EUROPEAN JOURNAL OF CANCER 46 (2010) 2913–2918

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Elevated LDH predicts poor outcome of recurrent germ cell tumours treated with dose dense chemotherapy ☆

Marco Gerlinger *, *Peter Wilson*, *Thomas Powles*, *Jonathan Shamash*

Department of Medical Oncology, St Bartholomew's Hospital, Barts and the London School of Medicine and Dentistry, West Smithfield, London EC1A 7BE, United Kingdom

ARTICLE INFO

Article history:
Received 1 May 2010
Accepted 7 July 2010
Available online 13 August 2010

Keywords:
Dose dense chemotherapy
Lactate dehydrogenase
Prognostic factors
Recurrent germ cell tumours
Salvage chemotherapy

ABSTRACT

Aims of the study: Prognostic factors for recurrent germ cell tumours (GCTs) treated with dose dense salvage chemotherapy have not been identified. This study determines whether lactate dehydrogenase (LDH) or established prognostic models can predict the outcome of recurrent GCTs treated with dose dense cisplatin-based chemotherapy.

Patients and methods: Retrospective analysis of 117 consecutive male patients with a first recurrence of a GCT treated with dose dense chemotherapy at a single cancer centre. Characteristics associated with progression-free survival (PFS) and overall survival (OS) were identified by univariate and multivariate analyses. Prognostic criteria published by the Medical Research Council (MRC) and the Memorial Sloan Kettering Cancer Centre (MSK) were also applied in an attempt to validate them and to compare their performance to that of LDH.

Results: Raised LDH was significantly associated with poor PFS (hazard ratio (HR) = 3.7; $p < 0.001$) and OS (HR = 3.4; $p = 0.001$). Further factors associated with poor PFS and OS, respectively, were failure to achieve a complete response or marker negative partial response for at least 6 months (HR = 2.1; $p = 0.033$) and seminoma histology (HR = 3.4; $p = 0.003$). The MRC prognostic model, but not the MSK model, identified groups of patients with statistically significant differences in PFS and OS but raised LDH predicted OS and PFS with a higher HR.

Conclusions: Raised LDH is associated with a poor prognosis in recurrent GCTs and outperforms established prognostic models in this setting. LDH as a prognostic factor should be validated prospectively and should also be assessed in patients receiving conventional dose chemotherapy regimens.

1. Introduction

Prognostic markers for patients with relapsed germ cell tumours allow risk stratification and patient allocation to conventional chemotherapy, high dose treatment or experimental regimens. The two prognostic models published by the Memorial Sloan Kettering Cancer Center (MSK)[1,2] and the Medical Research Council (MRC)[3] are widely used for the selection of good risk patients suitable for treatment with conventional dose salvage chemotherapies. Both have been established by analysing treatment outcomes of patients who received heterogeneous salvage chemotherapy regimens, the majority of which has been administered in 3-weekly intervals. At St Bartholomew's Hospital, patients with

☆ Presented in abstract form at the EAU Annual Congress in Stockholm 2009.

* *Corresponding author:* Tel.: +44 20 7601 7313; fax: +44 20 7601 7577.
E-mail address: marco.gerlinger@bartsandthelondon.nhs.uk (M. Gerlinger).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.07.004

recurrent germ cell tumours have successfully been treated with weekly dose dense cisplatin-based chemotherapy in the context of clinical trials[4,5] since 1986. Neither the MRC or the MSK prognostic models nor any other prognostic models have been validated for such dose dense salvage chemotherapy. However, we have recently found a statistically significant association between raised lactate dehydrogenase (LDH) and poor outcome in an exploratory analysis of a phase II dose dense chemotherapy trial in relapsed germ cell tumours.[5]

The presented data aim to further define the role of LDH as a potential prognostic marker by comparing its association with progression-free (PFS) and overall survival (OS) to that of other clinical characteristics in a cohort of 117 consecutive patients with a first recurrence of a germ cell tumour who were treated with dose dense chemotherapy. Furthermore, we attempted to validate the MSK and the MRC prognostic models, which do not include LDH, in our patient cohort and to compare their performance to that of LDH as a potential new prognostic factor.

2. Patients and methods

One hundred and seventeen male patients with recurrent germ cell tumours who received dose dense chemotherapy as first line salvage treatment were identified from our prospectively maintained database. Clinical trials had been approved by the relevant ethics boards and all the patients had provided informed consent for treatment. Patients were all-comers treated at a single cancer centre. Patients with mediastinal primary tumours were not included in the analysis because they routinely received high-dose salvage therapy at the time of first recurrence at our institution. All the patients had received platinum-based first line chemotherapy.

Between 1986 and 1999, patients received MBOP[4] (vincristine 2 mg on days 1, 8 and 15; cisplatin 50 mg/m^2 on days 1, 2, 15 and 16; bleomycin 15 units on days 1, 8–12 and 15; methotrexate 25 mg on day 8; repeated every 5 weeks until cycle 3, omit days 15 and 16 from cycle 3 on and repeat every 4 weeks; repeat until marker negative partial response maintained for at least 6 weeks) and from 1999 to 2007 GAMEC chemotherapy[5] (actinomycin 1 mg/m^2 on day 1; methotrexate dosed according to the glomerular filtration rate (maximum 10 g/m^2) on day 1; etoposide 90 mg/m^2 on days 1–4; cisplatin 50 mg/m^2 on days 3, 4 and 8; G-CSF from day 4; repeat every 14 days, allow 1 week break after second cycle and omit day 8 from cycle 3 on; 4 cycles total). Patients with a resectable residual mass were offered surgery after salvage chemotherapy. Treatment outcomes were classified as previously described.[4]

The MRC prognostic system[3] defines the poor risk group by: less than a complete response to initial treatment (excluding surgically induced complete response) and a progression-free interval of less than 2 years and alpha-fetoprotein (AFP) above 100 kU/L or human chorionic gonadotropin (HCG) above 100 IU/L at relapse. Patients who fulfil two or less of these criteria are in the good risk group. Seminomas had not been included when the MRC model was developed and our analyses with the MRC model also excluded patients with seminomas. According to the original MSK prognostic criteria published in 1991,[1] patients fulfilling all of the following criteria are in the good risk group: gonadal primary tumours, complete response to prior chemotherapy and pre-treatment with no more than six cycles of cisplatin-containing chemotherapy. These criteria were recently modified by replacing complete response with complete response or marker negative partial response for at least 6 months and validated in patients treated with TIP chemotherapy.[2] We used these modified criteria to determine the MSK risk group.

Progression-free survival (PFS) was defined from the start of chemotherapy to progression or death from germ cell tumour, and overall survival (OS) from the start of chemotherapy to death from germ cell tumour or treatment complications. Survival estimates were calculated by the Kaplan–Meier method. Univariate analyses were performed by the log rank test to identify clinical characteristics associated with differences in PFS and OS. A Cox regression model with stepwise selection was used to develop a multivariate model from variables that were significantly ($p < 0.1$) related to PFS or OS in the univariate analysis. Univariate Cox regression was used to calculate hazard ratios (HR) for comparison of individual prognostic factors and established prognostic models.

3. Results

The characteristics of 117 patients who received dose dense cisplatin-based salvage therapy for recurrent germ cell tumours are shown in Table 1. The median follow-up of alive patients was 6 years (range: 1–17 years) and 5-year PFS and OS were 45% and 59%, respectively.

Variables analysed previously by the MSK and the MRC authors and by our group,[5] with the exception of the number and location of metastatic sites which were not recorded in our database, were included in the univariate analysis to identify individual patient characteristics which correlated with PFS and OS after dose dense chemotherapy. A raised LDH (>480 U/L) at the time of relapse, refractoriness to first line chemotherapy (defined as progression during or within 4 weeks of chemotherapy) and seminoma histology were significantly ($p < 0.05$) associated with a short PFS (Table 2). Raised LDH and seminoma histology were also significantly associated with poor OS. Factors with $p < 0.1$ were entered into the multivariate analysis (Table 3) which identified a raised LDH and a failure to achieve a complete response or marker negative PR for at least 6 months as the only significant predictors of poor PFS. Raised LDH had the highest hazard ratio in the PFS-based analysis. Raised LDH and seminoma histology were significantly associated with a poor OS in the multivariate analysis. Kaplan–Meier survival curves of patients with raised versus normal LDH are shown (Fig. 1A). Patients treated before 1999 received MBOP chemotherapy and those treated from 1999 received GAMEC chemotherapy. In order to investigate whether LDH consistently predicted outcome over time and with different chemotherapy regimens, we analysed the association of raised LDH with poor outcome separately for both subgroups. Hazard ratios were similar in both groups for PFS (patients treated with MBOP:

Table 1 – Patients characteristics.

Characteristic		No. of patients (%)
Median age at relapse (years)		32 (range: 17–62)
Age	<35 years	73 (62)
	⩾35 years	44 (38)
Histology	Non-seminoma	99 (85)
	Seminoma	18 (15)
Primary site	Gonadal	109 (93)
	Extragonadal	8 (7)
IGCCCG prior to first line chemotherapy	Good	57 (48)
	Intermediate	30 (26)
	Poor	29 (25)
	Missing	1 (1)
First line chemotherapy	BEP	83 (71)
	EBCa	24 (21)
	Other	10 (8)
Sensitivity to first line therapy	Sensitive	89 (76)
	Refractory	27 (23)
	Unknown	1 (1)
Response to first line chemotherapy	CR	35 (30)
	IR	77 (66)
	Unknown	5 (4)
Progression-free interval	⩾2 years	15 (13)
	<2 years	102 (87)
Markers (AFP or HCG)	<100	42 (36)
	>100	73 (62)
	Missing	2 (2)
LDH	Normal	66 (57)
	Raised	26 (22)
	Missing[a]	25 (21)
Salvage chemotherapy	MBOP	66 (56)
	GAMEC	51 (44)
Response to salvage chemotherapy	CR	55 (47)
	M–ve PR	27 (23)
	M+ve PR	8 (7)
	SD	11 (9)
	PD	10 (9)
	TRD	4 (3)
	Missing	2 (2)
Sensitivity to salvage chemotherapy	Sensitive	100 (85)
	Refractory[b]	11 (9)
Further chemotherapy	High dose chemotherapy	27 (23)
	Non-high dose chemotherapy	24 (21)

IGCCCG: International Germ Cell Cancer Collaborative Group Classification; BEP: bleomycin, etoposide, cisplatin; EBCa: etoposide, bleomycin, carboplatin; CR: complete response; IR: incomplete response (patients who did not achieve a complete response); AFP: alpha-fetoprotein; HCG: human chorionic gonadotropin; LDH: lactate dehydrogenase; M–ve PR: marker negative partial response; M+ve PR: marker positive partial response; SD: stable disease; PD: progressive disease; and TRD: treatment related death.

[a] Missing LDH values: MBOP era: 22 missing and GAMEC era: 3 missing.

[b] Refractory disease: progression during or within 4 weeks of chemotherapy.

HR = 2.7; confidence interval (CI): 1.1–6.4; $p = 0.027$; patients treated with GAMEC: HR = 3.7; CI: 1.6–8.7; $p = 0.003$) and OS (patients treated with MBOP: HR = 4.7; CI: 1.9–11.6; $p = 0.001$; patients treated with GAMEC: HR = 3.2; CI: 1.9–9.6; $p = 0.036$) indicating that raised LDH was robustly associated with poor outcome in both the groups.

We then applied the prognostic criteria by the MRC and the MSK in an attempt to validate them in patients treated with dose dense therapy. The MRC prognostic model identified good and poor prognostic groups with a statistically significant difference in PFS (HR = 1.9; CI: 1.1–3.3; $p = 0.02$) and OS (HR = 2.2; CI: 1.1–4.5; $p = 0.03$). Although there was a trend to

Table 2 – Univariate analysis.

Variables	Progression-free survival (PFS)			Overall survival (OS)		
	HR (95% CI)	*p*	2 year PFS	HR (95% CI)	*p*	2 year OS
Characteristics at diagnosis and response to first line chemotherapy						
Seminoma versus NSGCT	2.0 (1.0–3.8)	0.05	29% versus 54%	3.3 (1.7–6.5)	<0.001	36% versus 72%
Extragonadal versus gonadal primary	0.9 (0.3–2.4)	0.75	50% versus 51%	1.4 (0.5– 4.0)	0.51	50% versus 68%
IGCCCG good versus intermediate	1.3 (0.7–2.3)	0.47	54% versus 45%	1.0 (0.5–2.0)	0.94	65% versus 64%
IGCCCG good versus poor	1.0 (0.5–1.9)	0.90	54% versus 53%	0.6 (0.2–1.3)	0.16	65% versus 74%
BEP versus other chemotherapy	0.7 (0.4–1.2)	0.18	53% versus 44%	1.0 (0.5–2.0)	0.91	66% versus 66%
Refractory versus sensitive	1.8 (1.0–3.1)	0.04	37% versus 56%	1.7 (0.9–3.2)	0.11	46% versus 74%
IR versus CR	1.3 (0.7–2.4)	0.34	50% versus 58%	1.6 (0.8–3.1)	0.22	61% versus79%
Characteristics at diagnosis of relapse						
Age $\geqslant$35 years versus <35 years	1.6 (0.9–2.6)	0.09	37% versus 58%	1.7 (0.9–3.0)	0.1	57% versus 71%
Less than CR or M–ve PR for 6 months versus rest	1.6 (0.9–2.8)	0.09	46% versus 61%	1.6 (0.9–3.1)	0.14	58% versus 78%
PFI $\geqslant$ 2 years versus < 2 years	1.4 (0.6–3.2)	0.48	49% versus 62%	1.2 (0.5–3.0)	0.73	66% versus 71%
AFP or HCG > 100 versus AFP and HCG $\leqslant$ 100	1.3 (0.7–2.2)	0.38	45% versus 60%	1.1 (0.6–2.1)	0.71	62% versus 75%
Raised LDH versus normal LDH	3.2 (1.7–5.9)	<0.001	23% versus 65%	3.8 (1.9–7.5)	<0.001	52% versus 74%
Type of salvage chemotherapy						
MBOP versus GAMEC	0.9 (0.6–1.6)	0.79	52% versus 48%	1.0 (0.6–1.9)	0.91	65% versus 69%

Table 3 – Multivariate analysis.

	HR (95% CI)	*p*
Cox regression model for PFS		
Raised LDH	3.7 (1.9–7.1)	<0.001
<CR or M–ve PR for 6 months	2.1 (1.1–4.2)	0.033
Cox regression model for OS		
Raised LDH	3.4 (1.7–6.8)	0.001
Seminoma	3.4 (1.5–7.5)	0.003

predict PFS and OS based on the MSK criteria, this was not statistically significant (for PFS: HR = 1.5; CI: 0.9–2.7; $p = 0.14$ and for OS: HR = 1.6; CI: 0.9–3.1; $p = 0.14$). Kaplan–Meier survival curves for groups defined by these criteria are shown (Fig. 1B and C).

Finally, we compare the performance of LDH as a prognostic factor to that of the validated MRC prognostic model directly in this patient cohort. A raised LDH significantly predicted both, PFS and OS, with a higher hazard ratio in the univariate analysis (for PFS: HR = 3.7; CI: 1.9–7.1; $p < 0.001$ and for OS: HR = 3.4; CI: 1.7–6.8; $p < 0.001$) than the MRC model (for PFS: HR = 1.9; CI: 1.1–3.3; $p = 0.03$ and for OS: HR = 2.2; CI: 1.1–4.5; $p = 0.03$). Only seminoma histology had a similarly high hazard ratio compared to LDH to predict poor OS (HR = 3.1; CI: 1.7–6.5; $p = 0.003$).

4. Discussion

Our analysis shows that patients with relapsed germ cell tumours with raised pre-treatment LDH have a significantly worse PFS and OS after second line dose dense chemotherapy. Importantly, LDH had the highest hazard ratio to predict poor PFS in the multivariate analysis. Thus, a normal LDH may be the most useful factor to identify patients who are likely to benefit from dose dense salvage treatment. We also demonstrated that the MRC prognostic model, but not the MSK model, is valid for the prediction of PFS and OS in patients treated with dose dense chemotherapy for recurrent germ cell tumours. Interestingly, none of the individual factors included in the MRC model was significantly associated with outcome in our patient cohort. This model was based on data from patients treated with a variety of chemotherapy regimens between 1982 and 1986 which may account for the differences. The MSK prognostic model was not significantly associated with outcome although patients who achieved a complete response or marker negative partial response for at least 6 months, which is one of the three MSK criteria of good risk patients, had a significantly better PFS in the multivariate analysis. Our cohort did not include patients with primary mediastinal tumours or patients pre-treated with more than six cycles of cisplatin-based chemotherapy which are both poor prognostic factors according to the MSK model. The absence of these patients may explain the poor performance of the MSK model in this analysis. Importantly, LDH alone showed a stronger association with PFS and OS than the MRC prognostic model and may therefore outperform complex scoring systems in this setting.

Our data are consistent with the results from Motzer et al.[1] who found an association of raised LDH and poor prognosis, but this was not included in the final MSK prognostic model. In contrast, an analysis of prognostic factor in patients with relapsed germ cell tumours by Beyer found no association between LDH measurements before high-dose therapy and outcome[6] but many patients had received conventional dose induction therapy before high-dose treatment which could have led to LDH normalisation. Hartmann et al.[7] also did not identify an association of raised LDH with adverse outcome but LDH measurements were only available in a small number of patients in this analysis.

The main factor associated with poor outcome that is already present at the time of initial diagnosis is seminoma his-

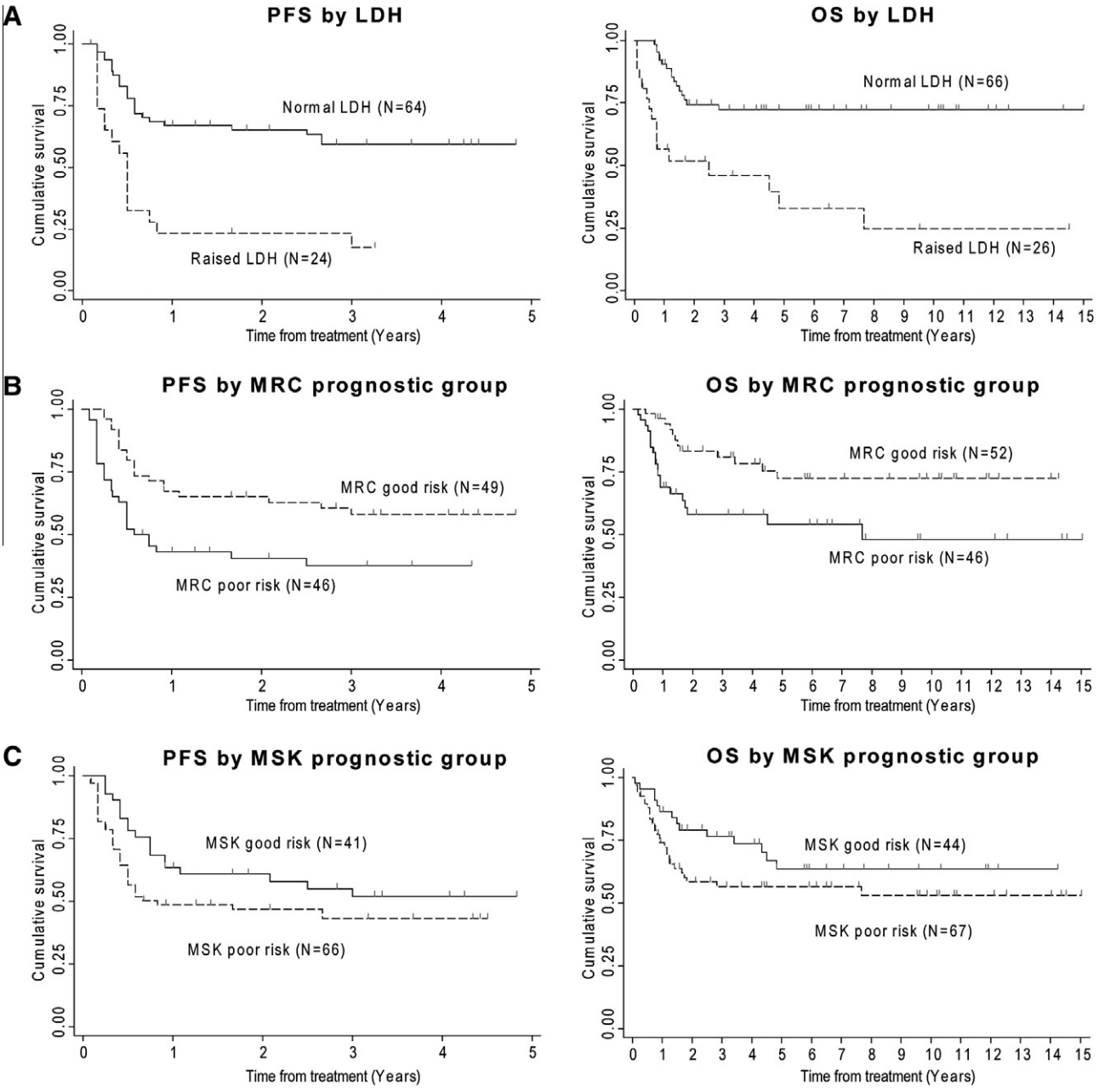

Fig. 1 – Kaplan–Meier survival estimates according to (A) raised LDH versus normal LDH; (B) MRC good risk versus MRC poor risk group and (C) MSK good risk versus MSK poor risk group. The numbers of patients do not add up to 117 patients because LDH data and data to assign patients to the MSK or MRC prognostic group were not available for all patients.

tology. This is contrary to several reports which identified seminoma histology as a good prognostic factor in patients with relapsed germ cell tumours.[8,9] Their poor outcome in our cohort may be a specific shortcoming of dose dense chemotherapy. However, the number of patients with seminoma in our analysis is relatively small and this result could be due to chance alone. These findings should be further investigated in bigger patient cohorts.

Because of the retrospective nature of our data, these results are mainly hypothesis generating. The exclusion of patients with primary mediastinal germ cell tumours who receive high-dose treatment at the time of first recurrence at our institution is a potential source of bias of our analysis. Furthermore, our analysis is based on patients treated with dose dense chemotherapy and further prospective studies should be initiated to determine whether LDH as a prognostic marker is applicable in patients treated with widely used 3 weekly salvage chemotherapy regimens like VIP (etoposide, ifosfamide, cisplatin) or TIP (paclitaxel, ifosfamide, cisplatin). Finally, a retrospective analysis cannot distinguish whether LDH is a truly prognostic factor that identifies patients with a poor prognosis in general or a predictive factor that identi-

fies those patients who will fail to gain benefit from chemotherapy. Only a randomised control trial could answer this question.

5. Conclusions

To our knowledge this is the first analysis of prognostic factors in dose dense chemotherapy of relapsed germ cell tumours. The data show that the MRC prognostic model is useful in this setting but that LDH alone may be a better predictor of treatment outcome. LDH is routinely used as a prognostic marker for several haematological malignancies and solid tumours and has proved to be a robust test in routine use despite the low specificity. LDH testing is widely available and a further major advantage of the use of LDH as a prognostic factor is that it can be used even if the previous treatment history is unclear. LDH as a potential prognostic factor in recurrent germ cell tumours should be further validated in independent patient cohorts treated with dose dense and conventional dose chemotherapy.

Sources of support

M.G. was funded in part by an Academic Clinical Fellowship from the National Institute for Health Research. We thank the Orchid Cancer Appeal for the support of clinical nurse specialists involved in delivering the treatment and of the germ cell tumour database.

Conflict of interest statement

None declared.

REFERENCES

1. Motzer RJ, Geller NL, Tan CC, et al. Salvage chemotherapy for patients with germ cell tumors. The Memorial Sloan-Kettering Cancer Center Experience (1979–1989). *Cancer* 1991;**67**(5):1305–10.
2. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol* 2005;**23**(27):6549–55.
3. Fossa SD, Stenning SP, Gerl A, et al. Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumours. *Brit J Cancer* 1999;**80**(9):1392–9.
4. Shamash J, Oliver RT, Ong J, et al. Sixty percent salvage rate for germ-cell tumours using sequential m-BOP, surgery and ifosfamide-based chemotherapy. *Ann Oncol* 1999;**10**(6):685–92.
5. Shamash J, Powles T, Ansell W, et al. GAMEC – a new intensive protocol for untreated poor prognosis and relapsed or refractory germ cell tumours. *Brit J Cancer* 2007;**97**(3):308–14.
6. Beyer J, Kramar A, Mandanas R, et al. High-dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variables. *J Clin Oncol* 1996;**14**(10):2638–45.
7. Hartmann JT, Einhorn L, Nichols CR, et al. Second-line chemotherapy in patients with relapsed extragonadal nonseminomatous germ cell tumors: results of an international multicenter analysis. *J Clin Oncol* 2001;**19**(6):1641–8.
8. Miller KD, Loehrer PJ, Gonin R, Einhorn LH. Salvage chemotherapy with vinblastine, ifosfamide, and cisplatin in recurrent seminoma. *J Clin Oncol* 1997;**15**(4):1427–31.
9. Vuky J, Tickoo SK, Sheinfeld J, et al. Salvage chemotherapy for patients with advanced pure seminoma. *J Clin Oncol* 2002;**20**(1):297–301.