Anti-Cancer Drugs 2000, **11,** pp. 143–148

Review paper

Combined chemoimmunotherapy in metastatic melanoma—is there a need for the double?

Andres Jan Schrader
Department of Cell Biology, Immunology and Experimental Oncology, National Research Centre for Biotechnology (GBF), 38124 Braunschweig, Germany.

The therapeutic benefit of adding immunotherapeutic agents such as interferon (IFN)-α and interleukin (IL)-2 to established single-agent or combination chemotherapy regimens for the treatment of metastatic melanoma has not been proven. On the contrary, recent studies indicate a significantly higher incidence of severe toxic side effects in patients treated with combined biochemotherapy. This article summarizes recent trials using either chemotherapy alone or chemotherapy plus the administration of IFN-α and/or IL-2 to evaluate the benefit of a combined biochemotherapy. [© 2000 Lippincott Williams & Wilkins.]

Key words: Malignant melanoma, combined biochemotherapy, review.

Introduction

The incidence of malignant melanoma has increased at an alarming rate over the past few decades. At present, it has risen to over 10/100 000 in western Europe, and up to 50/100 000 in Australia and in the south of the US.[1] Indications are that it will continue to rise in the foreseeable future. While primary melanomas can often be cured by wide local excision alone, the therapy for metastatic melanoma remains unsatisfactory—the prognosis for patients with metastatic disease is discouraging with a median survival of about 6–8 months.[2,3] Less than 10% of the patients remain alive 5 years after the diagnosis of metastatic disease. Therapeutic strategies for disseminated malignant melanoma include both single and combination chemotherapy, immunotherapy, chemo/immunotherapy, and, more recently, the use of vaccines and gene therapy.[4,5]

Correspondence to A Schrader, Department of Cell Biology, Immunology and Experimental Oncology, National Research Centre for Biotechnology (GBF), Mascheroder Weg 1, 38124 Braunschweig, Germany.
Tel: (+49) 531 6181 315; Fax: (+49) 531 6181 444;
E-mail: ajschrader@gmx.de.

At present, in patients with progressive metastatic melanoma, conventional chemotherapy regimens produce only short-lived remissions (3–7 months) with almost no sustained treatment benefits.[3,6,7] Achieved responses are usually partial, and are more likely to occur in skin, soft-tissue, lymph node and lung metastases than in other sites.[8] The combination of chemotherapy with immunotherapeutic agents such as interferon (IFN)-α and interleukin (IL)-2 has been reported to provide improved treatment results in patients with metastatic melanoma, compared with the use of chemotherapy alone.[9] However, more recently, several randomized trials failed to show a therapeutic benefit of combined biochemotherapy compared with established single-agent or combination chemotherapy regimens.[10,11] In addition, careful toxicity assessment revealed a significantly higher incidence of severe side effects in patients treated with combined biochemotherapy.[12,13] This article will focus on recent trials and findings about the feasibility, efficacy and toxicity of different single-agent and combination regimens for the treatment of metastatic malignant melanoma.

Treatment strategies for metastatic melanoma

At present, dacarbazine (DTIC) is the most widely accepted agent for the treatment of metastatic melanoma. The response rate achieved with DTIC as a single agent ranges from 15 to 20%, with response durations of 4–6 months, and the survival benefit is still uncertain.[14] Two or more drug chemotherapy combinations may increase response rates up to 40% at the cost of considerable toxicity; however, ongoing response rates do not exceed 10% and, again, survival rates could not be significantly improved.[2,3,14]

Recombinant IL-2 and recombinant IFN-α are biologic substances involved in the regulation of the immune system. IL-2 has been administered at various doses and schedules, and has shown reproducible activity against advanced melanoma with response rates ranging from 15 to 20%.[15,16] IFN-α alone produces objective responses in approximately 16% of patients with disseminated melanoma.[2,17] The mechanism of response to immunotherapy is still uncertain but may involve activation of cellular immunity by the stimulation of natural killer cells or the expansion of specific cytotoxic T cells. In a number of experimental murine models, the combined administration of IL-2 and IFN-α has shown better antitumor effects than the administration of either agent alone.[18,19] Based on this data, several clinical trials combining these two agents have been carried out; however, unfortunately, the majority have failed to demonstrate response rates significantly superior to those achieved with IL-2 monotherapy.[20]

Given the effectiveness and feasibility of chemotherapy, on the one hand, and biotherapy for the treatment of malignant melanoma, on the other, there have also been numerous trials of combined chemoimmunotherapy in an attempt to further improve response rates and duration of response by using potential additive or synergistic interactions between both therapeutic strategies. Studies using combination biochemotherapy adding IFN-α or IL-2 to mono- or polychemotherapy are summarized in Tables 1 and 2. Moreover, several reports have suggested that chemotherapeutic agents administered in combination with both IFN-α and IL-2 can further improve response rates up to 60%, with complete response rates between 10 and 20%,[21]

Table 1. Different chemotherapeutic regimens combined with IFN-α

Regimen	No. of patients	Response rate (CR+PR)[a] (%)	Median response duration (months)	Median survival (months)	Reference
DTIC/IFN-α	76	26	11	17	Hersey *et al.* [23]
DTIC/IFN-α	87	21	8.5	7.5	Thomson *et al.* [10][c]
DTIC/IFN-α	160	25	6.9	12	Bajetta *et al.* [24]
DTIC/IFN-α	53	17	9	4.5	Betticher *et al.* [25]
DTIC/IFN-α	61	28	10.9	8.8	Strojan *et al.* [26]
DTIC/IFN-α	60	21	3[b]	9.3	Falkson *et al.* [11][c]
DTIC/tamoxifen/IFN-α	62	19	2.6[b]	9.5	Falkson et al. [11][c]
DTIC/5-FU/IFN-α	26	38	5	12	Mulder *et al.* [27]
Vinblastine/IFN-α	17	12	4	data not shown	Gunderson *et al.* [28]
Cisplatin/IFN-α	42	24	5	7.4	Margolin *et al.* [29]
DTIC/BCNU/cisplatin/tamoxifen/ IFN-α	33	42	6	5	Feun *et al* [30]
DTIC/bleomycin/vincristine/ lomustine/IFN-α	45	62	6.8	data not shown	Pyrhönen *et al.* [31]
DTIC/bleomycin/vincristine/ lomustine/IFN-α	48	33	9	15	Vuoristo *et al.* [32]

[a]CR, complete remission; PR, partial remission.
[b]Time to treatment failure; median response duration not shown.
[c]Prospective randomized trial, that indicates no substantial benefit of a combined biochemotherapy.

Table 2. Different chemotherapeutic regimens combined with IL-2

Regimen	No. of patients	Response rate (CR+PR)[a] (%)	Median response duration (months)	Median survival (months)	Reference
DTIC/IL-2	30	22	5	data not shown	Shiloni *et al.* [33]
DTIC/IL-2	27	26	6	10	Dillman *et al.* [34]
DTIC/IL-2	32	22	5	9	Flaherty *et al.* [35]
DTIC/IL-2	25	24	8.6	13.3	Stoter *et al.* [36]
STIC/IL-2	13	0	–	5.4	Flaherty *et al.* [37]
DTIC/IL-2	55	15.8	13.9	9.3	Dummer *et al* [38]
DTIC/cisplatin/IL-2	32	41	8	10.2	Flaherty *et al.* [39]
DTIC/cisplatin/IL-2	24	42	5	8	Guida *et al.* [40]
DTIC/cisplatin/tamoxifen/IL-2	38	42	5	11	Atkins *et al.* [41]

[a]CR, complete remission; PR, partial remission

(Table 3). However, the toxicity associated with combining polychemotherapy with IL-2 and IFN-α was substantial, and the benefit of this combination approach was based largely on phase II studies compared with historical controls (Table 3).

Based on these promising data gained with combination biochemotherapy, Thomson *et al.*[10] were the first to perform a prospective, randomized, controlled trial to compare a DTIC plus IFN-α combination regimen with DTIC alone as a systemic therapy for metastatic melanoma. Eighty-seven patients were randomized to the combination and 83 patients to DTIC monotherapy. Therapy consisted of DTIC given in combination in escalating doses of 200, 400 and 800 mg/m^2 i.v. every 3 weeks or alone at 800 mg/m^2 i.v. every 3 weeks. IFN-α was administered s.c. starting at 3 mIU daily on days 1–3, 9 mIU daily on days 4–70, then 9 mIU 3 times per week. Response rates for DTIC plus IFN-α and DTIC alone were 21 and 17%, respectively, median duration of response was 258 versus 286 days, and survival of the whole group 229 and 269 days. Toxicity was significantly worse in the combination arm. A similar study was performed by Falkson *et al.*[11] who also concluded that IFN-α neither improved the response rate nor the time to treatment failure or overall survival when added to DTIC, but significantly increased toxicity.

Johnston *et al.*[12] used a randomized phased II trial to evaluate the efficacy and toxicity of combination biotherapy plus combination chemotherapy compared with polychemotherapy alone. Sixty-five patients with metastatic disease were randomized to receive i.v. BCNU 100 mg/m^2 (day 1, alternate courses), cisplatin 25 mg/m^2 (days 1–3), DTIC 220 mg/m^2 (day 1–3) and oral tamoxifen 40 mg with (n=35) or without (n=30) s.c. IL-2 18×10^6 IU t.d.s (day −2), 9×10^6 IU b.d. (day −1 and 0) and IFN-2α 9 mIU (days 1–3). The overall response rate for the biochemotherapy arm was 23%, and 27% for chemotherapy alone; the median durations of responses were 2.8 and 2.5 months, respectively. There was no significant difference between the two groups in progression-free survival or overall survival (5 versus 5.5 months). Toxicity assessment revealed a significantly higher incidence of severe thrombocytopenia in patients treated with combination chemotherapy than with chemotherapy alone (37 versus 13%) and a higher incidence of side effects like flu-like syndromes (20 versus 10%), fatigue (26 versus 13%), nausea (17 versus 10%) and breathlessness (9 versus 0%).

Rosenberg *et al.*[13] have performed a similar trial to compare treatment with chemoimmunotherapy to treatment with chemotherapy alone in patients with metastatic melanoma. One hundred and two patients were prospectively randomized to receive cisplatin

Table 3. Different chemotherapeutic regimens combined with IFN-α and IL-2

Regimen	No. of patients	Response rate (CR+PR)[a] (%)	Median response duration (months)	Median survival (months)	Reference
Cisplatin/IL-2/IFN-α	60	33	8	9	Keilholz *et al.* [22][c]
Cisplatin/tamoxifen/IL-2/IFN-α	15	13	data not shown	8	Naglieri *et al.* [42]
Cisplatin/tamoxifen/IL-2/IFN-α	127	49	5[b]	11	Antoine *et al.* [43]
DTIC/cisplatin/IL-2/IFN-α	21	24	6.4	data not shown	Proebstle *et al.* [44]
DTIC/cisplatin/tamoxifen/IL-2/IFN-α	19	37	5.1	10.6	Kashani-Sabet *et al.* [45]
DTIC/carboplatin/IL-2/IFN-α	16	37	11	data not shown	Ron *et al.* [46]
DTIC/cisplatin/vinblastine/IL-2/IFN-α	53	64	6.5	11.8	Legha *et al.* [47]
DTIC/cisplatin/tamoxifen/IL-2/IFN-α	50	44	6	10.7	Rosenberg *et al.* [13][c]
Carboplatin/vinblastine/IL-2/IFN-α	23	17	5	6	Bafaloukos *et al.* [48]
BCNU/cisplatin/DTIC/IL-2/IFN-α	42	57	8+	11.5	Richards *et al.* [21]
BCNU/cisplatin/DTIC/Il-2/IFN-α	83	55	7	12.2	Richards *et al.* [49]
BCNU/cisplatin/DTIC/tamoxifen/IL-2/IFN-α	53	42	8	12	Thompson *et al.* [50]
BCNU/cisplatin/DTIC/tamoxifen/IL-2/IFN-α	69	39	5	11	Hoffmann *et al.* [51]
BCNU/cisplatin/DTIC/tamoxifen/IL-2/IFN-α	35	23	2.8	5	Johnston *et al.* [12][c]
BCNU/cisplatin/DTIC/tamoxifen/IL-2/IFN-α	58	33	7	11	Atzpodien *et al.* [52][c]

[a]CR, complete remission; PR, partial remission.
[b]Median disease-free survival; median response duration not shown.
[c]Prospective randomized trial, that indicates no substantial benefit of a combined biochemotherapy.

25 mg/m^2 i.v. (days 2–4, 23–25), DTIC 220 mg/m^2 i.v. (days 2–4, 23–25) and oral tamoxifen (40 mg day 1 and 10 mg days 2–29) with (n=50) or without (n=52) IFN-α2b at 6×10^6 IU/m^2 s.c. and IL-2 at 0.72×10^6 IU/kg i.v. (days 5–8, 26–29). In 50 patients randomized to receive chemoimmunotherapy, there were 22 objective responses (44%); in those patients randomized to receive chemotherapy, only (n=52) 14 objective responses were achieved (27%; p=0.71). In both treatment groups, the duration of responses was often short (6 versus 11 months) and there was a trend toward a survival advantage for patients receiving chemotherapy alone (median survival of 10.7 months compared with 15.8 months; p=0.52). Once more, this study demonstrated that treatment-related toxicities were greater in patients receiving both chemo- and immunotherapy.

Keilholz *et al.*[22] used a different strategy to evaluate the benefit of a combined biochemotherapy. They performed a randomized multicenter study to determine whether the addition of cisplatin to a cytokine treatment regimen with IFN-α and high-dose IL-2 influences survival of patients with advanced disease. All patients received IFN-α 10×10^6 IU/m^2 s.c. on days 1–5 and a high-dose i.v. decrescendo regimen of IL-2 on days 3–8 (18 mIU/m^2/6 h, 18 mIU/m^2/12 h, 18 mIU/m^2/24 h and 4.5 mIU/m^2/24 h ×3) with (n=60) or without (n=66) cisplatin 100 mg/m^2 on day 1. The objective response rate was 33% with and 18% without the addition of cisplatin (p=0.04); the progression-free survival was 92 days with and 53 days without cisplatin (p=0.09; log-rank). There was also no statistically significant difference in survival between both treatment arms in this study (9 months for both groups). A combination of bio- and chemotherapy again resulted in an increase of various side effects; 65 versus 58% of patients experienced grade III and even 20 versus 0% grade IV toxicities.

Conclusions

Although several studies have suggested that the combination of chemotherapy with immunotherapeutic agents such as IFN-α and IL-2 may improve response rates and produce some prolonged complete remissions in comparison with either chemotherapy or immunotherapy alone, few prospectively randomized trials have been carried out comparing both therapeutic strategies. However, recent studies suggest that the addition of immunotherapy to single-agent or polychemotherapy may increase response rates without a significant survival benefit for patients with metastatic melanoma. In addition, combination treatment regimens significantly increase toxicity and may negatively affect quality of life. Thus today the use of combination chemoimmunotherapy regimens cannot be recommended in the absence of well-designed, prospective, randomized trials, which are needed to establish whether this treatment strategy can provide a meaningful benefit to patients with advanced melanoma as compared with conventional single-agent therapy.

References

1. Rigel DS. Malignant melanoma: perspectives on incidence and its effects on awareness, diagnosis and treatment. *CA Cancer J Clin* 1996; **46**: 195–8.
2. Legha SS. Current therapy for malignant melanoma. *Semin Oncol* 1989; **16** (suppl 1): 34–44.
3. Margolin KA, Liu PY, Flaherty LE, *et al*. Phase II study of carmustine, dacarbazine, cisplatin, and tamoxifen in advanced melanoma: a Southwest Oncology Group study. *J Clin Oncol* 1998; **16**: 664–9.
4. Boon T, Gajewski TF, Coulie PG. From defined human tumor antigens to effective immunization? *Immunol Today* 1995; **16**: 334–6.
5. Ribas A, Butterfield LH, McBride WH, *et al*. Genetic immunization for the melanoma antigen MART-1/Melan-A using recombinant adenovirus-transduced murine dendritic cells. *Cancer Res* 1997; **57**: 2865–9.
6. Hochster H, Strawderman MH, Harris JE, *et al*. Conventional dose melphalan is inactive in metastatic melanoma: results of an Eastern Cooperative Oncology Group study (E1687). *Anti-Cancer Drugs* 1999; **10**: 245–8.
7. Agarwala SS, Ferri W, Gooding W, Kirkwood JM. A phase III randomized trial of dacarbazine and carboplatin with and without tamoxifen in the treatment of patients with metastatic melanoma. *Cancer* 1999; **85**: 1979–84.
8. Koh HK. Cutaneous melanoma. *New Engl J Med* 1991; **325**: 171–82.
9. Agarwala SS, Kirkwood JM. Interferons in the therapy of solid tumors. *Oncology* 1994; **51**: 129–36.
10. Thomson DB, Adena M, McLeod GR, *et al*. Interferon-alpha 2a does not improve response or survival when combined with dacarbazine in metastatic malignant melanoma: results of a multi-institutional Australian randomized trial. *Melanoma Res* 1993; **3**: 133–8.
11. Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma. An Eastern Cooperative Oncology Group study. *J Clin Oncol* 1998; **16**: 1743–51.
12. Johnston SRD, Constenla DO, Moore J, *et al*. Randomized phase II trial of BCDT [carmustine (BCNU), cisplatin, dacarbazine (DTIC) and tamoxifen] with of without interferon alpha (IFN-alpha) and interleukin (IL-2) in patients with metastatic melanoma. *Br J Cancer* 1998; **77**: 1280–6.
13. Rosenberg SA, Yang JC, Schwartzentruber DJ, *et al*. Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alfa-2b. *J Clin Oncol* 1999; **17**: 968–75.

14. Keilholz U. Chemoimmunotherapy of melanoma. *Cancer* 1994; **75**: 905–7.
15. Rosenberg SA. The immunotherapy and gene therapy of cancer. *J Clin Oncol* 1992; **10**: 180–99.
16. Atzpodien J, Körfer A, Franks CR, Poliwoda H, Kirchner H. Home therapy with recombinant interleukin-2 and interferon-alpha 2b in advanced human malignancies. *Lancet* 1990; **335**: 1509–12.
17. McLeod GRC, Thomson DB, Hersey P. Recombinant interferon alfa-2a in advanced malignant melanoma. A phase I–II study in combination with DTIC. *Int J Cancer* 1987; suppl 1: 31–5.
18. Rosenberg SA, Schwarz SL, Spiess PJ. Combination immunotherapy for cancer: synergistic antitumor interactions of interleukin-2, alfa interferon, and tumor-infiltrating lymphocytes. *J Natl Cancer Inst* 1988; **80**: 1393–7.
19. Iigo M, Sakurai M, Tamura T, Saijo N, Hoshi A. *In vivo* activity of multiple injections of recombinant interleukin-2, alone and in combination with three different types of recombinant interferon, on various syngeneic murine tumors. *Cancer Res* 1988; **48**: 260–4.
20. Chowdhury S, Vaughan MM, Gore ME. New approaches to the systemic treatment of melanoma. *Cancer Treat Rev* 1999; **25**: 259–70.
21. Richards JM, Mehta N, Ramming K, Skosey P. Sequential chemoimmunotherapy in treatment of metastatic melanoma. *J Clin Oncol* 1992; **10**: 1338–43.
22. Keilholz U, Goey SH, Punt CJA, *et al*. Interferon alfa-2a and interleukin-2 with or without cisplatin in metastatic melanoma: a randomized trial of the European organization for research and treatment of cancer melanoma cooperative group. *J Clin Oncol* 1997; **15**: 2579–88.
23. Hersey P, McLeod GRC, Thomson DB. Treatment of advanced malignant melanoma with recombinant interferon alpha-2a in combination with DTIC: long term follow-up of two phase II studies. *Br J Haematol* 1991; **79** (suppl 1): 60–6.
24. Bajetta E, Di Leo A, Zampino MG, *et al*. Multicenter randomized trial of dacarbazine alone or in combination with two different doses and schedules of interferon alfa-2a in the treatment of advanced melanoma. *J Clin Oncol* 1994; **12**: 806–11.
25. Betticher DC, Lee SM, Morris C, Clemons M, Thatcher N. Dacarbacine and interferon-alpha 2a in advanced malignant melanoma: high response rate and prolongation of response duration occur in different patient subpopulations. *Melanoma Res* 1995; **5**: 277–82.
26. Strojan P, Rudolf Z. Immunochemotherapy with recombinant interferon-alpha 2b plus dacarbazine in the treatment of advanced malignant melanoma. *Melamoma Res* 1997; **7**: 420–7.
27. Mulder NH, de Vries EGE, Sleijfer DT, Schraffordt H, Willemse PHB. Dacarbazine (DTIC), human recombinant interferon alpha 2a (Roferon) and 5-fluorouracil for disseminated malignant melanoma. *Br J Cancer* 1992; **65**: 303–4.
28. Gunderson S, Flokkmann A. Interferon in combination with vinblastine in advanced malignant melanoma. A phase I–II study. *Cancer* 1989; **64**: 1617–9.
29. Margolin KA, Doroshow JH, Akman SA, *et al*. Phase II trial of cisplatin and alpha-interferon in advanced malignant melanoma. *J Clin Oncol* 1992; **10**: 1574–8.
30. Feun LG, Savaraj N, Moffat F, *et al*. Phase II trial of recombinant interferon-alpha with BCNU, cisplatin, DTIC and tamoxifen in advanced malignant melanoma. *Melanoma Res* 1995; **5**: 273–6.
31. Pyrhönen S, Hahka-Kemppinen M, Muhonen T. A promising interferon plus four-drug chemotherapy regimen for metastatic melanoma. *J Clin Oncol* 1992; **10**: 1919–26.
32. Vuoristo MS, Grohn P, Kellokumpu-Lehtinen P, *et al*. Intermittent interferon and polychemotherapy in metastatic melanoma. *J Cancer Res Clin Oncol* 1995; **121**: 175–80.
33. Shiloni E, Pouillart P, Janssens J, *et al*. Sequential dacarbazine chemotherapy followed by recombinant interleukin-2 in metastatic melanoma. A pilot multicentre phase I–II study. *Eur J Cancer Clin Oncol* 1989; **25** (suppl 3): S45–9.
34. Dillman RO, Oldham RK, Barth NM, Birch R, Arnold J, West WH. Recombinant interleukin-2 and adoptive immunotherapy alternated with dacarbazine therapy in melanoma: a National Biotherapy Study Group trial. *J Natl Cancer Inst* 1990; **82**: 1345–9.
35. Flaherty LE, Redman BG, Chabot GG, *et al*. A phase I–II study of dacarbazine in combination with outpatient interleukin-2 in metastatic malignant melanoma. *Cancer* 1990; **65**: 2471–7.
36. Stoter G, Aamdal S, Rodenhuis S, *et al*. Sequential administration of recombinant human interleukin-2 and dacarbacine in metastatic melanoma: a multicenter phase II study. *J Clin Oncol* 1991; **9**: 1687–91.
37. Flaherty LE, Liu PY, Fletcher WS, *et al*. Dacarbazine and outpatient interleukin-2 in treatment of metastatic malignant melanoma: phase II Southwester Oncology Group trial. *J Natl Cancer Inst* 1992; **84**: 893–4.
38. Dummer R, Gore ME, Hancock BW, *et al*. A multicenter phase II clinical trial using dacarbazine and continuous infusion interleukin-2 for metastatic melanoma. Clinical data and immunomonitoring. *Cancer* 1995; **75**: 1038–44.
39. Flaherty LE, Robinson W, Redman BG, *et al*. A phase II study of dacarbazine and cisplatin in combination with outpatient administered interleukin-2 in metastatic malignant melanoma. *Cancer* 1993; **71**: 3520–5.
40. Guida M, Latorre A, Mastria A, De Lena M. Subcutaneous recombinant interleukin-2 plus chemotherapy with cisplatin and dacarbazine in metastatic melanoma. *Eur J Cancer* 1996; **32A**: 730–3.
41. Atkins MB, O'Boyle KR, Sosman JA, *et al*. Multiinstitutional phase II trial of intensive combination chemoimmunotherapy for metastatic melanoma. *J Clin Oncol* 1994; **12**: 1553–60.
42. Naglieri E, Procacci A, Galetta D, Abbate I, Dell Erba L, Colucci G. Cisplatin, interleukin-2, interferon-alpha and tamoxifen in metastatic melanoma. A phase II study. *J Chemother* 1999; **11**: 150–5.
43. Antonie EC, Benhammouda A, Bernard A, *et al*. Salpetriere hospital experience with biochemotherapy in metastatic melanoma. *Cancer J Sci Am* 1997; **3** (suppl 1): S16–21.
44. Proebstle TM, Scheibenbogen C, Sterry W, Keilholz U. A phase II study of dacarbazine, cisplatin, interferon-alpha and high-dose interleukin-2 in poor risk metastatic melanoma. *Eur J Cancer* 1996; **32A**: 1530–3.
45. Kashani-Sabet M, Sagebiel RW, Collins HE, *et al*. Outpatient combination chemoimmunotherapy for patients with metastatic melanoma: results of a phase I/II trial. *Cancer* 1999; **86**: 2160–5.

46. Ron IG, Mordish Y, Eisenthal A, Skornick Y, Inbar MJ, Chaitchik S. A phase II study of combined administration of dacarbazine and carboplatin with home therapy of recombinant interleukin-2 and interferon-alpha 2a in patients with advanced malignant melanoma. *Cancer Immunol Immunother* 1994; **38**: 379–84.
47. Legha SS, Ring S, Eton O, *et al*. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alpha, and interleukin-2 for patients with metastatic melanoma. *J Clin Oncol* 1998; **16**: 1752–9.
48. Bafaloukos D, Fountzilas G, Skarlos D, *et al*. Subcutaneous low doses of interleukin-2 and recombinant interferon alpha with carboplatin and vinblastine in patients with advanced melanoma. *Oncology* 1998; **55**: 48–52.
49. Richards JM, Gale D, Mehta N, Lestingi T. Combination of chemotherapy with interleukin-2 and interferon alfa for the treatment of metastatic melanoma. *J Clin Oncol* 1999; **17**: 651–7.
50. Thompson JA, Gold PJ, Markowitz DR, Byrd DR, Lindgren CG, Fefer A. Updated analyses of an outpatient chemoimmunotherapy regimen for treating metastatic melanoma. *Cancer J Sci Am* 1997; **3** (suppl 1): S29–34.
51. Hoffmann R, Müller I, Neuber K, *et al*. Risk and outcome in metastatic malignant melanoma patients receiving DTIC, cisplatin, BCNU and tamoxifen followed by immunotherapy with interleukin-2 and interferon-alpha2a. *Br J Cancer* 1998, **78**: 1076–80.
52. Atzpodien J, Schrader AJ. Chemoimmuntherapie des malignen Melanoms. In: Plewig G, Wolff H, eds. *Fortschritte der praktischen Dermatologie und Venerologie*, 16th edn. Berlin: Springer 1998: 325–9.

(Received 18 January 2000; accepted 22 January 2000)