherapy at Relapse (25 trials, 1666 patients)						All High Dose Chemotherapy Trials (32 trials, 2176 patients)					
	Survival with NED [?]			Overall Survival			Survival with NED [?]			Overall Survival		
	β	t	P	β	t	P	β	t	P	β	t	P
Publication Year (?2002 vs. >2002)	0.03	0.21	0.834	0.13	0.72	0.479	0.40	3.55	0.001	-	-	-
Type of Trial (Retrospective vs. Prospective)	-	-	-	0.17	0.99	0.337	-	-	-	-	-	-
Randomisation (Absent vs. Present)	-	-	-	-0.12	-0.58	0.569	-	-	-	-	-	-
Median age*	0.24	1.24	0.228	0.39	2.46	0.023	-	-	-	-	-	-
Cisplatin Refractory Fraction*	-	-	-	-	-	-	-0.43	-3.77	0.001	-	-	-
Poor Risk Fraction*	-	-	-	-	-	-	0.15	1.08	0.288	-	-	-
Mediastinal Germ Cell Cancer Fraction*	-0.01	-0.12	0.909	-	-	-	-	-	-	-	-	-
Seminoma Fraction*	0.53	4.57	<0.001	0.21	0.97	0.345	-	-	-	-	-	-
HDC cycles administered (1 vs. 1 to 2 vs. ?2 cycles)	-	-	-	-	-	-	0.42	3.88	0.001	0.20	2.46	0.021
Number of chemotherapeutics in HDC (2 vs. ?3)	-0.43	-3.75	0.001	-	-	-	-	-	-	-	-	-
Line of Chemotherapy Index*	-0.23	-2.04	0.054	-0.52	-3.24	0.004	-0.26	-1.24	0.224	-0.18	-10.44	<0.001

? : No evidence of disease, *: Analysed as continuous variables, β: regression coefficient, t: t value, P: P value

linked with OAS (p=0.047). Refer to Table 2 for details of univariate regression analyses.

– Survival with NED

When all trials were considered, univariate predictors of weighted survival with NED were line of chemotherapy index (p<0.001), number of HDC cycles administered (p=0.004), poor risk fraction (p=0.001), Cisplatin refractory fraction (p=0.001), and publication year (p=0.001). For trials with HDC usage for relapsed disease, line of chemotherapy index (p=0.010), number of chemotherapeutics in HDC (p=0.001), Seminoma fraction (p<0.001), mediastinal germ cell fraction (p=0.045), median age (p<0.001), and publication year (p=0.002) were predictors of survival with NED. In the subgroup of trials where upfront HDC was utilized, number of chemotherapeutics in HDC predicted survival with NED. The details of the univariate regression analyses and corresponding size weighted survival figures are presented in Table 2.

Multivariate Analysis of Predictors of Survival

Multivariate analyses were conducted for all trials and trials using HDC in the relapsed disease setting. For all trials, the independent predictors of OAS were line of chemotherapy index (1st line: 71 % vs 2nd or higher line: 40 %, p<0.001) and HDC cycles administered (1 cycle: 43 %, 1 to 2 cycles: 43 %, 2 or more cycles: 64 %, p=0.021). In all trials, the associates of survival with NED were HDC cycles administered (p=0.001), Cisplatin refractory fraction (p=0.001) and publication year (p=0.001). In trials where HDC was given at relapse, line of chemotherapy index (p=0.004) and Cisplatin refractory fraction p=0.023) were linked with OAS, and number of chemotherapeutics in HDC (p=0.001) and seminoma fraction were associated with survival with NED.

The multivariate analysis is detailed in Table 3. The associations of some of the independent prognostic factors with the survival outcomes are graphically presented in Figure 2 (from 2a to 2e).

Discussion

Our study is the largest review in MGCC patients receiving HDC, and characterizes the prognostic value of some of the clinically important features in this patient population. First, we show that the number of HDC cycles administered is independently associated with survival. A minimum of 2 cycles seems to be necessary for better survival, as giving only 1 cycle of HDC, as opposed to 2 or more cycles, is associated with 20 % less OAS and 25 % less survival with NED. However, the experience with using 2 or more HDC cycles is limited in the literature. Among the trials evaluated by this review, only 2/7 (29 %) of upfront HDC trials, and 7/25 (28 %) of HDC trials in the relapsed setting made use of >2 HDC cycles. Likewise, there is only 1 RCT published so far comparing HDC with CDC in relapsed MGCC, and although this is a negative trial, it uses only 1 cycle of HDC (5). Similarly, in 2 other RCTs that question the role of HDC as an initial treatment modality (4, 49), all made use of 1 to 2 cycles of HDC. The importance of the number of HDC cycles has been highly controversial up to now. Although a retrospective series of MGCC patients suggested improved 2-year failure free survival with 2 cycles as opposed to 1 cycle of salvage HDT, 37 % vs 21 %, respectively (39), a RCT failed to demonstrate an effect of number of the HDT cycles on the outcome (50). Obviously, further RCTs both in the initial and relapsed disease settings that utilize 2 or more cycles of HDC are needed to further test if HDC is more effective than CDC.

Older patient age in this study appears to be another positive predictive factor for OAS in relapsed MGCC patients. To our knowledge, this is the first report showing this association. Older patient age may theoretically be associated with less aggressive biology, or better response to HDC. At this stage, the reasons for this association remain unknown. It is also impossible to exclude that this association may have arisen purely by chance.

Another influential prognostic factor from this study, confirming previous reports, emerged as the line of HDC administration. Indeed, a recent retrospective review revealed that in

Figure 2a. Line of High-Dose Chemotherapy and Overall Survival

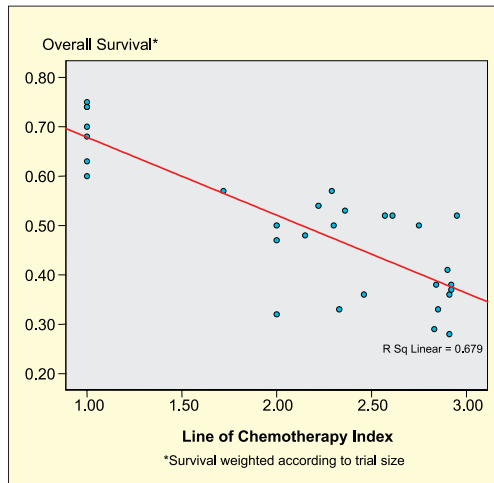


Figure 2d. Cisplatin Refractoriness and Survival with No Evidence of Disease

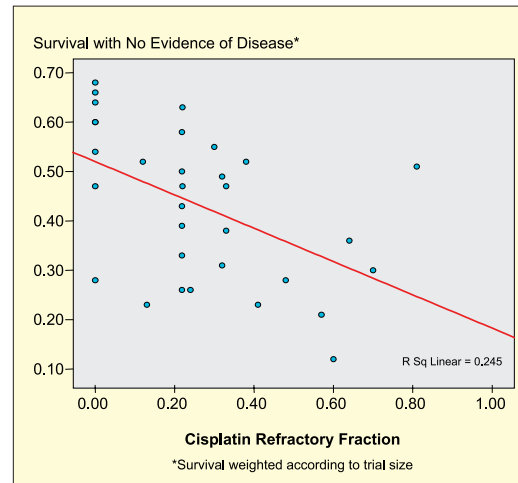


Figure 2b. High-Dose Chemotherapy cycles and Overall Survival

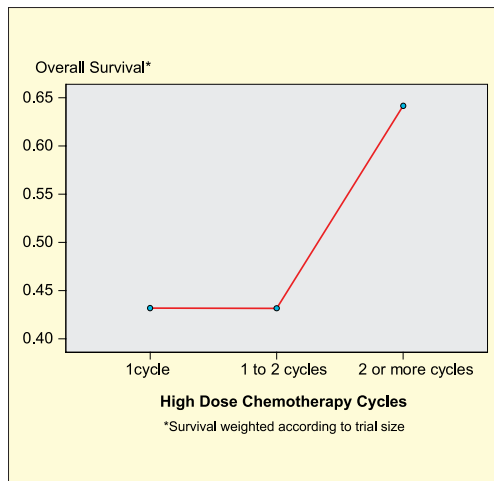


Figure 2e. Publication Year and Survival with No Evidence of Disease

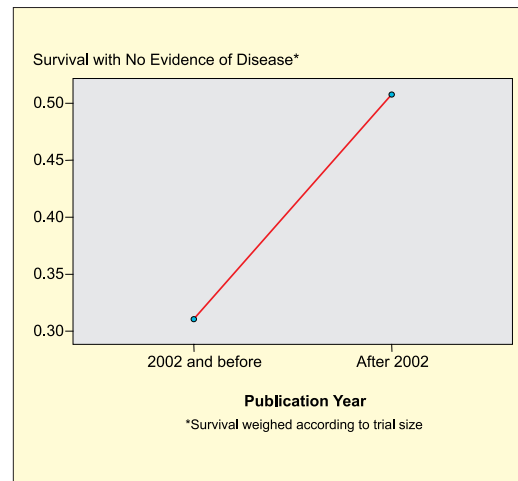


Figure 2c. High-Dose Chemotherapy cycles and Survival with No Evidence of Disease

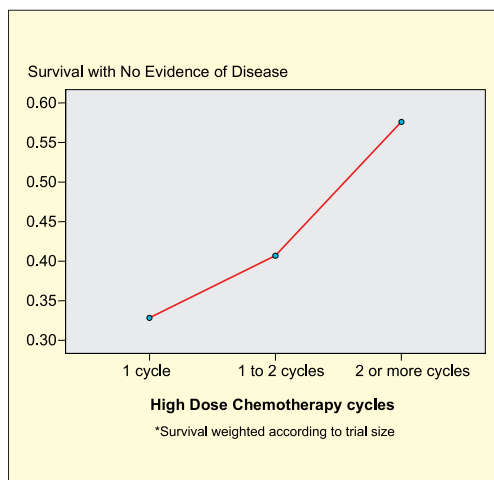


Fig. 2 (2a to 2e): Impact of significant prognosticators on survival in metastatic germ cell patients treated with high-dose chemotherapy. Treatment, disease and trial features that predict improved benefit from high-dose chemotherapy in metastatic germ cell cancer.

patients with progressive MGCC and treated with HDC, line of HDC administration was the most important prognostic factor (6). Similarly, line of chemotherapy was the most influential prognostic factor in this study, both in relapsed disease trials, and in all trials. Specifically, we found that 1st line versus 2nd or higher line HDC usage was associated with a 31% improvement in OAS. Thus, it may be important from a clinical point of view to select patients that are unlikely to respond to CDC, and treat them early during the course of MGCC with HDC. One such strategy can be to select patients according to their rate of marker response to CDC, since usage of HDC, when compared with continuation of CDC, in patients who have unsatisfactory marker decline to CDC was associated with improved durable complete response rates (49).

There was a trend to significance between Cisplatin refractoriness and OAS in relapsed disease trials, as well as a powerful link with survival with NED in all trials. This finding again confirms the findings of Einhorn et al., and Beyer et al (6, 9), where Cisplatin refractoriness was found to be among the most important prognostic factors for this patient population.

Another influential prognostic factor that is also new in this study is the seminoma fraction, implying HDC treatment results are better in patients with that histopathology. Although it was shown in MGCC patients treated with CDC that cases with seminoma had survival figures similar to those with non-seminoma histology (52), in patients treated with salvage HDC, there was a non-significant decrease in the hazard of death in the univariate analysis for patients with seminoma histopathology (6).

We also found that the more recent publication year was closely associated with the outcome among the HDC trials evaluated in this study, with a 20 % improved rate of survival with NED after 2002. This may reflect better patient care, improved experience in the treatment of this disease, or technical refinements in the field of stem cell transplantation like usage of peripheral stem cells instead of bone marrow stem cells. Indeed, peripheral stem cell transplantation has been shown after HDC to reduce time to transfusion independence, but it did not improve outcome over bone marrow transplantation (17). Similar to our findings, a previous report had shown in relapsed MGCC patients treated with CDC that more recent year of relapse treatment was associated with a 22 % better 2-year survival rate (52).

Number of chemotherapeutics used in the HDC protocols emerged as another novel prognostic factor in this patient population. Interestingly, treatment with 2 agents (Etoposide and Carboplatin) in HDC protocol for relapsed MGCC was a superior approach compared to 3 or more agents, where as in the upfront setting, the latter was better. This is a new finding and may indicate different tumor characteristics in different settings. In order to overcome the drug resistance problem in relapsed or progressive MGCC, increasing the dosages of chemotherapeutics while keeping the number of drugs limited, i.e., 2 agents only, may be the best approach. This approach was favored especially by centers in USA (6, 24, 33) However, in the initial treatment of MGCC, it may be important to administer at least 3 drugs to maximize cell killing. Indeed, when CDC is used initially, BEP is the current gold standard to treat MGCC, and has been shown to yield better outcomes compared to 2 agents (53). Obviously, more and better evidence is required to conclude further on the number of agents necessary in HDC protocols to ensure the best outcome.

The debate over the superiority of HDC over CDC or dose intense chemotherapy is still open. In the light of our findings, we believe that further RCTs with tandem HDC, both as upfront treatment and in the relapsed disease setting, are needed to answer whether HDC should be preferred to CDC in the 1st or 2nd line settings. For these trials, integration of targeted therapies in these study protocols like trastuzumab, thalidomide, imatinib (54), and testing of surrogate markers that may prove useful in predicting subgroup of patients likely to benefit from HDC over CDC,

may represent other important strategies that may improve the treatment results. In the 3rd line treatment setting, HDC appears to be the main curative modality with a limited success rate (6).

In short, in this paper, we propose new treatment and patient factors that may help shape further HDC clinical trials in MGCC. It is likely that a subgroup of high-risk patients may be better served by HDC, but further studies are needed to select these patients and to treat them using more effective protocols. Especially further RCTs in this setting are still needed to guide treatment in patients with progressive MGCC.

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