Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumours

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Summary The aim of this study was to define prognostic parameters for survival in patients with malignant germ cell tumours progressing after platinum-based induction chemotherapy with or without surgery. A total of 164 progressing patients (testicular: 83%, extragonadal: 17%) were identified out of 795 patients treated with platinum-based induction chemotherapy for metastatic germ cell malignancy with or without surgery. Progressive disease included patients who had progressed after a previous partial or complete remission as well as patients who failed primary therapy. Salvage chemotherapy consisted of ‘conventional’ platinum-based chemotherapy. Prognostic factors for survival were assessed by uni- and multivariate analyses. The resulting prognostic model was validated in an independent data set of 66 similar patients. For all 164 patients the median time from start of induction chemotherapy to progression was 10 months (range: 0–99). Thirty-eight (23%) patients relapsed after 2 years. The 5-year survival rate for all progressing patients was 30% (95% confidence interval 23–38%). In the univariate analysis the following factors most importantly predicted a poor prognosis: progression-free interval < 2 years: initial poor prognosis risk group. Those patients with progression-free interval < 2 years, < CR to induction chemotherapy and high markers at relapse (AFP >100 kU l⁻¹ or hCG >100 IU l⁻¹) formed a poor prognosis group of 30 patients, none of whom survived after 3 years. Patients with at most two of these three risk factors formed a good prognosis group of 94 patients (76%) with a 47% (37–56%) 5-year survival. Thirty-eight patients from the good prognosis group with a progression-free interval of >2 years had a 2-year survival of 74% (60–88%) and 5-year survival of 61%. These prognostic groups were validated in the independent data set, in which 5-year survival rates in the good and poor risk groups were 51% and 0% respectively. One-third of patients progressing during or after platinum-based induction chemotherapy for metastatic germ cell malignancy may be cured by repeated ‘conventional’ platinum-based chemotherapy. Good prognosis parameters are: progression-free interval of > 2 years, CR to induction treatment and normal or low serum markers at relapse (hCG < 100 IU l⁻¹ and AFP < 100 kU l⁻¹). The results of high-dose salvage chemotherapy should be interpreted on the background of these prognostic factors.

Keywords: germ cell malignancy; relapse; cisplatin-based chemotherapy; survival

Cisplatin-based chemotherapy represents an effective treatment for the majority of patients with advanced malignant germ cell tumour. However, about 20% of the patients progress during or after such chemotherapy and require salvage treatment (Mead et al, 1992). A variety of salvage treatments have been established which, in addition to platinum, usually include cytotoxic agents to which the patient has not been exposed previously, such as ifosfamide (Loehrer, et al, 1986), vinblastine (Loehrer et al, 1998, doxorubicin (Lederman and Garnick, 1986), methotrexate (Levi et al, 1990), actinomycin D (Levi et al, 1990) and paclitaxel (Motzer et al, 1994).

High-dose chemotherapy (Broun et al, 1992; Siegert et al, 1994; Beyer et al, 1996; Margolin et al, 1996) with stem cell support is increasingly accepted as the treatment of choice for patients progressing during or after primary chemotherapy for germ cell malignancy. Disease-free survival rates of 40–50% have been reported after such treatment which seems superior to the 20% disease-free survival rates obtained with ‘conventional’ chemotherapy schedules. Although the toxicity of high-dose chemotherapy has decreased with increasing experience there remains a considerable risk of severe and even lethal toxicity associated with the treatment approach in these patients. Therefore, until the superiority of a high-dose approach as salvage treatment has been demonstrated in randomized trials, patients should not be subjected to such treatment unnecessarily. It is thus important to identify prognostic factors for salvage treatment for patients with disease activity of their germ cell malignancy during or after induction chemotherapy.
Table 1 Pretreatment characteristics and induction treatment

| Characteristic                  | Group               | Number of patients |
|--------------------------------|---------------------|--------------------|
| Histology*                     | MTU                 | 71                 |
|                                | MTI                 | 52                 |
|                                | MTT                 | 21                 |
|                                | TD                  | 7                  |
|                                | Unspecified NSGCT   | 13                 |
| Primary tumour site            | Testis             | 136                |
|                                | Retroperitoneal     | 20                 |
|                                | Mediastinal         | 5                  |
|                                | Unknown             | 3                  |
| Prognostic group (MRC)         | Good               | 57                 |
|                                | Poor                | 106                |
|                                | Not classifiable    | 1                  |
| Age                            | Median              | 30 years           |
|                                | Range               | 14–83 years        |
| Treatment centres              | Large*              | 90                 |
|                                | Small               | 74                 |
| Primary chemotherapy           | PVB                 | 14                 |
|                                | BEVIP               | 4                  |
|                                | POMB/ACE            | 32                 |
|                                | Cisplatin+etoposide+others | 114             |
| Number of courses             | 2–3                 | 7                  |
|                                | 4                   | 63                 |
|                                | 5–6                 | 52                 |
|                                | >6                  | 29                 |
|                                | not known           | 13                 |
| Response to induction treatment| Complete response   | 53                 |
|                                | Incomplete response | 52                 |
|                                | Partial response, marker negative | 48             |
|                                | Progressive disease | 11                 |
| Total patients                 | 164                 |

*Pugh classification (see text). #>75 patients with metastatic non-seminoma in the original study (see text). 

Few series have been published dealing with prognostic factors in patients with recurrent malignant germ cell tumours, and most are based on the experience of specialized institutions (Motzer et al, 1991; Horwich et al, 1993; Josefsen et al, 1993; Ledermann et al, 1994; Gerl et al, 1995). The aim of the present study was to establish prognostic factors based on a series of patients presenting to unselected oncological units. Such analyses may represent an appropriate background for the interpretation of the results of modern high-dose salvage chemotherapy and may also assist the clinician to identify future patients for risk-adapted salvage treatment.

PATIENTS AND METHODS

In a previously published study prognostic factors were identified in 795 patients with advanced germ cell tumours (Mead et al, 1992). The present series represents a further analysis of those patients who progressed during or following cisplatin-based induction chemotherapy. This includes patients who never achieved a response and those with new disease activity after achieving a complete or partial response to primary chemotherapy. All patients had been treated with first-line platinum-based chemotherapy between 1982 and 1986.

As a rule patients with residual post-chemotherapy masses underwent surgery to remove them, and they received adjuvant cisplatin-based chemotherapy if residual germ cell malignancy was demonstrated in the post-chemotherapy resection specimen. Histological subtyping of the primary germ cell cancer was based on the Pugh Classification: MTU: malignant teratoma undifferentiated; MTI: malignant teratoma intermediate; MTT: malignant teratoma trophoblastic; TD: teratoma differentiated. In 13 patients with elevated serum AFP the malignant germ cell tumour could not be subtyped histologically.

For the present study all patients had data on baseline characteristics, and updated survival data. Seven centres provided further retrospective data on their patients and recorded details of the marker levels and sites of disease at progression. Based on the number of patients entered into the original series (Mead et al, 1992) ‘large oncological units’ were separated from ‘small’ ones. The former had contributed more than 75 patients with metastatic non-seminoma as opposed to < 75 for ‘small’ oncological units. This division was supported by patient entry by these centres into other Medical Research Council (MRC) trials. All patients in this study had received both induction and relapse chemotherapy at their local centre; patients referred to centres participating in this study for relapse treatment only were not included.

Complete response (CR) to treatment was defined as the clinical and radiological absence of all tumour manifestations (including normalization of serum alpha fetoprotein (AFP) – human chronic gonadotrophin (hCG), or the complete resection of residual mature teratoma or necrotic/fibrotic tumour tissue. Incomplete response (IR) comprised patients with persistently elevated markers (without serially rising values) or the histological demonstration of residual cancer in resection specimen. Patients with unresected residual tumour masses with normal tumour markers were included in the category Partial remission (PR) marker negative. Progression (PD) was defined as the development of new metastases and/or clearly rising serum tumour markers.

Factors predictive of survival from the date of progression were then identified. Potential prognostic factors included patient characteristics at initial diagnosis (site and extent of metastatic disease sites), response to initial chemotherapy, duration of relapse-free interval, and patient characteristics at relapse. An independent data set of 66 patients (provided by Dr A Gerl, Munich) was available on which to test the resulting prognostic models.

Survival times were measured from the date of diagnosis of progression to the date of death or date last seen. Survival curves were compared using the logrank test, and Cox’s proportional hazards regression model was used to identify independent
prognostic factors. A forward stepwise variable selection procedure was used.

RESULTS

One hundred and sixty-four of the 795 patients (21%) relapsed. Of these, 116 (71%) have died and the median follow-up time of those still alive is 8.5 years (range 1–12.5 years). Patient characteristics at the time of initial diagnosis and details of primary chemotherapy are described in Table 1. The primary tumour site was identified in our study as the testis in 83% of the patients. Fifty-seven patients belonged at the start of induction chemotherapy to the good and 106 to the poor prognosis groups as defined by the previous MRC study (Mead et al, 1992). (One patient could not be classified.) The majority of patients received at least four courses of combination chemotherapy including both cisplatinum and etoposide. Twenty-one of the 164 patients had undergone adjuvant chemotherapy as histology of masses had demonstrated viable residual cancer. Detailed data on characteristics at relapse were available for a subset of 110 patients, and these are included in Table 2. Relapse treatment was given between 1982 and 1991. In 103 patients a great variety of salvage regimens were employed, eighty-nine patients received cisplatin-based combinations, and no patient received high-dose chemotherapy. Ifosfamide-containing salvage

| Parameter | Number of patients | 2-Year survival rate | Log-rank |
|-----------|--------------------|----------------------|----------|
| Prognostic group at 1st diagnosis (MRC) | | | |
| Good | 57 | 51% | 9.2 | 0.0024 |
| Poor | 106 | 32% | | |
| Site of primary tumour | | | |
| Testis | 136 | 38% | 0.03 | 0.86 |
| Extragonadal | 28 | 41% | | |
| Age | | | |
| <30 | 99 | 41% | 1.15 | 0.28 |
| 30–39 | 42 | 40% | | |
| 40–49 | 13 | 31% | | |
| ≥50 | 10 | 20% | | |
| Response to induction treatment | | | |
| Complete | 53 | 58% | 43.4 | ≤0.0001 |
| Incomplete | 52 | 27% | (3 d.f.) | |
| PR marker negative | 48 | 37% | |
| Progression | 11 | 0% | | |
| Time from initiation of primary therapy to progression (months) | | | |
| <6 | 37 | 22% | 20.4 | <0.0001 |
| 6–12 | 57 | 28% | | |
| 13–24 | 32 | 33% | | |
| 25–36 | 15 | 73% | | |
| >36 | 23 | 74% | | |
| hCG at relapse (IU l⁻¹)a | | | |
| Normal | 57 | 39% | 1.40 | 0.24 |
| <100 | 23 | 48% | | |
| 100–1000 | 19 | 32% | | |
| >1000 | 11 | 27% | | |
| AFP at relapse (kU l⁻¹)a | | | |
| Normal | 55 | 45% | 3.65 | 0.056 |
| <100 | 33 | 37% | | |
| 100–1000 | 13 | 23% | | |
| >1000 | 9 | 22% | | |
| Year of relapse treatment | | | |
| Before 1986 | 94 | 29% | 7.15 | 0.008 |
| 1986–1991 | 70 | 51% | | |
| Treatment centre | | | |
| ‘Large’ | 90 | 45% | 5.12 | 0.02 |
| ‘Small’ | 74 | 29% | | |
| Sites of relapse (1)* | | | |
| Markers only | 16 | 38% | | |
| Abdominal nodes | 29 | 45% | | |
| Mediastinal/neck nodes (± abdo nodes) | 8 | 63% | 3.08 | 0.54 |
| Lung (± abdo/med/neck nodes) | 28 | 36% | (4 d.f.) | |
| Other visceral mets (± other sites) | 29 | 28% | | |
| Sites of relapse (2)a | | | |
| No lung or other visceral mets | 53 | 45% | 1.03 | 0.31 |
| Lung or other visceral mets present | 57 | 32% | | |

aData available in a subgroup of 110 patients. aChi square on 1 d.f. unless otherwise stated. (t) indicates chi square test for trend.
survival by prognostic group – developmental data set. (−) Good risk (≤ two risk factors) \(n = 94\); (−−) Poor risk (all three risk factors) \(n = 30\).

The role of surgery in addition to salvage chemotherapy was analysed specifically: of 31 patients in whom a residual mass was completely resected immediately before or after salvage chemotherapy, 16 are alive after 5 years. In 36 patients who after salvage chemotherapy had a complete radiological response, the 5-year survival rate was only 14%, whereas those with residual mass left unresected \(n = 32\) had a 3-year survival rate of 31%.

The multivariate analysis (Table 3) identified three factors of independent prognostic importance \((P\)-value for inclusion < 0.1\); progression-free interval, response to induction treatment and marker levels. The hazard ratios for patients with either IR or PR marker negative were very similar. The small group of six patients with PD had the poorest outcome. As the hazard ratios for the three above factors were dissimilar, a number of prognostic models were considered which applied different weightings to the

Figure 2 Time from first relapse/progression to death

Figure 3 Survival by prognostic group – developmental data set. (−) Good risk \(\leq\) two risk factors \(n = 94\); (−−) Poor risk (all three risk factors) \(n = 30\)
Table 3  Cox regression analysis: final model

| Variable                                      | Regression coefficient (s.e.) | Hazard ratio |
|-----------------------------------------------|------------------------------|-------------|
| Time to progression (≤ 2 vs > 2 years)       | 0.80 (0.34)                  | 2.22        |
| High markers at relapse (AFP > 100 ku l⁻¹ and/or hCG > 100 IU l⁻¹) | 0.60 (0.25)                  | 1.82        |
| Response to induction treatment              |                              |             |
| CR (reference category)                      |                              |             |
| IR (reference category)                      |                              |             |
| PR marker negative                           | 0.39 (0.31)                  | 1.49        |
| PD                                            | 1.46 (0.46)                  | 4.28        |

Table 4  Validation data summary: independent data set of 66 patients

| Characteristic                          | Group                                      | Number of patients |
|-----------------------------------------|--------------------------------------------|--------------------|
| Response to induction treatment         | CR to chemo + surgery                      | 37                 |
|                                        | Elevated markers/residual malignant tumour | 25                 |
| Time to progression                     | ≤2 years                                   | 53                 |
|                                        | >2 years                                   | 13                 |
| AFP at relapse (ku l⁻¹)                 | ≤ 100                                      | 7                  |
|                                        | >100                                       | 18                 |
| hCG at relapse (IU l⁻¹)                 | ≤ 100                                      | 11                 |
|                                        | >100                                       | 17                 |
| Sites of relapse                        |                                            |                    |
| Abdomen                                 | No                                         | 34                 |
|                                        | Yes                                        | 32                 |
| Lung                                    | No                                         | 43                 |
|                                        | Yes                                        | 23                 |
| Mediastinum                             | No                                         | 61                 |
|                                        | Yes                                        | 5                  |
| Extrapulmonary                          | No                                         | 42                 |
|                                        | Yes                                        | 24                 |
| Year of relapse treatment               | 1980–1985                                  | 32                 |
|                                        | 1986–1990                                  | 21                 |
|                                        | 1990–1995                                  | 13                 |
| Total patients                          |                                            | 66                 |

Table 5  Efficacy of salvage treatment in (excluding high-dose regimens) in patients with malignant non-seminomatous germ cell tumours, progressing/relapsing after cisplatin-based induction chemotherapy

| 1st Author | Year | No. of patients | Chemotherapy schedule | CR rate | Long-term survival |
|------------|------|----------------|------------------------|---------|--------------------|
| Loehrer    | 1986 | 48             | VIP<sup>a</sup>b       | 33%     | NA<sup>c</sup>     |
| Motzer     | 1991 | 94             | Various<sup>a</sup>    | 23%     | 15%                |
| Josefsen   | 1993 | 55             | Various                | NA      | 23%                |
| Horwich    | 1993 | 105            | Various                | NA      | 35%                |
| Ledermann  | 1994 | 38             | Various<sup>a</sup>    | 47%     | 46%                |
| Motzer     | 1994 | 31             | Paclitaxel             | 10%     | NA                 |
| Gerl       | 1995 | 67             | Various<sup>1</sup>    | NA      | 37%                |
| McCaffrey  | 1997 | 56             | VIP/VeiP               | 36%     | 40%                |
| Loehrer    | 1998 | 135            | VeiP                   | 50%     | 46%                |
| Fosså      |      | 164            | Various                | NA      | 30%                |

<sup>a</sup> V: VP-16, E: Etoposide, I: Ifosfamide, P: cis-platin, Ve: Vinblastine (Velbe<sup>2</sup>), B: Bleomycin. <sup>b</sup>After P Ve B. <sup>c</sup>Not available. <sup>1</sup>Mostly BEP after P Ve B. <sup>2</sup>Containing vincristine, MTX, actinomycin D. Ifosfamide in 38 patients.
various factors. As the overall survival for patients with and
without information on markers at progression was very similar,
patients without marker information were also included in the
models where possible. The simplest model separated patients into
two groups on the basis of the number of adverse risk factors they
had. Given the three risk factors:

• progression-free interval < 2 years
• < CR to induction chemotherapy
• high markers at progression (AFP >100 kU l–1 and/or
  hCG > 100 IU l–1)

Patients with all three had a very poor prognosis; this group
comprised 30 patients with a median survival time of 7 months and
a 2-year survival rate of 7% (95% CI 0–15%). None of these
patients survived beyond 3 years. Ninety-four patients (81 with
data on all three factors and a further 13 without data on markers at
relapse), that is those with at most two risk factors, formed a ‘good
prognosis’ group with a 2-year survival rate of 56% (95% CI
46–66%), and a 5-year survival rate of 47% (37–56%). The
survival curves for these two groups are shown in Figure 3. It was
possible to subdivide the good prognosis group further, on the
basis of progression-free interval – the 38 patients with a progres-
sion-free interval of more than 2 years had a 2-year survival rate of
74% (60–88%), while those with a shorter progression-free interval
has a 2-year survival rate of 45% (32–58%).

Model validation
The independent data set was used to test the prognostic model.
The data included 66 patients with disease progression during
or after platinum-based induction chemotherapy, none of whom
received high-dose therapy on progression. Sixty patients received
‘conventional’ regimens for progressive germ cell malignancy (of
whom 40 received cisplatin- and ifosfamide-based regimens with
either vinblastine or etoposide), while six were treated with surgery
and/or radiotherapy alone. Forty-three patients have died;
of the 23 alive, median follow-up is 8 years (range 6 months to 14
years). The characteristics of these patients are described in Table
4, using the same criteria for response as defined for the principle
data set collected by the MRC.

The two-group prognostic model was applied to this data, and
the resulting survival curves are shown in Figure 4. The number of
patients falling into the good and poor risk groups were 49 (74%) and
17 (26%) and the corresponding 2-year survival rates were
58% and 0% (43–72%), respectively. Five of the patients within
the good risk group were categorized as ‘absolutely platinum
refractory’, whereas this was the case for six patients within the
poor prognosis group.

DISCUSSION

Progressive germ cell malignancy
Progression after IR/PR marker negative or relapse after CR was
observed in 164 (21%) of the original 795 patients with malignant
germ cell tumours treated with cisplatin-based induction
chemotherapy. This percentage is comparable to other reports
(Motzer et al, 1991; Horwich et al, 1993; Jossefson et al, 1993; Gerl
et al, 1995). Although about 70% of the cases of progression
occurred within the first year after the start of induction treatment,
reactivation of the disease was observed in 23% patients after 2
years. This observation together with the possibility of cure in
patients with ‘late’ progression indicate the necessity to continue
regular follow-up in patients with metastatic germ cell tumours for
at least 5 years and probably longer.

Induction chemotherapy
Four 3-weekly cycles of BEP (bleomycin 90 mg cycle–1, etoposide
500 mg m–2 cycle–1, cisplatin 100 mg m–2 cycle–1) are today consid-
ered to be the standard treatment with metastatic malignant germ
cell tumour. The PVB (cisplatin, vinblastine, bleomycin) combina-
tion used during the early 1980s has been shown to be significantly
inferior to the BEP combination both with regard to efficacy and
toxicity (Williams et al, 1987), whereas ifosfamide-containing
regimens have not proved to be superior as induction treatment
(Nichols et al, 1995). Carboplatin-based induction chemotherapy
is, however, less effective than BEP (Horwich et al, 1997). Failure
of induction chemotherapy may be due to primary or secondary
drug resistance or to insufficient dosing or incorrect drug selec-
tion. So far no study has addressed the role of induction
chemotherapy as regards the outcome of salvage treatment
(number of cycles, type, dose-intensity). In the present series data
were not available to evaluate any inadequacy of the induction
treatment in relapsing patients. In future studies concerning
relapsing patients, information on type and intensity of the induc-
tion treatment should be provided, and analysed with regard to its
prognostic significance.

Salvage treatment
The present analysis concentrates on prognostic factors evaluable
before salvage treatment. However, the importance of resection
of residual masses in patients with recurrent germ cell malignancies
is increasingly recognized (Cassidy et al, 1992). The present retro-
spective analysis supports this view, though the results have to be
interpreted having selection bias in mind.

It was not possible to study the role of the different salvage
chemotherapy regimens due to the considerable heterogeneity of
the drugs and regimens used. Today ifosfamide- and vinblastine-
containing combinations (Loehrer et al, 1998) would be those
drugs most frequently selected in patients who have not received
these agents during their induction treatment (or a methotrexate-
containing regimen (Levi et al, 1990)). However, only 15 of our
patients received ifosfamide. Recently, paclitaxel (Motzer et al,
1994) has been identified as an active drug for salvage
chemotherapy of patients with relapsing germ cell tumours. The
use of these drugs after a standard BEP regimen (bleomycin,
etoposide, cisplatin) would, if at all, have increased the overall
outcome of salvage treatment as compared to the present series,
but with one or little impact on the presented prognostic pretreat-
ment factors.

The overall long-term survival (and probably cure rate) for our
progressing patients was 30% which is comparable to other reports
(Table 5). On the other hand, McCaffrey et al’s (1997) survival
curves visualize an almost 40% long-term overall survival rate
in patients treated with ifosfamide-containing cisplatin-based
salvage chemotherapy. A different composition of prognostic
groups in large versus small institutions may be one reason for
such differences. A further reason for varying results may be that
corner to McCaffrey et al’s report, we analysed our series
according to the ‘intention to treat’ principle. This included five
patients who finally refused all treatment (three) or died before the start of salvage chemotherapy (two).

The use of high-dose chemotherapy with carboplatin, etoposide and ifosfamide together with haematopoietic stem cell support has been explored in single institution phase II studies (Broun et al., 1992; Siegert et al., 1994; Margolin et al., 1996). A multicentre experience has been analysed recently by Beyer et al (1996) Several of these studies have emphasized the role of patient selection and of prognostic factors. Beyer et al (1996) have determined independent poor prognosis parameters which made subgrouping of progressing patients possible with respectively 50%, 30% and 4% overall long-term survival after high-dose chemotherapy for treatment of first or subsequent relapse. These authors identified the following poor prognosis parameters: mediastinal non-seminomatous primary tumour, progressive disease before high-dose chemotherapy, disease refractory to conventional-dose cisplatin, hCG >1000 IU l–1. Using conventional cisplatin-based salvage chemotherapy Gerl et al (1995), Josefsen et al (1993) and Motzer et al (1991) identified a complete response to induction treatment as an additional positive independent prognostic factor which is confirmed in the present study.

In contrast to the report by Nichols et al (1994) on relapsing patients (after CR) a long interval from induction therapy to first progression proved to be the most powerful prognostic parameter. This discrepancy is difficult to explain but may be related to slightly different selection of patients: our analysis include patients with primary IR/PR who progressed after > 2 years, whereas Nichols et al only discuss patients with initial CR. Daniel et al (1995) emphasized the role of surgery in patients with late relapses and suggested that chemotherapy was only limitedly effective in these patients, progressing after > 2 years. Our series does not allow an analysis concerning these aspects as the majority of evaluable patients underwent both surgery and chemotherapy. Our finding supported by data from Horwich et al (1993) although it should be noted that some of these patients were included in our data set also. Interestingly, raised markers in patients with a long progression-free interval were not an adverse feature, but this was the case when the progression-free survival was short.

The good prognosis group comprised 94 patients (76%) and had a 47% 5-year survival when treated with ‘conventional’ salvage chemotherapy. This survival rate is quite comparable with the results of high-dose chemotherapy followed by stem cell support if possible (Broun et al., 1992; Siegert et al., 1994; Beyer et al., 1996; Margolin et al., 1996). The present observations are not directly comparable with the prognostic parameter analysis performed by Beyer et al (1996). Most of Beyer et al’s patients had developed progressive disease twice when receiving high-dose chemotherapy. Beyer et al assessed survival from the time when high-dose treatment was given. The patients from the present series had progressed only once after start of induction chemotherapy, and their survival was calculated from the time of their first progression. In the present series all progressing patients were included in the analysis, even those who did not receive (planned) salvage chemotherapy, whereas all patients evaluated by Beyer et al had been treated with high-dose chemotherapy. Furthermore, as also pointed out by Beyer et al, 65 of their patients received high-dose chemotherapy while responding to conventional chemotherapy (even CR), whereas all our patients had progressed at commencement of salvage treatment. However, Beyer et al’s results of salvage high-dose chemotherapy, although not directly comparable with the present series, represent a clear indication that high-dose chemotherapy may be effective in some patients who relapse despite conventional salvage treatment. This aspect will be further dealt with in a future case control study.

In conclusion, about 20% of the patients with metastatic non-seminoma are not cured by standard conventional induction chemotherapy. The overall 5-year survival rate for these patients is 30% after conventional cisplatin-based salvage chemotherapy used in a multicentre setting. The group consists of two prognostic subgroups: a good prognosis group (about 75%) with a 5-year survival rate of 47% and a poor prognosis group (about 25%) with no patient surviving after 3 years. The results from non-randomized new approaches of salvage therapy should be interpreted on the background of the above prognostic groups, keeping in mind that about one-third of the progressing patients may be cured by ‘conventional’ means.

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