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POMB/ACE Chemotherapy in Non-seminomatous Germ Cell Tumours: Outcome and Importance of Dose Intensity

David J. Husband and John A. Green

This study reports the outcome of POMB/ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, etoposide) chemotherapy in 53 male patients with metastatic non-seminomatous germ cell tumour (NSGCT) treated between 1983 and 1989 in one centre. The overall complete response (CR) rate was 62% [95% confidence interval (CI) 49–75%), and for patients with large or very large volume disease (L/VL, MRC criteria), the CR rate was 56% (95% CI 41–71%). The overall 5 year survival was 61%, and for L/VL volume disease 67%. Comparison with previous studies suggests that POMB/ACE chemotherapy is not superior to BEP, even in patients with adverse prognostic factors. Increased average relative dose intensity and increased relative dose intensity of cisplatin over the first seven courses were not associated with improved survival. However, in patients receiving a relative dose intensity of etoposide ≥ 0.75, survival at 5 years was significantly improved compared with those in whom this parameter was < 0.75 (79% vs. 44%, $P < 0.05$), suggesting that dose intensity of etoposide may be an important determinant of outcome in the chemotherapy of metastatic NSGCT.
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INTRODUCTION

IT IS now well recognised that a majority of patients with non-seminomatous germ cell tumours (NSGCT) who have advanced metastatic disease at diagnosis will survive if treated with cisplatin-containing combination chemotherapy. After the demonstration by Einhorn and Donohue that the combination of cisplatin, vinblastine and bleomycin (PVB) was associated with an 85% complete response (CR) rate, and a 64% long term survival rate [1], subsequent developments have been along two main lines. At the Royal Marsden Hospital, vinblastine was replaced by etoposide, resulting in equivalent survival but decreased toxicity [2, 3], and the BEP regimen has become the standard chemotherapy for metastatic NSGCT [4]. At other centres more complex protocols were developed incorporating

cisplatin and etoposide into existing regimes [5, 6]. In the POMB/ACE regimen [7] alternating courses of POMB (cisplatin, vincristine, methotrexate, bleomycin) and ACE (actinomycin D, cyclophosphamide, etoposide) are given as frequently as the blood count will allow (drug free interval 9–11 days) [8]. Reports from Charing Cross have shown excellent results with the POMB/ACE regimen, with over 90% long term survival [8, 9], and 70–80% long term survival in poor prognosis subgroups [10]. Despite these results, POMB/ACE has not been widely accepted. The only report of the POMB/ACE regimen from a centre other than Charing Cross supported its effectiveness in advanced subgroups [11], but others noted that these results in large volume disease were comparable with standard regimens [12]. In view of the continuing controversy we have reviewed the results of POMB/ACE chemotherapy for patients with metastatic NSGCT treated in our centre between 1983 and 1989.

Dose intensity is an important determinant of outcome of chemotherapy at a number of sites [13]. The intensity of administered treatment has been reported to affect the chance of relapse after achievement of a complete response in germ cell tumours treated with POMB/ACE [14]. We have therefore examined the effect of dose intensity on the risk of relapse after CR, and on survival in our patients.

PATIENTS AND METHODS

The study comprises 53 male patients treated in one centre between June 1983 and October 1989 and followed up for a median period of 41 months (range 12–86). Initially all patients with metastatic NSGCT were treated with POMB/ACE. Over the last 4 years patients with small volume disease were treated with BEP, and only patients with large or very large volume disease according to the MRC Working Party criteria received POMB/ACE. The mean age was 31 years (range 17–62 years). The primary sites were: testis 47, mediastinum 3, retroperitoneum 2, unknown 1. The histology was reviewed in 52 patients and confirmed to be NSGCT in all cases (malignant teratoma intermediate 10; malignant teratoma undifferentiated 30; yolk sac tumour 6; malignant teratoma trophoblastic 2; combined tumour 5).

Staging

Patients were staged by clinical examination, serum AFP and βHCG levels, computed tomography (CT) scan of thorax or conventional whole lung tomography and abdominal CT scan or bipedal lymphangiography and abdominal ultrasound, according to the Royal Marsden Hospital classification [15]. The extent of disease at presentation was then grouped according to the 1985 criteria of the Medical Research Council Working Party on Testicular Tumours [16]: small volume (S) = IM, IIA, IIB, IIIA, IIIB, $IVAL_1$, $IVAL_2$, IV BL_2; large volume (L) = IIC, IIIC, $IVCL_1$, $IVCL_2$ (i) and very large volume (VL) = L3, liver, central nervous system or bone metastases. 12 patients had small volume, 17 large volume and 24 very large volume disease.

Treatment

The POMB/ACE regimen employed is based on that used at Charing Cross [10]:

POMB

Day 1 Vincristine 1 mg/m² intravenously
Methotrexate 100 mg/m² intravenous bolus followed by Methotrexate 200 mg/m² as a 12 h infusion

Day 2 Bleomycin 15 mg by 24 h infusion
Folinic acid rescue commenced 24 h after start of methotrexate in a dose of 15 mg 12 hourly for 4 doses.

Day 3 Bleomycin 15 mg by 24 h infusion

Day 4 Cisplatin 120 mg/m² over 30 min with pre and post hydration, and magnesium sulphate supplementation

ACE

Actinomycin D 0.5 mg days 1–3
Cyclophosphamide 500 mg/m² day 3
Etoposide 120 mg/m² days 1–3
(all intravenously)

7 patients treated early in the series received etoposide 100 mg/m² on days 1–5 [7], and the other 46 the 3 day schedule above. The aim was to give courses of chemotherapy at 14 day intervals (i.e. 10 drug free days after POMB and 11 after ACE), as allowed by the blood count. Patients received two initial cycles of POMB, then alternating ACE/POMB for a minimum of seven cycles (i.e. 4 POMB × 3 ACE) and two–four cycles after the tumour markers had become normal. The policy of omitting cisplatin, but continuing alternating POMB/ACE for 12 weeks after marker remission [7] was followed in 10 patients; in the remaining patients cisplatin was not omitted. In the presence of CNS metastases the dose of methotrexate was increased to 1 g/m² with prolonged folinic acid rescue, and methotrexate 12.5 mg given intrathecally with each course of ACE. Prophylactic intrathecal methotrexate [7] was given to 6 patients. 2 patients had initial cisplatin and etoposide alone in reduced dose because of renal failure and impaired liver function, respectively [10]. Residual tumour masses, with normal serum markers, were resected or biopsied where feasible. Complete response (CR) was defined as normal tumour markers and no clinical or radiological evidence of disease, or surgery/biopsy indicating no viable cancer cells in a residual mass.

Dose intensity

Average relative dose intensity (ARDI) was calculated as described by Hryniuk *et al.* [13]. Using the standard regimen as described above, ARDI was calculated during the first seven courses of treatment (4 POMB, 3 ACE), assuming a standard intercycle time (ICT) of 14 days. The mean intercycle time (MICT) is the average time between cycles 1–7. The dose intensity of each drug in the standard regimen is expressed in form of mg/m² week, except for bleomycin and actinomycin D, whose doses are not based on surface area and are expressed as mg/week. The dose intensity of each drug actually given to individual patients during courses 1–7 was calculated in the same way. The relative dose intensity (RDI) for each drug was calculated as a fraction of the dose intensity for that drug in the standard regimen. The average relative dose intensity (ARDI) for the patient is the mean of those for each individual drug. When the patient received less than seven courses of chemotherapy the dose intensity was calculated over the number of cycles given. When carboplatin was substituted for cisplatin,

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Table 1. Haematological toxicity

	POMB	ACE
No evaluable cycle	261 (91%)	201 (92%)
WBC Nadir median (range)	2.1 (0.42–8.7)	1.35 (0.17–5.3)
WHO grade 3/4	33 (12.6%)	97 (48%)
grade 4	5 (2%)	23 (11%)
Platelet nadir median (range)	108 (8–785)	102 (11–285)
WHO grade 3/4	10 (3.8%)	8 (4%)
grade 4	6 (2.5%)	0

carboplatin 400 mg/m^2 was assumed to be equivalent to cisplatin 100 mg/m^2 for the purpose of calculating dose intensity.

The relative dose (RD) of each drug is the ratio of the dose (mg/m^2 or mg as appropriate) given in cycles one–seven to that in the standard regimen. The average relative dose (ARD) is the mean of the individual RDs. In order to compare our data with that of Cullen *et al.* [11], we calculated an index of dose rate (IDR) where IDR = (% planned dose cisplatin course 1–5) × 100 ÷ (days course 1–5).

Statistical methods

Survival analysis was performed by the method of Kaplan and Meier with comparison of survival by the logrank test [17]. Confidence intervals for survival were calculated as described by Machin and Gardner [18].

RESULTS

Chemotherapy given

The median number of courses given was nine (range 5–15) with median 5 (range 3–8) course of POMB and 4 (range 2–7) of ACE. 5 patients received less than seven courses; 3 because of progressive disease and 2 because of intolerance of further chemotherapy after five and six courses, respectively (these last 2 patients remain relapse free after 39 and 63 months, respectively). The median duration of treatment was 24 weeks (range 9–44 weeks).

Toxicity

Haematological toxicity was evaluable in 91% (261/286) cycles of POMB and 92% (201/218) cycles of ACE. (Table 1). There were 16 episodes of neutropenic fever in 16 (30%) patients. WHO grade 1 peripheral neuropathy occurred in 5 (9.5%) patients. Ototoxicity occurred in 5 patients, with significant residual bilateral high frequency hearing loss in one patient. Symptomatic bleomycin pulmonary toxicity did not occur. There were no chemotherapy related deaths.

Outcome

The overall CR rate is 62% [95% confidence interval (CI) 49–75%] with a 5 year relapse free survival (RFS) rate of 82% (95% CI 63–100%). The CR rate in patients with large or very large volume disease was 56% (95% CI 41–71%) with a 5 year RFS rate of 84% (95% CI 60–100%). After chemotherapy 16 patients (30%) had a residual mass. Biopsies were performed in 2, showing fibrosis in both, and 8 resected showing malignant teratoma in 3, differentiated teratoma in 2 and fibrosis in 3.

There have been 18 deaths (34%), of which 17 were due to progressive disease and one due to post-operative death in a patient with residual disease. Survival is shown for all patients

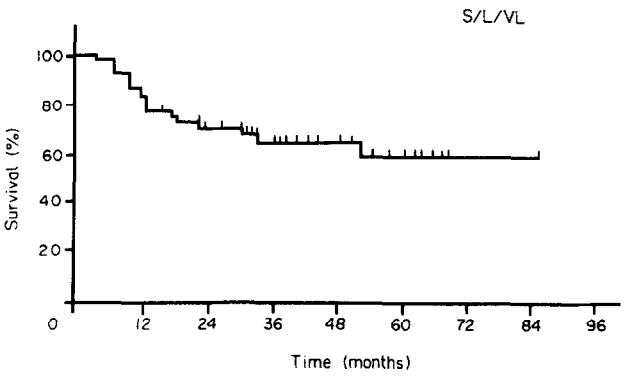

Fig. 1. Overall survival.

in Fig. 1, and divided according to the MRC Working Party prognosis criteria in Fig. 2. Of 12 patients with disease at poor prognostic sites (liver, bone, CNS metastases and mediastinal primary) 6 have died of disease.

Dose and dose intensity

The mean and range for the indices of dose and dose intensity calculated are shown in Table 2. A patient who received full protocol doses of all drugs at 14 day intervals through cycles 1–7 would have a MICT of 14 days, ARDI and RDI of 1, and an IDR of 178. Table 2 also shows the change in dose and dose intensity with time of treatment. In the second half of the study there was a significant fall in the MICT and increase in the ARDI, RDI of cisplatin and IDR, but no change in the ARD, and the RD of cisplatin. The RDI of etoposide was unchanged and the RD fell. There were no differences in ARDI, RDI of etoposide or RDI of cisplatin between those patients who did and those who did not achieve a CR. Similarly these indices did not differ between those patients achieving a CR who subsequently relapsed, and those who did not relapse.

The effects of ARDI, and RDI for cisplatin and etoposide on survival is shown in Figs 3–5, with the patients divided into two approximately equal groups, with ARDI/RDI < 0.75 and $\geqslant 0.75$, respectively. There is a trend for ARDI $\geqslant 0.75$ to be associated with increased survival (Fig. 3), but the difference is not significant. The RDI of cisplatin has no effect on survival (Fig. 4). A RDI etoposide $\geqslant 0.75$ is associated with a significant increase in survival for all patients (79% vs. 44%, 95% CI of difference 4–65%, hazard ratio 0.35, $\chi^2 4.34$, $P < 0.05$) (Fig. 5). The effect for the L/VL volume group is similar (survival 79% vs. 48%, 95% CI difference 0–62%, hazard ratio 0.37, $\chi^2 3.11$,

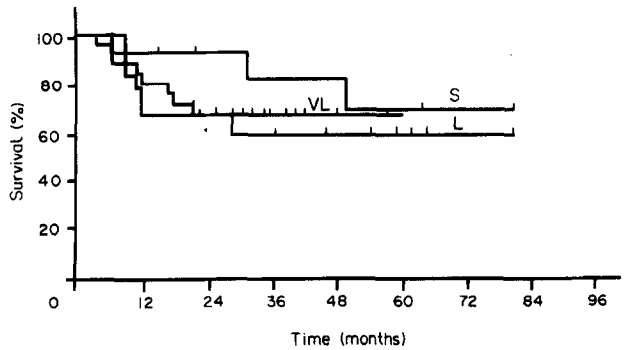

Fig. 2. Survival classified by MRC prognostic criteria.

Table 2. Dose and dose intensity and change with time of treatment

	Overall	Patients treated: December 1986 or earlier	Patients treated: January 1987 or later	*P*
Mean ICT (day)	19.2 (3.6) 13.5–26.7	21.5 (3.3)	17.2 (2.8)	< 0.001
Average RDI	0.73 (0.15) 0.45–0.99	0.66 (0.14)	0.80 (0.14)	< 0.001
Average RD	0.97 (0.09) 0.78–1.23	0.98 (0.09)	0.96 (0.07)	> 0.05
RDI cisplatin	0.66 (0.18) 0.32–1.11	0.55 (0.14)	0.77 (0.16)	< 0.001
RD cisplatin	0.87 (0.15) 0.50–1.1	0.82 (0.16)	0.92 (0.13)	< 0.02
RDI etoposide	0.70 (0.18) 0.38–1.17	0.68 (0.17)	0.72 (0.18)	> 0.05
RD etoposide	0.93 (0.19) 0.50–1.38	1.01 (0.19)	0.86 (0.14)	< 0.01
IDR	125 (34.2) 68 –221	105 (29.8)	145 (27)	< 0.001

Mean (S.D.) range.
ICT, Intercycle time; RDI, Relative dose intensity; RD, Relative dose; IDR, Index of dose rate.

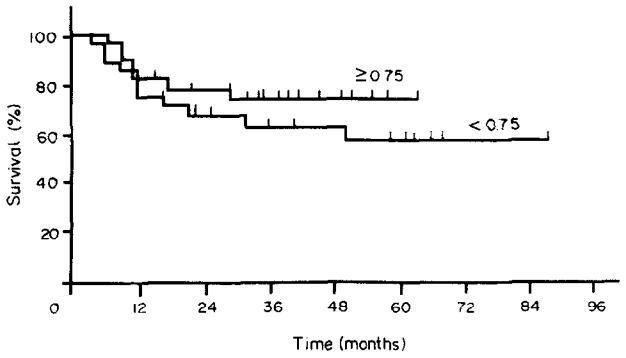

Fig. 3. Effect of average relative dose intensity (ARD) on survival.

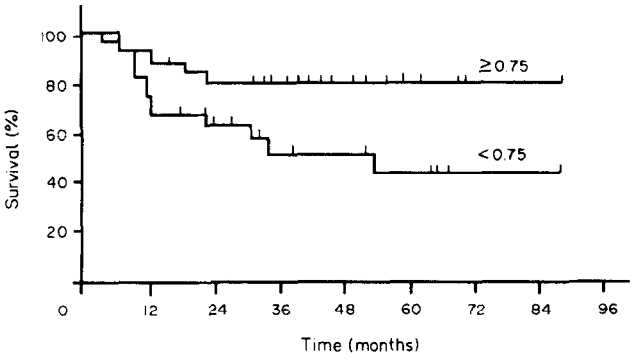

Fig. 5. Effect of relative dose intensity (RDI) of etoposide on survival.

$0.10 > P > 0.05$). The distribution of patients in the MRC prognostic groups is similar in the high and low RDI etoposide groups (< 0.75; S6, L10,VL12. ≥ 0.75; S6, L7, VL12). When the 7 patients who received the 5 day etoposide regimen are excluded, the effect of the RDI etoposide on survival remains. The length of the mean intercycle time has no effect on survival (Fig. 6).

The cause of the variation in RDI etoposide was investigated by examining the relationship between RDI etoposide and mean ICT, between which there was a highly significant correlation ($r = 0.65, P < 0.001$). Since $R^2 = 0.42$, this implies that delay accounts for 40% of the variation in RDI etoposide, and that 60% of the variation must be due to dose reduction. Delays in chemotherapy due to neutropenia occurred in 47 patients (89%). A dose reduction of etoposide because of neutropenia was made in 21 patients (40%). For patients with a planned etoposide dose of 100 mg/m^2 × 5 ($n = 7$), the RDI etoposide was 0.83 (S.D. 0.18), compared with 0.68 (S.D. 0.12) for those with a planned dose of 120 mg/m^2 × 3 ($n = 46$) (95% CI difference 0.01–0.29, $P < 0.05$).

DISCUSSION

The results reported here for POMB/ACE are comparable with those reported from Birmingham/Guys Hospital [11], and

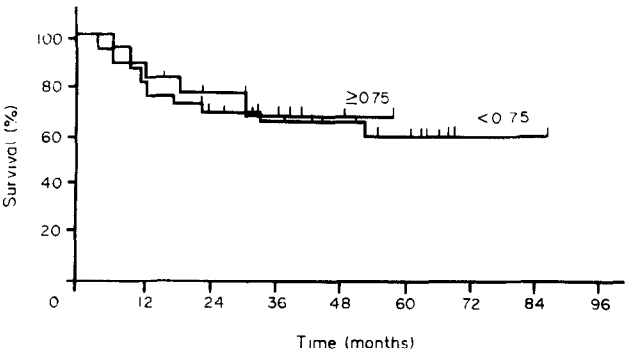

Fig. 4. Effect of relative dose intensity (RDI) of cisplatin on survival.

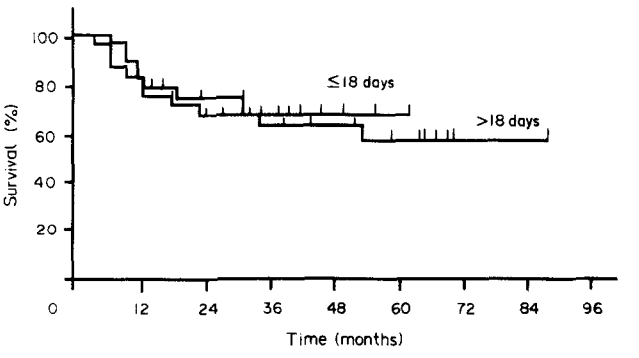

Fig. 6. Effect of mean intercycle time (MICT) on survival in all patients.

Table 3. Survival with chemotherapy in metastatic NSGCT

	Survival (2 years)				
	POMB/ACE			Other chemotherapy	
	MRCRO	Birmingham/ Guys	Charing Cross	Royal Marsden	MRCWorking Party
n	53	55	206	320	458
Date of treatment	1983–1989	1982–1987	1977–1988	1976–1985	1976–1982
MRC Prognostic group					
S	91% (73–100)	—	97%	96%	88%
L	65% (43–87%)	80%	90%	90%	77%
VL	65% (45–85%)	65%	80%	58%	58%

Royal Marsden—PVB/BEP.
MRC Working Party—PVB/BEP-311; POMB/ACE 87.
MRCRO date given as survival (95% CI).

the survival reported from both these centres is lower than that reported by Charing Cross Hospital [10] (Table 3). We found that increasing experience of the regimen was associated with increased delivered dose intensity. The mean IDR achieved at Clatterbridge Hospital was 125, compared with 113 and 119 in the Birmingham/Guys [11] groups who did and did not fail treatment, respectively implying close similarity in the dose intensity (at least of cisplatin) achieved, as well as in the outcome in these two studies. Dose/dose intensity data comparable with the present have not been reported from Charing Cross, nor has the mean intercycle time achieved, rather than that aimed for, been reported. The incidence of neutropenic fever at Charing Cross (25%) [8] is comparable with our figure of 30%, implying a similar intensity of treatment with respect to myelosuppression drugs. Though we did not continue OMB/ACE (i.e. omiting cisplatin) for 12 weeks after marker remission, we did give a further 2–4 courses of POMB/ACE, as was done in the majority of the Birmingham/Guys patients. The experience with BEP in metastatic NSGCT suggests that short courses of chemotherapy are sufficient, and we doubt if the duration of treatment is an explanation of our results being poorer than those reported by Charing Cross.

Most investigators accept that POMB/ACE is over treatment of patients with good prognosis disease [12]. The claim that POMB/ACE is associated with improved outcome in large volume disease, when compared with BEP or PVB, can only be definitely substantiated in a randomised controlled trial and this has not been performed to date. Table 3 compares the results reported with POMB/ACE, with those from the Royal Marsden Hospital [19] using PVB or BEP, and the 1985 MRC Working Party results [16], using the MRC Working Party prognostic groups. This comparison supports the overall view [12] that the survival rate using POMB/ACE (in centres other than Charing Cross) for poor prognosis patients is similar to that with standard regimens.

The toxicity of chemotherapy for NSGCT is a major concern, given the expectation of long term survival in a majority of patients. Myelosuppression, alopecia, and emesis are accepted complications of a curative regimen. While 30% of patients developed neutropenic fever in the present series, there were no treatment related deaths. Charing Cross report no treatment related deaths in 149 patients [9] but 3 patients (5.5%) died of treatment related causes in the Birmingham/Guys study [11]. This compares favourably with 3.2% reported for conventional regimens at the Royal Marsden Hospital [19], and 4.7% in a randomised controlled trial of BEP vs. PVB [3]. Bleomycin pulmonary toxicity occurred in 4–8% of patients receiving BEP/PVB [2, 19], with an associated mortality of up to 2% [3]. Fatal bleomycin pulmonary toxicity has not been reported with POMB/ACE, presumably because of the lower dose of bleomycin and the use of infusion rather than bolus administration. However it may be possible to reduce the dose of bleomycin in BEP without loss of efficacy [20].

The major cause of treatment failure in metastatic NSGCT is the development of drug resistance. Dose intense chemotherapy during the initial phase of treatment may reduce the probability of resistance developing [21]. Retrospective analysis has suggested that dose intensity is of importance in the treatment of other solid tumours [13]. Using POMB/ACE chemotherapy in metastatic NSGCT, one analysis has shown that reduced treatment intensity was associated with increased chance of relapse after complete response [14]. Our data does not support this, but the number of patients relapsing after CR ($n = 5$) is too few for a firm conclusion to be reached. A non significant trend was found for increased ARDI to be associated with increased survival. This is a small study, and the apparent effect substantial (hazard ratio 0.68 for all patients, and 0.77 for L/VL patients), thus an effect of ARDI cannot be excluded. It is surprising that the RDI cisplatin did not affect survival, as a dose–response relationship has been described for cisplatin (in the PVB regimen) comparing 75 mg/m^2 with 120 mg/m^2 monthly [22]. However increasing from 100 mg/m^2 to 200 mg/m^2 monthly (in the BEP regimen) did not improve efficacy [23]. POMB/ACE in standard dose gives an average of 160 mg/m^2/month of cisplatin over the first 3 months, and this may be on the plateau of the dose–reponse curve, explaining the lack of effect of the RDI of cisplatin on survival in this study. In support of this, the Birmingham/Guys study found that IDR (equivalent to RDI of cisplatin) was not related to treatment outcome [11].

The highly significant effect of RDI of etoposide on survival is a new finding of considerable importance. Retrospective analysis of dose intensity is subject to considerable potential bias for a number of reasons, including the tendency of both treatment outcome and dose intensity to be associated with performance status, leading to a possible spurious association. This is unlikely to be the case here, since only 2 patients who had sufficiently poor initial performance status to require reduced dose chemotherapy and both fell into the high RDI etoposide group. A maldistribution of other prognostic factors

Table 4. Dose intensity of POMB/ACE compared with other regimens

	Dose intensity (mg/m²/week)			
	POMB/ACE (etoposide 120mg/m²× 3)	(etoposide 100mg/m²× 5)	BEP (etoposide 120mg/m²× 3)	BOP/VIP
Cisplatin	40	40	33	50
Etoposide	90	125	120	75

Dose intensity calculated over first 12 weeks.

is possible but the distribution of S/L/VL volume disease is similar in the high and low RDI etoposide subgroups. The effect is similar if the patients receiving the 5 day etoposide schedule are excluded, suggesting that it is due to variation in dose intensity rather than an effect of the schedule dependency of etoposide described previously in the treatment of small cell lung cancer [24]. The lesser effect of ARDI and the lack of effect of mean intercycle time on survival suggest that this is a specific effect of the dose intensity of etoposide. Supportive evidence for this point of view comes from analysis of the data from the Charing Cross group, which found that the cause of reduced treatment intensity in most patients who relapsed was a reduced dose of etoposide [14].

If the dose intensity of etoposide is an important determinant of outcome, then there are a number of implications. Firstly attempts should be made to avoid dose reduction of etoposide, and treatment delay. In the event of myelosuppression it may be important to protect the dose of etoposide in preference to other myelosuppressive agents such as actinomycin D and cyclophosphamide. If POMB/ACE is used, the 100 mg/m2 × 5 schedule is to be preferred to 120 mg/m2 × 3, since it results in a higher ARDI. Table 4 compares the planned dose intensity of cisplatin and etoposide over the first 12 weeks of 3 regimens, and it can be seen that the supposed least intensive, standard regimen (BEP), has a higher dose intensity of etoposide than BOP/VIP, an intensive regimen [25]. The use of additional drugs may be counterproductive if it leads to reduced achievable dose intensity of the most effective drugs. Finally, if dose intensity of etoposide is of importance then dose intensity escalation of etoposide in conjunction with myeloid growth factors would be a rational therapeutic strategy for large volume disease, although the schedule may also be critical.

In summary we have shown that POMB/ACE chemotherapy can be given to patients with metastatic NSGCT with acceptable levels of drug related toxicity, but with an outcome that is similar to that of standard regimens such as BEP. An analysis of dose intensity suggests that high dose intensity of etoposide is associated with improved survival, and this observation has important implications for the design of future studies.

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