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Prediction of Long-term Response after High-dose Chemotherapy with Autologous Bone Marrow Transplantation in the Salvage Treatment of Non-seminomatous Germ Cell Tumours

Jean-Pierre Droz, Andrew Kramar and José-Luis Pico

High-dose chemotherapy (HDCT) and autologous bone-marrow transplantation (ABMT) are widely used in the salvage treatment of non-seminomatous germ cell tumours (NSGCT). We compiled 10 published series with NSGCT patients treated by HDCT and ABMT. Several prognostic factors for long-term non-evolutive disease (NED) were studied: dose of etoposide (ETO), oxazaphosphorine derivate (OXA) (expressed in cyclophosphamide equivalents using a cyclophosphamide/ifosfamide ratio of 1:3), platin-derivate (PLAT) (expressed in cisplatin equivalents using a cisplatin/carboplatin ratio of 1:4), disease status (refractory or responder), OXA and PLAT compounds. Strong interactions were shown between disease status and PLAT and ETO. In refractory patients, logistic regression analysis showed that the doses of OXA and PLAT increase the probability of NED. Conversely, in responder patients only ETO and OXA dosages increase the probability of NED. It is concluded that the status of the disease is the most important prognostic factor for long-term NED after HDCT + ABMT in NSGCT.
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INTRODUCTION

THE ROLE of high-dose chemotherapy (HDCT) and autologous bone marrow transplantation (ABMT) in non-seminomatous germ cell tumours (NSGCT) is currently under investigation in the settings of both salvage [1, 2] and first-line treatments [3, 4]. The major drugs used are etoposide, cyclophosphamide, ifosfamide, cisplatin and carboplatin. The response rates and long-term non-evolutive disease (NED) rates seem dramatically different in cisplatin refractory and responder patients [5, 6]. We compiled results of HDCT + ABMT as salvage treatment in NSGCT patients published either in peer reviewed journals or congress abstracts [4, 7–17]. The data were then analysed

Table 1. Data base of the major trials with high-dose chemotherapy and autologous bone marrow transplantation in germ cell tumours

Etoposide (mg/m²)	Oxazaphosphorine* (mg/m²)	Platin† (mg/m²)	Responder No.	Responder NED	Refractory No.	Refractory NED	Reference
1000	4000 I	200 P	8	4	—	—	Biron [7]
1750	6400 C	200 P	14	7	18	1	Baume-Droz [4–8]
2400	0	750 CP	18	4	50	9	Broun-Nichols [9–10]
2000	0	375 CP	11	5	17	0	Rosti [11]
1500	4800 C	500 CP	17	4	21	5	Linkesch [12]
1200	4000 C	375 CP	4	0	10	2	Motzer [45]
1750	6400 C	400 CP	3	1	10	2	Pico [5]
2400	7200 C	300 CP	15	12	4	0	Barnett [15]
1200	2300 I	375 CP	28	4	8	1	Siegert [16]
2500	5000 I	500 CP	—	—	15	2	Lotz [17]
			118	41	153	22	
				271			

No. = Number of patients; NED = number of non-evolutive disease patients at 1 year; C = cyclophosphamide; I = ifosfamide; P = cisplatin; CP = carboplatin.
* Expressed in cyclophosphamide equivalent dose.
† Expressed in cisplatin equivalent dose.

using multivariate regression to estimate the probability of long-term NED for different drug dose combinations with this treatment procedure.

PATIENTS AND METHODS

Ten series totalling 271 patients with various dose drug combinations were studied and the data base used for this analysis is summarised in Table 1.

Patients were considered to be long-term NED after a minimum follow-up of 1 year without recurrence.

In order to compare the long-term NED rates according to different drug combinations we assumed an equivalence ratio between carboplatin (CP) and cisplatin (P) of 4:1 [18] and between ifosfamide (I) and cyclophosphamide (C) of 3:1 [19]. Thus, the equivalent dose of oxazaphosphorine (OXA) was expressed in mg/m² of C and the equivalent dose of platin derivate (PLAT) was expressed in mg/m² of P. P refractory disease was defined according to the Indiana University definition [6]: progressive disease while receiving optimal P combination therapy or within 1 month of the last P dose. Patients with disease response status other than refractory status were considered responders.

A logistic regression analysis [20] was used to estimate the probability of NED as a function of the different drug dose combinations and status (P refractory disease = 0, P responding disease = 1). The following variables were entered into the model: ETO (dose of etoposide in mg/m²), OXA, PLAT, disease status (STATUS). Interaction terms between each factor were also studied. Variables with a significance level $P < 0.10$ were retained in the analysis.

RESULTS

In a univariate analysis, STATUS ($P < 0.001$), OXA ($P = 0.02$) and PLAT ($P = 0.08$) attained statistical significance.

In the first step of the stepwise multivariate procedure including only main effects, OXA ($P = 0.03$) and ETO ($P = 0.06$) were significant when adjusted for STATUS.

In the second step, ETO ($P = 0.02$) was significant when adjusted for STATUS and OXA.

In the final step of the multivariate analysis including only main effects, three variables attained significance: ETO ($P = 0.02$), OXA ($P = 0.01$) and STATUS ($P < 0.001$) [deviance = 27.37, with 14 degrees of freedom (df)]. PLAT did not add any further information (deviance = 27.33 with 13 df) when added to the model. Also, the addition of the nature of either OXA (I or C) or PLAT (P or CP) did not increase the predictive ability of the model. This observation does not invalidate the use of the equivalent doses previously established.

At this stage, the goodness of fit statistic indicated that the model described only by main effects was not adequate ($P < 0.01$), so the next step involved the inclusion of interaction terms.

Table 2. Impact of drug dosage in marrow-ablative therapy for non-seminomatous germ cell tumours

	Disease status: Responder No. of patients	Responder NED	Refractory No. of patients	Refractory NED
Etoposide				
≤ 1500 mg/m²	57	21%	39	21%
> 1500 mg/m²	61	48%	114	12%
Oxazaphosphorine derivative*				
≤ 2500 mg/m²	57	23%	75	13%
> 2500 mg/m²	61	46%	78	15%
Platin derivative†				
≤ 400 mg/m²	83	40%	67	9%
> 400 mg/m²	35	23%	86	19%

* Cyclophosphamide equivalent dose.
† Cisplatin equivalent dose.

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No significant interaction between OXA and STATUS was observed. However, a strong interaction appeared between PLAT and STATUS ($P = 0.006$) and ETO and STATUS ($P < 0.001$). The deviance was equal to 8.1 with 11 df. Thus, the final model included the following variables indicating a good fit: ETO–OXA–PLAT–STATUS–(STATUS–PLAT) and (STATUS–ETO). The probability of long-term NED for a particular protocol can be estimated from the equation: $P = \exp(h)/(1+\exp(h))$ where h is a linear function of the selected variables.

$$h = -2.548 + 0.178\,\text{STATUS} + 0.00012\,\text{OXA} - 0.0012\,\text{ETO} + 0.0028\,\text{STATUS} \times \text{ETO} + 0.0053\,\text{PLAT} - 0.009\,\text{STATUS} \times \text{PLAT}$$

The multiple correlation coefficient between observed and fitted values, estimated from the model likelihood χ^2 statistic is 0.72, significant at $P < 0.0001$.

DISCUSSION

The results of this study show that disease status at the time of HDCT + ABMT is the most important prognostic variable in achieving NED status. This formal finding was suggested by different investigators in small series of patients. The multivariate analysis in this article enforces this observation. Nonetheless, an in-depth study of patient characteristics would help to adjust this finding. Other important variables could include the number of lines of previous chemotherapy, the details of drug combinations, the cumulative dose of each drug, the response after previous chemotherapy regimens, the time interval between CR and relapse. These factors were shown to be strong prognostic factors of salvage chemotherapy results [21, 22, 23, 24].

Another important issue is the role of the dose of each drug in the long-term results of HDCT + ABMT, which is expressed in the formula. The drug dosage limits were chosen to separate patients in two groups of relatively equal size and also to be of clinical significance. The dosage limits used were 400, 2500 and 1500 mg/m^2 for PLAT, OXA and ETO, respectively (Table 2).

In refractory disease patients (STATUS = 0), P derivates may play a role in achieving long-term NED. In these patients the linear function becomes:

$$h = -2.548 - 0.0012\,\text{ETO} + 0.00012\,\text{OXA} + 0.0053\,\text{PLAT}$$

The coefficients of PLAT and OXA are positive, implying that these drugs tend to increase the probability of NED. This hypothesis was suggested by Nichols *et al.* in the report of the experience of the Eastern Cooperative Oncology Group protocol with high-dose CP and ETO in refractory germ cell cancer patients [10].

In responder patients (STATUS = 1), the linear function becomes:

$$h = -2.37 + 0.0016\,\text{ETO} + 0.00012\,\text{OXA} - 0.0037\,\text{PLAT}.$$

The coefficients for ETO and OXA are positive suggesting that these drugs increase the probability of long-term NED. The function also suggests a decreased effect for increased cisplatin doses in responder patients. This finding is debatable. One major subject of doubt is the value used for establishing equivalent dose between P and CP. Several investigators have demonstrated a strong correlation between renal function and carboplatin pharmacokinetics with standard dosages of carboplatin [25]. However, similar observations were also made with high carboplatin doses [14]. On the other hand, other investigators showed that neither variability of the systemic clearance of CP nor of the area under curve (AUC) for patients treated at the same CP dose level was observed. A strong correlation, however, was observed between dose and AUC despite the fact that CP dose was not determined according to renal function [26]. Finally, in responder patients, the role of PLAT compound dose remains questionable. The role of higher dosages of ETO and OXA derivates seem important [27]. Another subject of doubt addresses the definition of refractory and responder patients in the published series. However, the disease status at the time of high-dose chemotherapy seems to be the stronger prognostic factor of success and responder patients may benefit from this procedure. Such observations must be considered in the interpretation of future trials.

Nonetheless, determining the exact role of marrow-ablative chemotherapy in the salvage setting will need prospective randomised trials.

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Evaluation of the Effect of Oral Clodronate on Skeletal Metastases with Type 1 Collagen Metabolites. A Controlled Trial of the Finnish Prostate Cancer Group

T. Kylmälä, T. Tammela, L. Risteli, J. Risteli, T. Taube and I. Elomaa

Clodronate relieves bone pain in patients with skeletal metastases. Since the pain relieving mechanism of clodronate may be associated with the antiosteoclastic activity, we have investigated whether the drug has simultaneous actions on bone resorption and pain. Although osteosclerotic metastases are characteristic of prostate carcinoma, bone resorption is also accelerated. The resorbing process can be investigated using a specific immunoassay for ICTP (cross-linked carboxyterminal telopeptide region of type I collagen) which allows the measurement of the degradation of type I collagen in serum samples. We have also determined serum concentration of PICP (carboxyterminal propeptide of type I procollagen) which reflects the synthesis of type I collagen (osteoid). Patients who have relapsed after first-line hormonal therapy, were randomised to receive estramustine phosphate (E) with or without clodronate (C) (E+C, $n = 50$; E, $n = 49$). The dose of E was 560 mg and that of C 3.2 g for the first month, thereafter 1.6 g. We saw elevated ICTP and PICP levels in the majority of the patients. A transient decrease in ICTP values occurred simultaneously with pain relief. The changes were more accentuated in the E+C than in the E group but the difference was not significant. In each group serum phosphate concentration decreased markedly ($P = 0.001$) whereas the activity of alkaline phosphatase remained increased, both indicating a development of oesteomalacia during E therapy. The short-term antiosteoclastic effect of C may be explained by the dose reduction, hyperosteoidosis and osteomalacia which inhibit the binding of C on the crystal surfaces and by the late phase of disease.
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INTRODUCTION

BONE IS the only site of metastasis in 65% of patients with prostate cancer and 80% of patients who die from the disease have bone metastases [1]. Although most of the patients respond to the first-line hormonal therapy, the median survival is between 2 and 3 years and only 30% of patients are alive at 5 years [1]. The response rate to any therapy after first relapse is much less impressive and the median survival is only 4–15 months [1–4]. We have often used estramustine phosphate (E) as a second-line treatment [4].

The main problem of relapsing disease is bone pain. Recently, intravenously administered bisphosphonates have been shown