Anti-Cancer Drugs 1995, **6**, Suppl 4, pp. 19–24

Docetaxel: an interesting new drug for the treatment of head and neck cancers and soft tissue sarcomas

Jaap Verweij

Department of Medical Oncology, Rotterdam Cancer Institute, Rotterdam, The Netherlands.

Results are summarized for two phase II studies of docetaxel as first-line therapy for advanced squamous cell carcinoma of the head and neck (SCCHN) and one study of docetaxel as second-line therapy for advanced soft tissue sarcomas. In all three studies, docetaxel was administered at a dose of 100 mg/m^2 by intravenous infusion over 1 h every 3 weeks. A total of 62 patients were enrolled in the SCCHN trials, of whom 57 were evaluable for response. The combined overall response rate in the SCCHN patients was 35%. Median duration of overall response was 6.5 months in the EORTC–ECTG study. In the DFCI study, median durations of complete and partial remission were 6.75 months and 4.45 months, respectively. These results are at least comparable to those achieved with other single-agent therapies in this setting. In the soft tissue sarcoma study, 29 of the 31 patients enrolled were evaluable for response. Five patients (17%) achieved a partial response to docetaxel as second-line therapy and a further nine (31%) had stable disease. Median duration of response in these patients with soft tissue sarcomas was 5 months. Again, these results are similar to those seen with the three most active single agents in soft tissue sarcomas when used as second-line therapy. Docetaxel may therefore represent a useful drug in both advanced SCCHN and soft tissue sarcomas.

Introduction

Head and neck tumors and soft tissue sarcomas are two fields of cancer in which chemotherapy for advanced disease has produced disappointing results, with average response rates of around 20–30% and 25%, respectively.[1,2]

Worldwide, there are an estimated 500,000 new cases of head and neck cancer each year.[1] Surgery and/or radiotherapy is the treatment of choice for locally or regionally advanced disease, with chemotherapy largely reserved as standard therapy only for patients with recurrent or metastatic cancer.[1] Unfortunately, the majority of patients present with advanced disease.[3] Methotrexate remains the most commonly used agent for recurrent and metastatic head and neck cancers, although others such as cisplatin and 5-fluorouracil (5-FU) are also employed. While trials of some combination regimens have shown improved response rates compared to single-agent therapy in such patients, these do not appear to translate into improved survival.[4,5]

Soft tissue sarcomas are rare diseases, accounting for only about 1% of all neoplasms in humans.[2] Wide surgical excision followed by radiotherapy can often achieve adequate local control, but metastatic disease remains a serious problem, with poor response rates even to doxorubicin and ifosfamide, considered to be the most active drugs in this setting.[2,6] Combination therapy has achieved either no improvements or only minor increases in response rates, with no obvious survival benefit.[7–10]

Docetaxel, a novel semisynthetic taxoid, is currently being investigated for the treatment of locally advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN) and advanced soft tissue sarcomas. Data published to date are summarized here.

Head and neck cancer

Two phase II studies have been undertaken to assess the efficacy of docetaxel in locally advanced or metastatic SCCHN: one by the European Organization for Research on Treatment of Cancer (EORTC)–Early Clinical Trial Group (ECTG) in Europe,[11] the other by the Dana Farber Cancer Institute (DFCI) in the US.[12]

Patients

Patient eligibility criteria were similar in each study and included the following prerequisites: histologically proven disease, measurable or evaluable disease

Correspondence to Jaap Verweij
Department of Medical Oncology, Rotterdam Cancer Institute, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

© *1995 Rapid Communications of Oxford Ltd*

Table 1. Patient characteristics in two phase II studies of docetaxel in SCCHN [11,12]

	EORTC–ECTG study	DFCI study	Total
No. of patients registered	40	22	62
No. of patients evaluable for response	37	20	57
Median age, years (range)	55 (39–74)	61 (42–81)	58 (39–81)
Evaluable males / females	32 / 5	15 / 5	47 / 10
WHO performance status			
0	11	0	11
1	21	11 [a]	32
2	8	9 [a]	17
Disease extent			
Local	—	11 (50%)	11 (18%)
Regional	—	7 (32%)	7 (11%)
Local + regional	26 (65%)	1 (4.5%)	27 (43.5%)
Distant metastases	11 (27.5%)	3 (13.5%)	14 (22.5%)
Locoregional + distant metastases	3 (7.5%)	—	3 (5%)
Prior therapy			
Radiotherapy	33 (82.5%)	16 (73%)	49 (79%)
Surgery	24 (60%)	—	24 (39%)
Induction chemotherapy	10 (25%)	6 (27%)	16 (26%)

[a] Evaluable patients.

parameters, WHO performance status ≤ 2, and adequate bone marrow (WBC ≥ 4×10^9/l, platelets ≥ 100×10^9/l), liver (bilirubin within normal limits) and renal function. Patients were not allowed to have been treated previously for recurrent or metastatic cancer, but chemotherapy prior to or concurrent with initial loco-regional treatment was permitted as long as it had been completed 6 months (EORTC–ECTG study) or 12 months (DFCI study) prior to entry into the trial.

Treatment

In both studies docetaxel was administered at a dose of 100 mg/m^2 by intravenous infusion over 1 h every 3 weeks. Patients in the DFCI study but not in the EORTC–ECTG study received premedication with dexamethasone, diphenhydramine and cimetidine as prophylaxis against hypersensitivity reactions. Neither study allowed routine prophylactic use of growth factors or antiemetics.

Evaluation

Responses were evaluated according to WHO efficacy criteria.

Results

Patient characteristics. Patient characteristics are shown in Table 1. A total of 62 patients were enrolled in the trials, of whom 57 were evaluable for response. Patients in the DFCI study had slightly worse performance scores but a greater prevalence of local disease compared to those in the EORTC–ECTG study. None of the patients in the DFCI study had undergone surgery compared to 60% in the EORTC–ECTG study patients, but similar percentages of patients in each group had received radiotherapy and/or induction chemotherapy.

Response. The combined overall response rate (complete plus partial response) was 35%, with similar results in each study (Table 2). Median duration of overall response was 6.5 months (range 2.7–8.8) in the EORTC–ECTG study. In the DFCI study median duration of complete and partial remission was 6.75 months and 4.45 months, respectively.

Toxicity. The median number of cycles of docetaxel administered was comparable in both studies (4 [range 1–11] in the EORTC–ECTG study and ≥ 3 in the DFCI study). Neutropenia occurred in the majority of patients in each study, with neutrophil counts reaching a nadir between days 5 and 8 following docetaxel

Table 2. Response to docetaxel in two phase II studies in patients with SCCHN [11,12]

Study	CR	PR	SD	PD
EORTC–ECTG	2 (5%)	10 (27%)	13 (35%)	12 (32%)
	12 (32%)			
DFCI	2 (10%)	6 (30%)	7 (35%)	5 (25%)
	8 (40%)			
Total	4 (7%)	16 (28%)	20 (35%)	17 (30%)
	20 (35%) [a]			

[a] 95% CI: 23–49.

Table 3. Incidence of adverse events in two phase II studies of docetaxel in SCCHN [11,12]

	EORTC–ECTG study (% patients)	DFCI study (% patients)
Alopecia	90	100
Asthenia	69	72
Skin toxicity	54	NS
Nail toxicity	NS	36
Neuropathy	41	45
Stomatitis	38	NS
Nausea	36	NS
Vomiting	31	NS
Edema	31	9
Diarrhea	27	NS
Hypersensitivity	23	14
Myalgia	13	NS

NS: Not stated.

administration and then recovering very rapidly.[11] For unknown reasons, there was a greater incidence of grade 3–4 neutropenia in the DFCI study than in the EORTC–ECTG study (61% of courses). Other adverse events recorded in each study are shown in Table 3. The most frequently observed side effect was alopecia, occurring in 90–100% of patients. There was a lower incidence of both edema and hypersensitivity reactions in the DFCI study, which was almost certainly related to the administration of prophylactic premedication.

Soft tissue sarcomas

The efficacy of docetaxel as second-line therapy in patients with advanced soft tissue sarcomas was assessed in a study conducted by the EORTC Soft Tissue and Bone Sarcoma Group,[2] details of which are presented below.

Patients

As in the SCCHN studies described above, patients in the soft tissue sarcoma study were required to have histologically proven disease, measurable disease parameters, WHO performance status ≤ 2, and adequate bone marrow (WBC ≥ 4×10^9/l, platelets ≥ 100×10^9/l), liver (bilirubin within normal limits) and renal function. Prior chemotherapy with doxorubicin and/or ifosfamide was allowed but this had to have been discontinued more than 4 weeks before entering the study. No patients who had previously received immunotherapy were permitted to enter the trial.

Treatment

Docetaxel at a dose of 100 mg/m^2 was administered by intravenous infusion over 1 h every 3 weeks, with dose adjustments as necessary depending on neutrophil and platelet counts. There was no routine administration of antiemetics nor premedication against hypersensitivity reactions.

Evaluation

Responses were evaluated according to WHO efficacy criteria.

Results

Patient characteristics. Characteristics of the 31 patients entered into the EORTC Soft Tissue and Bone Sarcoma Group study are shown in Table 4. Most patients had previously received at least two chemotherapeutic agents, with the majority having been treated for advanced disease. Eleven patients had also received prior radiotherapy. There was a wide variety of histologic subtypes, with a prevalence of leiomyosarcomas (41% of cases), particularly among the female patients. Twenty-nine of the 31 patients were evaluable for response and 28 for toxicity.

Response. Five of the patients in this study (17% [95% CI: 6–36%]) achieved a partial response to docetaxel (Figure 1). The histologic subtypes in these patients were malignant fibrous histiocytoma, fibrosarcoma or liposarcoma. There were no complete responses but a further nine patients (31%) had stable disease. Responses became evident after five cycles in three patients and after seven cycles in the other two patients. Median duration of response was 5 months. Of the remaining 15 evaluable patients, 14 had progressive disease and one died after four cycles of docetaxel.

Toxicity. Adverse events observed in this group of patients with soft tissue sarcomas were similar to those previously observed in patients with other tu-

Table 4. Characteristics of 31 patients entered into the EORTC Soft Tissue and Bone Sarcoma Group trial [2]

	No. of patients
Age, years: median (range)	52 (27–73)
Male / female [a]	15 / 14
WHO performance status	
0	16
1	11
2	2
Prior radiotherapy [a]	
No	18
Yes, excluding hematopoietic sites	7
Yes, including hematopoietic sites	4
Prior chemotherapy [a]	
Yes, adjuvant	8
Yes, advanced	20
Yes, adjuvant and advanced	1
Histology, male / female [a]	
Malignant fibrous histiocytoma	2 / 1
Fibrosarcoma	2 / 0
Liposarcoma	3 / 2
Leiomyosarcoma	3 / 9
Rhabdomyosarcoma	1 / 0
Synovial sarcoma	1 / 0
Neurogenic sarcoma	2 / 0
Miscellaneous sarcoma	1 / 1
Unclassified sarcoma	0 / 1

[a] Characteristics of the 29 patients evaluable for response.

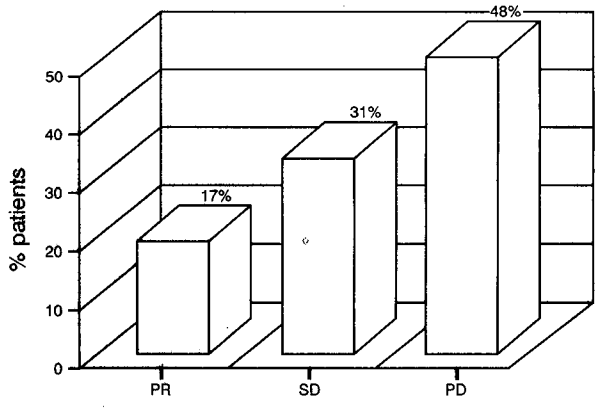

Figure 1. Response to docetaxel in a phase II study of 29 patients with soft tissue sarcomas.[2]

mor types. Twenty-six patients (89%) experienced at least one episode of grade 3–4 neutropenia, but there were only five documented infections. Peripheral edema and fluid retention were observed in 12 patients (41%). Other side effects included nausea (14%), vomiting (10%), stomatitis (13%), diarrhea (15%), constipation (12%), peripheral neurotoxicity (52%), which was mainly mild, and alopecia (86%).

Discussion

Head and neck cancer

The most commonly administered agent in patients with recurrent and metastatic head and neck cancers is methotrexate. In studies conducted in the early to mid-1980s, response rates to methotrexate as a single agent in such patients ranged from 24% to 35%, with median survival duration ranging from 5.6 to 6.1 months.[13–15] More recent trials, however, have reported response rates of only 11–25% (and median survival durations of 2.7–7.3 months),[16–21] probably as a result of more precise response definitions and improved scanning techniques. A similar pattern has been observed with other single-agent therapies in this setting, such as bleomycin, cisplatin, and carboplatin.[4,13–21] Furthermore, no consistently greater advantage has been shown with combination therapies (some including methotrexate) compared to methotrexate alone, with response rates ranging from 8 to 48% and median survival durations of between 4.0 and 6.8 months.[3,14–19] Conversely, response rates to 5-fluorouracil (5-FU) have increased in recent years. In earlier studies using bolus administration of 5-FU response rates were only around 15%, while more recent trials, using continuous infusion schedules, have achieved response rates of up to 33%.[22] The efficacy of combination therapy with cisplatin and 5-FU has also been compared to that of either agent alone or single-agent therapy with methotrexate.[4,5] Overall response rates were significantly higher with combination therapy (32%) than with single-agent therapy (cisplatin 17%, 5-FU 13% and methotrexate 10%) but this was not reflected in prolongation of survival.[4,5]

The results of single-agent docetaxel treatment of advanced SCCHN in the two phase II studies described above compare favorably therefore with previously published data on single-agent activity,[16–21] in terms of both overall response rate (35%) and duration of response (median 6.5 months).[11,12] Even combination chemotherapy with agents such as cisplatin and 5-FU does not appear to be superior to single-agent treatment as far as survival benefit is concerned.[4,5] A phase II study combining docetaxel with cisplatin

for the treatment of patients with SCCHN is about to be initiated by the EORTC–ECTG.

Soft tissue sarcomas

To date, even the most active drugs against advanced soft tissue sarcomas—doxorubicin and ifosfamide—have achieved response rates of only 23%[23] and 24%,[24] respectively, when used as first-line therapy for advanced disease. In a comparative study, the efficacy of epidoxorubicin was found to be slightly lower than that of doxorubicin (18% vs 25%).[25]

Studies of combination therapy have shown either an improved response rate but no survival benefit[8] or no improvement in either parameter compared to single-agent therapy.[7,9,10] In an Eastern Cooperative Oncology Group (ECOG) study, for example, doxorubicin alone (either weekly [n = 109] or every 3 weeks [n = 112]) was compared with doxorubicin plus dacarbazine (DTIC) (n = 110), with overall response rates of 16%, 18% and 30%, respectively.[8] However, overall survival was similar in each group and toxicity was more pronounced on the combination regimen.[6,8] Another ECOG study compared single-agent doxorubicin (n = 66) with two different combination regimens: (1) doxorubicin/cyclophosphamide/vincristine (n = 70); and (2) cyclophosphamide/vincristine/actinomycin-D (n = 64).[9] In this study, the results were actually better with single-agent doxorubicin than with the doxorubicin-containing combination, and particularly in comparison to the regimen that did not include any doxorubicin, with response rates of 27%, 19% and 11%, respectively (27% vs 11%, p = 0.003). Again, however, there was no difference between the patient groups in terms of overall survival. The lack of activity of both cyclophosphamide and actinomycin-D in soft tissue sarcomas has also been reported elsewhere.[26–28]

Even a combination of the two most active agents in this setting, doxorubicin and ifosfamide, has not been shown to improve response rates significantly compared to doxorubicin alone.[10] In this phase III study, an EORTC trial, overall response rates were 24% for single-agent doxorubicin (n = 244), 27% for the doxorubicin/ifosfamide combination (n = 233), and 27% for a combination of doxorubicin plus cyclophosphamide/vincristine/dacarbazine (n = 135).[9]

Fewer patients have received these agents as second-line therapy, where response rates of 17% for doxorubicin[6] and 13% for ifosfamide have been reported.[24] Single-agent dacarbazine has also been used for the second-line treatment of advanced soft tissue sarcomas, achieving an overall response rate of 17% but with responses lasting for only 5 weeks.[29,30]

The response rate of 17% observed in the second-line therapy study of docetaxel discussed above is thus similar to those obtained with the other active drugs in this disease when given as second-line chemotherapy. This suggests that docetaxel may be a useful alternative to the other three agents with single-agent activity in this tumor type (doxorubicin, ifosfamide and dacarbazine). However, further studies are required to confirm these early findings. A phase II study in non-pretreated patients is currently ongoing at the National Cancer Institute of Canada (NCIC), and the EORTC Soft Tissue and Bone Sarcoma Group has initiated a study comparing the efficacy of docetaxel with that of doxorubicin as first-line single-agent therapy. These studies will help to confirm the true role of docetaxel in the treatment of soft tissue sarcomas.

Conclusions

In the phase II studies described above docetaxel has shown significant activity in both head and neck cancer and soft tissue sarcomas. Docetaxel as a single agent for the treatment of advanced SCCHN achieved overall response rates and duration of response at least similar to those reported with other single-agent therapies. Similarly, docetaxel as second-line therapy for advanced soft tissue sarcomas achieved a comparable response rate to those achieved with the three most active agents in this setting. Docetaxel may therefore represent a useful drug in both advanced SCCHN and advanced soft tissue sarcomas. Several new studies are underway to investigate further the potential value of docetaxel for patients with these diseases.

References

1. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med* 1993; **328**: 184–194.
2. Van Hoesel QGCM, Verweij J, Catimel G, *et al.* Phase II study with docetaxel (Taxotere®) in advanced soft tissue sarcomas of the adult. *Ann Oncol* 1994; **5**: 539–542.
3. Clavel M, Vermorken JB, Cognetti F, *et al.* Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck: a phase II study of the EORTC Head and Neck Cancer Cooperative Group. *Ann Oncol* 1994; **5**: 521–526.
4. Forastiere AA, Metch B, Schuller DE, *et al.* Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a South-

west Oncology Group study. *J Clin Oncol* 1992; **10**: 1245–1251.
5. Jacobs C, Lyman G, Velez-Garcia E, *et al.* A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 1992; **10**: 257–263.
6. Verweij J, Pinedo HM. Changing the concepts in the systemic treatment of locally advanced or metastatic soft tissue sarcomas. In: Verweij J, Pinedo HM, Suit HD, eds. *Multidisciplinary Treatment of Soft Tissue Sarcomas.* Morwell: Kluwer Academic Publishers, 1993: 107–117.
7. Santoro A, Rouëssé J, Steward W, *et al.* A randomized EORTC study in advanced soft tissue sarcomas: adriamycin versus adriamycin/ifosfamide versus CYVADIC. *Proc Am Soc Clin Oncol* 1990; **9**: 309.
8. Borden EC, Amato DA, Rosenbaum C, *et al.* Randomized comparison of three adriamycin regimens for metastatic soft tissue sarcomas. *J Clin Oncol* 1987; **5**: 840–850.
9. Schoenfeld DA, Rosenbaum CH, Horton J, Wolter JM, Falkson G, De Conti RC. A comparison of adriamycin versus vincristine and adriamycin and cyclophosphamide versus vincristine, actinomycin-D and cyclophosphamide for advanced sarcoma. *Cancer* 1982; **50**: 2757–2762.
10. Santoro A, Tursz T, Rouëssé J, *et al.* Adriamycin vs adriamycin + ifosfamide vs CYVADIC in advanced soft tissue sarcomas: an EORTC randomized prospective study. *Eur J Cancer* 1991; **27** (Suppl 2): S350.
11. Catimel G, Verweij J, Mattijssen V, *et al.* Docetaxel (Taxotere®): an active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. *Ann Oncol* 1994; **5**: 533–537.
12. Dreyfuss A, Clark J, Norris C, *et al.* Taxotere (TXTR) for advanced, incurable squamous cell carcinoma of the head and neck (SCCHN). *Proc Am Soc Clin Oncol* 1994; **13**: 287 (Abstract 931).
13. Hong WK, Schaefer S, Issell B, *et al.* A prospective randomized trial of methotrexate versus cisplatin in the treatment of recurrent squamous cell carcinoma of the head and neck. *Cancer* 1983; **52**: 206–210.
14. Drelichman A, Cummings G, Al-Sarraf M. A randomized trial of the combination of cis-platinum, oncovin and bleomycin (COB) versus methotrexate in patients with advanced squamous cell carcinoma of the head and neck. *Cancer* 1983; **52**: 399–403.
15. Vogl SE, Schoenfeld DA, Kaplan BH, *et al.* A randomized prospective comparison of methotrexate with a combination of methotrexate, bleomycin, and cisplatin in head and neck cancer. *Cancer* 1985; **56**: 432–442.
16. Williams SD, Velez-Garcia E, Essessee I, *et al.* Chemotherapy for head and neck cancer: comparison of cisplatin + vinblastine + bleomycin versus methotrexate. *Cancer* 1986; **57**: 18–23.
17. Campbell JB, Dorman EB, McCormick M, *et al.* A randomized phase III trial of cis-platinum, methotrexate, cisplatinum + methotrexate and cis-platinum + 5-fluorouracil in end-stage head and neck cancer. *Acta Otolaryngol* 1987; **103**: 519–528.
18. Eisenberger M, Krasnow S, Ellenberg S, *et al.* A comparison of carboplatin plus methotrexate versus methotrexate alone in patients with recurrent and metastatic head and neck cancer. *J Clin Oncol* 1989; **7**: 1341–1345.
19. Forastière A, Metch B, Schuller D, *et al.* Randomized comparison of cisplatinum and 5-fluorouracil versus carboplatin + 5-FU versus methotrexate in advanced squamous cell carcinoma of the head and neck. *J Clin Oncol* 1992; **10**: 1245–1251.
20. Liverpool Head and Neck Oncology Group. A phase III randomized trial of cisplatinum, methotrexate, cisplatinum + methotrexate and cisplatinum + 5-FU in end-stage squamous cell carcinoma of the head and neck. *Br J Cancer* 1990; **61**: 311–315.
21. Al-Sarraf M. Head and neck cancer: chemotherapy concepts. *Sem Oncol* 1988; **15**: 70–85.
22. Vermorken JB, Dodion P, Verweij J, *et al.* Phase II study of 5-fluorouracil continuous i.v. infusion in patients with advanced squamous cell cancer of the head and neck. *Cancer Chemother Pharmacol* 1989; **23** (Suppl): 76.
23. Yang TC, Glatstein EJ, Rosenberg SA, *et al.* Sarcomas of soft tissue. In: de Vita V, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* Philadelphia: JB Lippincott, 1993: 1436–1488.
24. Bramwell VH, Mouridsen H, Santoro A, *et al.* Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. *Eur J Cancer Clin Oncol* 1987; **23**: 311–321.
25. Mouridsen HT, Bastholt L, Somers R, *et al.* Adriamycin versus epirubicin in advanced soft tissue sarcomas: a randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer Clin Oncol* 1987; **23**: 1477–1483.
26. Bramwell VHC, Mouridsen H, Santoro A, *et al.* Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. *Eur J Cancer Clin Oncol* 1987; **23**: 311–321.
27. Muss HB, Bundy B, DiSaia PJ, *et al.* Treatment of recurrent or advanced uterine sarcoma: a randomized trial of doxorubicin versus doxorubicin and cyclophosphamide (a phase III trial of the Gynecologic Oncology Group). *Cancer* 1985; **55**: 1648–1653.
28. Baker LH, Frank J, Fine G, *et al.* Combination chemotherapy using adriamycin, DTIC, cyclophosphamide and actinomycin-D for advanced soft tissue sarcomas: a randomized comparative trial — A phase III Southwest Oncology Group study (7613). *J Clin Oncol* 1987; **5**: 851–861.
29. Gottlieb JA, Benjamin RS, Baker LH. Role of DTIC (NSC-45338) in the chemotherapy of sarcomas. *Cancer Treat Rep* 1976; **60**: 199–203.
30. Buesa JM, Mouridsen HT, van Oosterom AT, *et al.* High dose DTIC in advanced soft tissue sarcomas of the adult. *Proc 5th NCI–EORTC New Drug Symp* 1986; **2**: 21.