EUROPEAN JOURNAL OF CANCER 44 (2008) 1663–1669

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Cerebral metastases in non-seminomatous germ cell tumour patients undergoing primary high-dose chemotherapy

K. Oechsle[a,*], C. Kollmannsberger[b], F. Honecker[a], I. Boehlke[a], C. Bokemeyer[a]

[a]Department of Oncology/Hematology/Pneumology, University Medical Center Eppendorf, Hamburg, Germany
[b]Division of Medical Oncology, British Columbia Cancer Agency, Vancouver Cancer Center, Vancouver, Canada

ARTICLE INFO

Article history:
Received 8 March 2008
Received in revised form 6 May 2008
Accepted 21 May 2008
Available online 10 July 2008

Keywords:
Germ cell tumour
Cerebral metastases
High-dose chemotherapy

ABSTRACT

Background: Retrospective analysis of characteristics and outcome of germ cell tumour (GCT) patients with cerebral metastases (CM) undergoing high-dose chemotherapy (HD-CTX) or relapsing with CM.

Patients and methods: Patients initially presenting with CM ($N = 50$ pts) or at first relapse ($n = 19$ pts) after primary HD-CTX (434 pts) were analysed.

Results: Patients with primary CM ($N = 50$) had elevated ß-human chorion gonadotropin (ß-HCG) in 88% and lung metastases in 90%. Eighty six percent responded to HD-CTX and 40% underwent CNS radiotherapy. Forty four percent achieved long-term survival after primary and 16% after salvage treatment (60% in total). All patients relapsing with CM ($n = 19$) presented initially with ß-HCG-elevation and pulmonary metastases. Treatment consisted of CTX in 78%, irradiation in 90% and surgery in 63%. Twenty six percent achieved long-term survival.

Conclusion: An interdisciplinary approach of HD-CTX, radiotherapy and surgery leads to long-term survival in 60% of patients with CM at initial diagnosis and 26% relapsing with CM.

1. Introduction

In patients with 'advanced disease' according to the Indiana University criteria at primary diagnosis cerebral metastases occur in about 10–15%. These patients exhibit a 'poor prognosis' with long-term survival rates of only 45–55% with standard-dose chemotherapy,[1] in contrast to patients with good or intermediate prognosis according to the International Germ Cell Cancer Cooperative Group (IGCCCG) criteria with approximate long-term cure rate of 80–90%.[2,3]

A number of clinical trials have demonstrated that first-line high-dose chemotherapy with autologous stem-cell transplantation is a feasible approach in germ cell tumour patients with poor prognosis criteria and seems to extend long-term survival rates up to 70–80%.[4–7] However, this advantage could not be confirmed in the only randomised phase III study published so far[8]. An overview on all included patients is presented in Fig. 1.

Since cerebral metastases are a rare event in germ cell tumour patients, only a few analyses have been published, showing heterogeneous results. Today, in patients with cerebral metastases at primary diagnosis, the combination of standard-dose cisplatin-based chemotherapy and cranial irradiation is considered to be the standard treatment by most centres.[9,10] In addition, surgery may be considered for patients with solitary or limited cerebral metastases with

* *Corresponding author:* Tel.: +49 40 42803 3715; fax: +49 40 42803 2903.
E-mail address: k.oechsle@uke.hamburg.de (K. Oechsle).
0959-8049/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2008.05.012

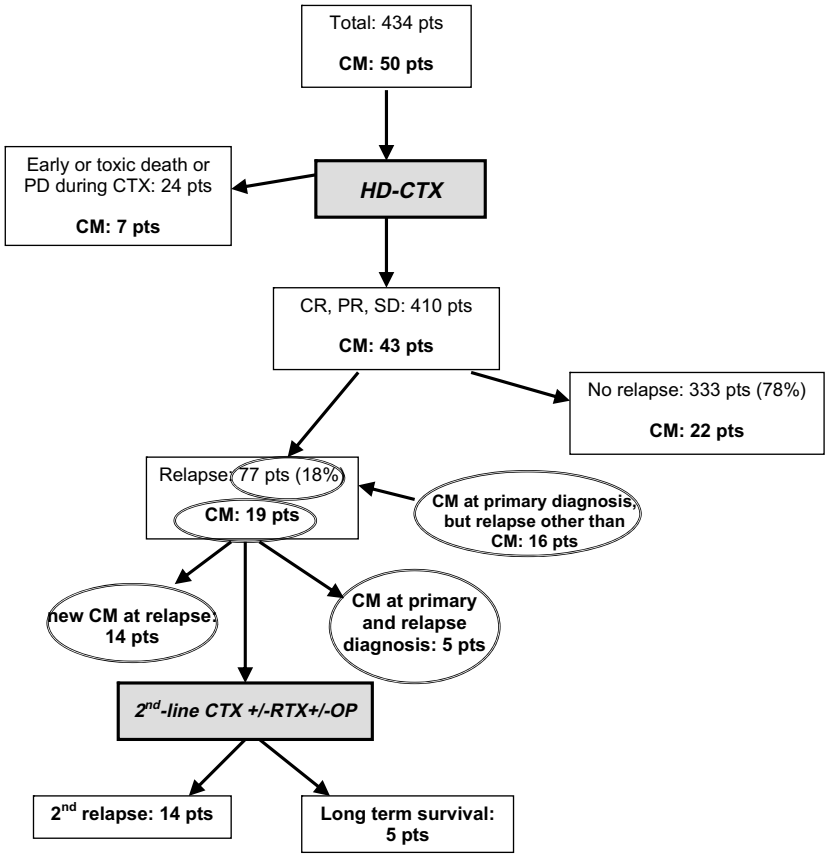

Fig. 1 – Overview of patients with primary HD-CTX, response to treatment and cerebral metastases (CM). CM, cerebral metastases; HD-CTX, high-dose chemotherapy; CTX, chemotherapy; RTX, radiotherapy; OP, secondary tumour resection; CR, complete remission; PR, partial remission; SD, stable disease and PD, progressive disease.

good resectability.[10–12] Some data suggest that cisplatin-based chemotherapy alone may be equally effective to the combination of chemotherapy and irradiation as first-line treatment in patients with cerebral metastases at primary diagnosis.[13]

The aim of this retrospective analysis was to examine the characteristics of patients with cerebral metastases at primary diagnosis and their treatment outcome after a multidisciplinary approach including high-dose chemotherapy. In addition, patients relapsing with cerebral metastases after primary high-dose chemotherapy were retrospectively analysed to explore risk patterns for cerebral relapses and to assess outcome after intensive treatment in this setting.

2. Patients and methods

Data from two multicentre phase II studies of the German Testicular Cancer Study Group on first-line cisplatin-based sequential high-dose chemotherapy were retrospectively analysed.[4,7] Inclusion criteria for both trials consisted of the following: patients with either 'poor prognosis' according to the IGCCCG-criteria or advanced disease according to the Indiana University criteria[1] at the time of first diagnosis; no prior chemotherapy; adequate bone marrow function, creatinine clearance >50 ml/min. In both studies, patients received one cycle of conventional dose combination chemotherapy with 20 mg/m^2 cisplatin, 75 mg/m^2 etoposide and 1.200 mg/m^2 ifosfamide for 5 days (VIP) for stem-cell mobilisation. A minimum of 3×10^6 CD34+ cells/kg peripheral blood stem cell was a prerequisite for the continuation of further study treatment. Patients received three consecutive cycles of high-dose chemotherapy plus autologous peripheral blood stem cell (PBSC) reinfusion either with cisplatin, etoposide and ifosfamide alone (HD-VIP)[4] or in combination with paclitaxel (HD-TaxVIP)[7]. HD-VIP was applied in four escalating dose levels consisting of 20 mg/m^2 cisplatin, 300–400 mg/m^2 etoposide and 2–2.4 g/m^2 ifosfamide on days 1–5 with PBSC retransfusion 2 d later. In the HD-TaxVIP-trial, paclitaxel was added on day 1 in three dose levels of 135, 175 and 225 mg/m^2 to 20 mg/m^2 cisplatin, 300 mg/m^2 etoposide and 2000 mg/m^2 ifosfamide on days 1–5 each with PBSC support. Follow-up including tumour marker evaluation and radiographic imaging was performed every 3 months within the first 2 years and 6-monthly thereafter up to 5 years. From the TaxVIP-study, only patients included before December 2004 were entered into this analysis. According to the study protocols, cerebral imaging for diagnosis of cerebral metastases, either computed tomography or MRI, had to be performed in the case of clinical symptoms. The study protocols of the clinical trials were approved by the Ethics Committees of the University Hospitals Halle and Tuebingen, respectively, as well as the local ethic committees of all participating centres. All

Table 1 – Characteristics and outcome of patients with cerebral metastases at primary diagnosis (n = 50 patients)

	N pts.	%
Median age	32 years (range, 20–53)	
Location of primary tumour		
Gonadal	43	86
Mediastinal	5	10
Retroperitoneal	2	4
Histology		
Embryonal Ca	10	20
Chorionic Ca	10	20
Teratoma	9	18
Mixed	16	32
Not evaluable	5	10
Tumour marker elevation at primary diagnosis		
AFP	21	42
	244 kU/l (range, 21–37,280)	
ß-HCG	44	88
	108,305 U/l (range, 70–2,800,000)	
LDH	39	78
	615 U/l (range, 331–2199)	
Location of further metastases		
Retroperitoneum	34	68
Mediastinum	18	36
Lungs	45	90
Liver	24	48
Bones	8	16
Other	8	16
Response to HD-CTX		
CR	2	4
PR–	23	46
PR+	15	30
SD	3	6
PD/early death	7	14
Secondary tumour resection		
Cerebral	4	8
Other	25	50
Secondary CM irradiation	20	40
Long-term relapse free	22	44
Relapse pattern		
CM only	2	4
CM + other	3	6
Other than CM	16	32
Median time to relapse	6 months (range, 1–15)	
Median overall survival	20+ (range, 1–98+)	

CM, cerebral metastases; CR, complete remission; PR–, tumour marker negative partial remission; PR+, tumour marker positive partial remission; SD, stable disease; PD, progressive disease; AFP, alpha-foetoprotein; ß-HCG, ß-human chorion gonadotropin; LDH, lactatdehydrogenase; HD-VIP, high-dose chemotherapy with cisplatin, etoposide and ifosfamide and HD-TaxVIP, high-dose chemotherapy with paclitaxel, cisplatin, etoposide and ifosfamide.

patients had given written informed consent prior to study inclusion.

A first cohort of 22 patients with cerebral metastases from the first study (HD-VIP) was published in 2000.[14]

For this retrospective analysis, individual patient data from both trials were used. Included were all patients either presenting with cerebral metastases at the time of first diagnosis or with cerebral metastases at the time of first relapse following primary high-dose chemotherapy. Survival was analysed using the method of Kaplan–Meier.

3. Results

Within these two multicentre phase II trials, a total of 434 patients with poor risk germ cell tumours were treated with sequential cycles of primary high-dose chemotherapy and autologous stem-cell transplantation between December 1993 and December 2004. The high-dose chemotherapy regimen consisted of HD-VIP in 293 patients (68%) and HD-TaxVIP in 141 patients (32%).

3.1. *Cerebral metastases at first diagnosis*

Fifty of 434 patients (12%) with a median age of 32 years (range, 20–53) presented with cerebral metastases at primary diagnosis. Primary tumour location in these patients was gonadal in 43 cases (86%) and extragonadal in seven cases (14%). Histology was mixed non-seminomatous germ cell tumour in 32% and embryonal carcinoma or chorion carcinoma in 20% each. Further details on patients' characteristics are presented in Table 1.

Forty-two percent of patients presented with a single cerebral metastasis whilst 58% of patients had multiple cerebral metastases at first diagnosis. Cerebral metastases were found in all regions of the brain, with a preference to parietal (30%) and occipital (20%) regions. In 24 patients (48%), clinical symptoms lead to diagnosis with paresis in 9 patients and convulsive attacks in 15 patients.

All 50 patients started treatment with high-dose chemotherapy without prior radiation or cerebral surgery. Overall response to high-dose chemotherapy was complete remission in 4%, marker negative remission in 46% and marker positive remission in 30%. Six percent of patients achieved disease stabilisation and 7 patients (14%) progressed during high-dose chemotherapy. Subsequent cerebral radiation was performed in 20 patients (40%) and secondary resection of residual cerebral lesions in 4 patients (8%). Half of the patients underwent secondary surgery of other than cerebral residual tumour masses revealing necrosis in 69% of the resected patients. No patient received intrathecal chemotherapy.

Twenty-two patients (44%) with cerebral metastases at initial diagnosis achieved long-term survival. Twelve of these 22 patients (54%) had received secondary brain irradiation. Twenty-one patients relapsed after initial response to primary high-dose chemotherapy, with a median time to progression of 6 months (range, 1–15). Two patients presented with an isolated cerebral relapse (10%), 3 patients relapsed both in the brain and at extracerebral locations (14%) and 16 patients relapsed exclusively outside the brain (76%).

Taking together primary responders and secondary responders to salvage treatment, consisting of chemotherapy, surgery and/or irradiation at the time of a localised relapse, a total of 30 of the initial 50 patients (60%) with primary brain metastases achieved long-term survival. The median overall survival time of all 50 patients was 20 months (range, 1–98+) from the time of initial diagnosis. Table 1 summarises

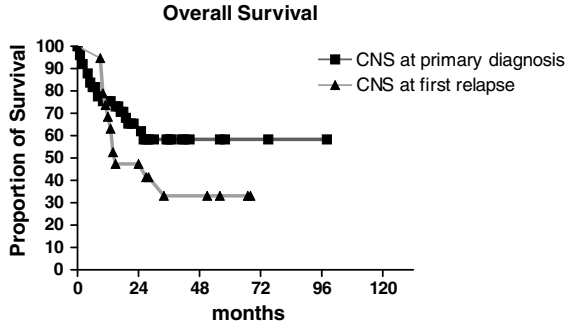

Fig. 2 – Overall survival according to Kaplan–Meier in patients with cerebral metastases at primary diagnosis (*n* = 50) or with cerebral metastases at first relapse after primary high-dose chemotherapy (*n* = 19).

primary treatment, outcome and follow-up, and survival curves according to Kaplan–Meier are presented in Fig. 2.

3.2. *Cerebral relapse after primary treatment*

Nineteen of 77 patients relapsing after response to primary high-dose chemotherapy presented with cerebral metastases at the time of first relapse. Five of these patients (27%) had presented with cerebral metastases at initial diagnosis, and relapse had occurred after response to primary high-dose chemotherapy. The other 14 patients (73%) had not had cerebral metastases at initial diagnosis. Interestingly, all patients with cerebral relapse had initially presented with metastases to the lungs and highly elevated ß-HCG levels (median ß-HCG 126,690 U/l, range 27–2,800,000). Additional lactatdehydrogenase (LDH)-elevations were found in 95%; AFP-elevations were seen in only 47% of patients at primary diagnosis. Response to primary high-dose chemotherapy was complete remission in 3 patients (15%), marker negative partial remission in 10 patients (53%) and marker positive remission in 6 patients (32%). Secondary resection of residual tumour masses had been performed in 10 patients (53%). The median time to relapse after primary high-dose chemotherapy was 3 months (range, 1–54).

At the time of first relapse after high-dose chemotherapy, median age was 31 years (range, 18–53). Thirteen patients (68%) presented with an isolated cerebral relapse. At relapse, ß-HCG elevations were found in 79% of patients, AFP in 37% and LDH in 42% (Table 2).

At first relapse all three modalities, chemotherapy, surgery and irradiation, were used in 8 patients (43%). A single modality was applied in 3 patients only, chemotherapy alone in 1 patient and radiotherapy alone in 2 patients. Isolated resection of cerebral metastases was not performed in this cohort. A total of 15 patients (78%) underwent second-line chemotherapy with different standard-dose regimens in 12 patients and second salvage high-dose chemotherapy in 3 patients. Brain irradiation was performed in 17 patients (90%), and 12 patients (63%) underwent surgical resection of cerebral metastases. Median overall survival from the time of first cerebral relapse diagnosis was 9 months (range, 2–51+) and from initial diagnosis 15 months (range, 9–68+). Table 3 summarises the applied salvage treatment modalities.

Table 2 – Characterstics of patients with cerebral metastases at first relapse after response to high-dose chemotherapy (n = 19 patients)

	N pts	%
Median age	31 years (range, 18–53)	
Location of primary tumour		
Gonadal	17	90
Mediastinal	1	5
Retroperitoneal	1	5
Histology		
Embryonal Ca	4	21
Yolk sack	0	
Chorionic Ca	1	5
Teratoma	1	10
Mixed	12	64
Tumour marker elevation at primary diagnosis		
AFP	9	47
ß-HCG	19	100
LDH	18	95
Location of metastases at primary diagnosis		
Retroperitoneum	16	84
Mediastinum	11	58
Lungs	19	100
Liver	9	47
Bones	2	10
CM	5	26
Other	5	26
Response to HD-CTX		
CR	3	15
PR	10	53
SD	6	32
Secondary tumour resection	10	53
Median time to relapse	3 months (range, 1–54)	
Treatment of relapse		
Tumour marker elevation at relapse diagnosis		
AFP	7	37
ß-HCG	15	79
LDH	8	42
Isolated cerebral relapse	13	68
Location of further metastases at relapse diagnosis		
Retroperitoneum	3	16
Lungs	4	21
CTX only	1	5
CTX + RTX	4	22
CTX + RTX + OP	8	43
OP only	0	
OP + RTX	3	15
RTX only	2	10
OP + CTX	1	5
Second relapse	14	7

CM, cerebral metastases; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; AFP, alpha-foetoprotein; ß-HCG, ß-human chorion gonadotropin; LDH, lactatdehydrogenase; CTX, chemotherapy; RTX, radiotherapy and OP, secondary tumour resection.

Due to combined modality salvage treatment, 5 of 19 patients (26%) with cerebral metastases at relapse after primary high-dose chemotherapy achieved long-term survival of more

Table 3 – Overview on patients achieving long-term survival after cerebral metastases at first relapse after primary high-dose chemotherapy

No.	Histology	CM at primary diagnosis	Response to HD-CTX	Time to relapse (months)	Relapse other than CM	AFP at relapse	ß-HCG at relapse	Chemotherapy regimen	Radiation	Secondary resection	Survival (months)
3	Mixed	No	CR	8	No	Normal	Normal	HD-carboplatin + etoposide	Yes	Yes	56+
57	Mixed	Yes	PR	4	Liver, lungs	21	142	Oral Etoposide	Yes	Yes (CNS, liver, lung)	67+
67	Mixed	No	PR	3	No	Normal	30	Gemcitabine	Yes	Yes	51+
81	Mixed	Yes	PR	12	No	Normal	Normal	No CTX	Yes	Yes	28+
99	Embryonal carcinoma	No	PR	6	No	Normal	Normal	No CTX	Yes	Yes	34+

CM, cerebral metastases; HD-CTX, high-dose chemotherapy; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; AFP, alpha-foetoprotein; ß-HCG, ß-human chorion gonadotropin; LDH, lactatdehydrogenase and CTX, chemotherapy.

than two years (28+ to 67+ months). Two of them had already presented with cerebral metastases at primary diagnosis. Tumour markers were normal or only slightly elevated at relapse in these patients and only one of them had presented with additional extracerebral tumour locations in the lungs and liver. Salvage treatment consisted of a different chemotherapy regimen in three of them, but brain irradiation and secondary resection of cerebral residual masses were performed in all of them (Table 3).

4. Discussion

Brain metastases are a rare event in germ cell tumour patients and are generally associated with poor prognosis, especially when occurring at relapse after initial cisplatin-based chemotherapy. Today, the combination of cisplatin-based combination chemotherapy followed by cranial irradiation is considered to be the standard treatment in patients with cerebral metastases.[9,10,15] A number of phase II trials have demonstrated that primary cisplatin- and etoposide-based high-dose chemotherapy with autologous stem-cell transplantation is feasible in patients with 'poor prognosis' advanced germ cell tumours and may achieve survival rates up to 70–80%.[4–7] In the only phase randomised phase III trial comparing primary high-dose chemotherapy with standard-dose chemotherapy in patients with poor or intermediate prognosis germ cell cancer patients, patients with cerebral metastases were excluded by study protocol.[8] As this single randomised phase III trial showed no significant difference between standard-dose and high-dose chemotherapy, primary high-dose chemotherapy does not present the standard of care in patients with 'poor prognosis' metastatic germ cell cancer, but might be considered in cases of very poor risk like patients with cerebral metastases.

Only one analysis on primary high-dose chemotherapy in patients with cerebral metastases in germ cell tumours, published by Kollmannsberger et al. in 2000, demonstrated that cisplatin-, etoposide- and ifosfamide-containing high-dose chemotherapy plus cerebral irradiation is feasible without increased treatment-related mortality.[14] This study included 22 patients with cerebral metastases and was conducted as a subgroup analysis of the phase II trial evaluating primary HD-VIP chemotherapy in patients with advanced/poor prognosis non-seminomatous germ cell cancer. For the current analysis, updated data of 27 patients with primary cerebral metastases receiving HD-VIP and 23 patients of the subsequent HD-TaxVIP-study were combined.[4,7]

The results show that most patients presenting with cerebral metastases at initial diagnosis are characterised by very high ß-HCG levels (88%) and metastases to the lungs (90%). This is in particular true for patients relapsing with cerebral metastases, who all had high ß-HCG-levels and pulmonary metastases at the time of relapse. Primary histology contained components of embryonal or chorionic carcinoma in 72% of patients. In 2007, Azar et al.presented a series of 5 patients with isolated cerebral relapse after initial cisplatin-based chemotherapy, who all had components of embryonal carcinoma and pulmonary metastases at primary

diagnoses.[16] Therefore, brain imaging should be considered in patients with embryonal or chorionic carcinoma, highly elevated ß-HCG-levels, and pulmonary metastases as part of the initial staging procedures.

In our study, 40% of patients with cerebral metastases underwent cerebral irradiation after completion of high-dose chemotherapy. Interestingly, patients achieving long-term survival had a higher rate of additional irradiation (55%). This could indicate that the combination of primary chemotherapy plus cerebral irradiation may be the optimal treatment in patients with cerebral metastases, as had previously been indicated by a number of trials.[9,10,17–19]

Since only 8% of patients with brain metastases at initial diagnosis underwent secondary cerebral surgery, the impact of neurosurgery on overall outcome cannot be conclusively assessed in this cohort. In contrast, in patients relapsing with cerebral metastases after primary high-dose chemotherapy, surgery was performed in 63% of patients. In all 5 patients with brain metastases at relapse who achieved long-term survival, treatment consisted of surgery and irradiation (100%) plus chemotherapy (60%). Data on treatment and outcome of patients relapsing with cerebral metastases are scarce, but our data suggest that a multidisciplinary approach combining all treatment modalities could have contributed to the long-term survival seen in these patients.

Raina et al. had postulated in their retrospective analysis that isolated cerebral metastases are very rare, occurring in only 2% of patients after initial treatment for all metastatic stages.[20] This is in contrast to our results, showing that patients relapsing after response to high-dose chemotherapy have isolated cerebral relapse in 68%. This could either be due to a different biology in patients with initially advanced disease, or be an effect of increased extracerebral efficacy of high-dose chemotherapy in this patient population, yet without reaching the same effect in the cerebrum which must be regarded a sanctuary for disseminated tumour cells. In the analysis by Azar et al., the authors discuss an incomplete penetration of cytostatic drugs through the blood-brain-barrier as the reason for isolated cerebral relapse after chemotherapy.[16] This may also be the reason for the large number of isolated cerebral relapses seen in this cohort after dose-intense chemotherapy and the relatively high rate of 60% of patients achieving long-term survival due to primary high-dose chemotherapy +/– irradiation and, in the case of relapse, additional multidisciplinary salvage treatment modalities.

In conclusion, patients with cerebral metastases at primary diagnosis are characterised by embryonal or chorionic carcinoma-containing primary histology, highly elevated levels of ß-HCG and the presence of pulmonary metastases. Therefore, cerebral imaging should be considered in patients fulfilling these characteristics as part of initial staging and follow-up procedures. Long-term survival despite poor prognostic features including brain metastases can be achieved in up to 60% of these patients, indicating that the presence of brain metastases in non-seminomatous germ cell tumours is not a death sentence. Even patients with relapsed non-seminomatous germ cell tumour cerebral metastases can safely be treated, and long-term survival is possible in about 25% of these patients.

Conflict of interest statement

None declared.

REFERENCES

1. Birch R, Wiliams S, Cone A, et al. Prognostic factors for favourable out come in disseminated germ cell tumors. *J Clin Oncol* 1996;**4**:400–7.
2. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers, *International Germ Cell Cancer Collaborative Group. J Clin Oncol* 1997;**15**:594–603.
3. Einhorn LH. Curing metastatic testicular cancer. *Proc Nat Acad Sci USA* 2002;**99**:4592–5.
4. Schmoll HJ, Kollmannsberger C, Metzner B, et al. Long-term results of first-line sequential high-dose etoposide, ifosfamide, and cisplatin chemotherapy plus autologous stem cell support for patients with advanced metastatic germ cell cancer: an extended phase I/II study of the German Testicular Cancer Study Group. *J Clin Oncol* 2003;**21**:4083–91.
5. Bokemeyer C, Kollmannsberger C, Meisner C, et al. First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: a multivariate and matched-pair analysis. *J Clin Oncol* 1999;**17**:3450–6.
6. Bokemeyer C, Schleucher N, Metzner B, et al. First-line sequential high-dose VIP chemotherapy with autologous transplantation for patients with primary mediastinal nonseminomatous germ cell tumours: a prospective trial. *Br J Cancer* 2003;**89**:29–35.
7. Hartmann JT, Gauler T, Metzner B, et al. Phase I/II study of sequential dose-intensified ifosfamide, cisplatin, and etoposide plus paclitaxel as induction chemotherapy for poor prognosis germ cell tumors by the German Testicular Cancer Study Group. *J Clin Oncol* 2007;**25**:5742–7.
8. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol* 2007;**25**:247–56.
9. Fossa SD, Bokemeyer C, Gerl A, et al. Treatment outcome of patients with brain metastases from malignant germ cell tumors. *Cancer* 1999;**85**:988–97.
10. Bokemeyer C, Nowak P, Haupt A, et al. Treatment of brain metastases in patients with testicular cancer. *J Clin Oncol* 1997;**15**:1449–54.
11. Spears WT, Morphis 2nd JG, Lester SG, Williams SD, Einhorn LH. Brain metastases and testicular tumors: long-term survival. *Int J Radiat Oncol Biol Phys* 1992;**22**:17–22.
12. Logothetis CJ, Samuels ML, Trindade A. The management of brain metastases in germ cell tumors. *Cancer* 1982;**49**:12–8.
13. Rustin GJ, Newlands ES, Bagshawe KD, Begent RH, Crawford SM. Successful management of metastatic and primary germ cell tumors in the brain. *Cancer* 1986;**57**:2108–13.
14. Kollmannsberger C, Nichols C, Bamberg M, et al. First-line high-dose chemotherapy +/– radiation therapy in patients with metastatic germ-cell cancer and brain metastases. *Ann Oncol* 2000;**11**:553–9.
15. Kobayashi T, Yoshida J, Ishiyama J, Noda S, Kito A, Kida Y. Combination chemotherapy with cisplatin and etoposide for malignant intracranial germ-cell tumors. An experimental and clinical study. *J Neurosurg* 1989;**70**:676–81.

16. Azar JM, Einhorn LH, Schneider BP. Is the blood-brain barrier relevant in metastatic germ cell tumors? *Int J Radiat Oncol Biol Phys* 2007;**69**:163–6.
17. Buckner JC, Peethambaram PP, Smithson WA, et al. Phase II trial of primary chemotherapy followed by reduced-dose radiation for CM germ cell tumors. *J Clin Oncol* 1999;**17**:933–40.
18. Raghavan D, Mackintosh JF, Fox RM, Rogers J, Duval P, Besser M. Improved survival after brain metastases in non-seminomatous germ cell tumours with combined modality treatment. *Br J Urol* 1987;**60**:364–7.
19. Salvati M, Piccirilli M, Raco A, et al. Brain metastasis from non-seminomatous germ cell tumors of the testis: indications for aggressive treatment. *Neurosurg Rev* 2006;**29**:130–7.
20. Raina V, Singh SP, Kamble N, et al. Brain metastasis as the site of relapse in germ cell tumor of testis. *Cancer* 1993;**72**:2182–5.