Chemoimmunotherapy with bleomycin, vincristine, lomustine, dacarbazine (BOLD) plus interferon α for metastatic melanoma: a multicentre phase II study

CJA Punt¹, CML van Herpen¹, RLH Jansen², G Vreugdenhil³, EW Muller⁴ and PHM de Mulder¹

¹Department of Medical Oncology, University Hospital Nijmegen; ²Department of Internal Medicine, University Hospital Maastricht; ³Department of Internal Medicine, St Joseph Hospital Veldhoven; ⁴Department of Internal Medicine, Slingeland Hospital Doetinchem, The Netherlands

Summary High response rates in patients with metastatic melanoma have been achieved with combination chemoimmunotherapy. A response rate of 62% in 45 patients has been reported for treatment with dacarbazine, bleomycin, vincristine, lomustine (BOLD) plus interferon α (IFN-α). We conducted a multicentre phase II study to confirm these results. Melanoma patients with distant metastases were treated as outpatients with dacarbazine 200 mg m⁻² on days 1–5, vincristine 1 mg on days 1 and 4, bleomycin 15 mg on days 2 and 5 i.v. and lomustine 80 mg orally on day 1, repeated every 4 weeks. IFN-α-2b was initiated s.c. on day 8 at 3 MU daily for 6 weeks, and 6 MU t.i.w. thereafter. Forty-three patients entered the study. The median number of metastatic sites was three (range 1–5), and 81% of patients had visceral metastases. Nine patients had brain metastases, and seven patients were systemically pretreated. Among the 41 patients that were evaluable for response, the response rate was 27% (95% CI 14–43%), with one complete and ten partial remissions. The response rate in 25 previously untreated patients without brain metastases was 40% (95% CI 21–61%). Median duration of response was 6 (range 2–14) months; median overall survival was 5 (1–26) months. The main toxicity was malaise/fatigue. We confirm that BOLD plus IFN-α has activity in metastatic melanoma. The lower response rate in our study compared with the previous report is probably related to patient selection, as in the previous study 46% of patients had stage III disease, whereas all our patients had stage IV disease, which is associated with a worse prognosis.

Keywords: metastatic melanoma; chemotherapy, interferon-α; chemoimmunotherapy

Although long-term remissions have been achieved in patients with metastatic melanoma, the regimen of choice remains controversial in these patients. Single-agent therapy with dacarbazine (DTIC) or immunotherapeutic agents such as interleukin 2 (IL-2) and interferon-α (IFN-α) results in response rates of 15–20% (Houghton et al, 1992; Kirkwood, 1995; Marincola and Rosenberg, 1995). With combination chemotherapy regimens, such as cisplatin, vinblastine and DTIC (CVD) (Legha et al, 1989) or cisplatin, carmustine, DTIC and tamoxifen (Del Prete et al, 1984; McClay et al, 1992), response rates of 40–52% have been observed. The response rate of 40% initially reported for bleomycin, vincristine, lomustine and DTIC (BOLD) (Seigler et al, 1980) was not confirmed by others (York and Foltz, 1988; Prudente Foundation Melanoma Study Group, 1989). Combination immunotherapy with IL-2 and IFN-α has not unequivocally improved the results of either agent alone (Kirkwood, 1995) and was very toxic when administered at high doses (Kruijt et al, 1994; Marincola et al, 1995; Kruijt et al, 1996). Several chemoimmunotherapy schedules have been clinically tested. The results of DTIC plus IFN-α are conflicting, with most trials failing to show a benefit of the combination over DTIC alone (Falkson et al, 1991; Thompson et al, 1993; Bajetta et al, 1994; Mulder et al, 1994; Falkson et al, 1996). Phase II results of DTIC plus IL-2 did not suggest a clear benefit for this combination (Stoter et al, 1991; Fiedler et al, 1992). High response rates of 42–73% have been achieved in (mostly single centre) phase II studies with combinations of IL-2, IFN-α and cisplatin (Khayat et al, 1993), IL-2, IFN-α and CVD (Buzaid and Legha, 1994), IL-2, cisplatin, DTIC and tamoxifen (Atkins et al, 1994), and IL-2, IFN-α, cisplatin, carmustine, DTIC and tamoxifen (Richards et al, 1992). The median duration of response and survival in these studies was reported to be up to 9 months and 14 months respectively.

Pyrhönen et al, (1992) reported a 62% response rate (95% confidence limit 48–77%) with 13% complete responses in 45 patients upon combination treatment consisting of BOLD plus IFN-α. Two patients with stable disease and two with progressive disease responded when the administration of IFN-α was changed from a weekly to an intermittent schedule. There was one toxic death, but overall toxicity was acceptable. Given these promising results, we performed a confirmatory study with the same schedule in patients with metastatic melanoma.

PATIENTS AND METHODS

Eligibility

Eligibility criteria included histologically proven metastatic melanoma, not amenable to surgery, bidimensionally measurable disease, WHO performance status 0–2, age 18–75 years, pretreatment with a maximum of one regimen containing ≤ 1 drug of the proposed regimen, serum values of creatinine ≤ 150 μmol l⁻¹,
bilateral ≤ 25 μmol l⁻¹, liver transaminases ≤ 1.5 times normal unless related to liver metastases, WBC ≥ 3.5 × 10⁹ l⁻¹ and platelets ≥ 100 × 10⁹ l⁻¹. Patients with a history of second malignancy, with the exception of adequately treated carcinoma in situ of the cervix or basal/squamous cell carcinoma of the skin, concomitant serious non-malignant illness, active infections, concurrent treatment with immunosuppressive agents and pregnant or lactating women were excluded. Patients with asymptomatic brain metastases were eligible provided they were not receiving treatment with steroids. Written informed consent was obtained from all patients. Before initiation of this trial, institutional review board approval was obtained at each of the participating centres.

Study design

Patients were treated as outpatients with chemotherapy (BOLD) consisting of lonidamine 80 mg administered orally on day 1, DTIC 200 mg m⁻² i.v. on days 1–5, bleomycin 15 mg i.v. on days 2 + 5, and vincristine 1 mg m⁻² i.v. on days 1 + 4. Cycles were repeated every 4 weeks. IFN-α₂b (Intron A, Schering Plough, The Netherlands) was administered s.c. at 3 MU daily for 6 weeks starting at day 8 and 6 MU i.v. thereafter. Patients received prophylactic antiemesis with 5HT₁ antagonists during the 5 days of chemotherapy administration. The use of corticosteroids was prohibited. Before and after IFN-α administration, patients received acetaminophen 1000 mg orally. The addition of naproxen 250 mg for constitutional symptoms caused by IFN-α was allowed. Patients were evaluated weekly for toxicity and every two cycles for response. WHO criteria for toxicity and response were used. Treatment was continued in the absence of tumour progression or severe toxicity. In the case of WHO grade 3 toxicities, treatment was withheld until complete resolution of the toxicity, and the dose of the responsible drug was reduced to 75% in subsequent cycles. Chemotherapy cycles were only restarted when WBC and platelet values were ≥ 3.5 × 10⁹ l⁻¹ and 100 × 10⁹ l⁻¹ respectively. In the case of WHO ≥ grade 3 vincristine-induced neurotoxicity or bleomycin-induced pulmonary toxicity, these drugs were permanently discontinued. A 50% dose reduction of IFN-α was allowed for ≥ grade 3 constitutional symptoms.

RESULTS

Forty-three patients were entered onto the study in seven different centres. Patients’ characteristics are listed in Table 1. All patients had stage IV disease, i.e. with distant metastases. The median age of all patients was 58 years (range 22–74), median WHO performance status 1 (0–2), median serum lactate dehydrogenase (LDH) 369 U l⁻¹ (161–4768, normal values up to 330 U l⁻¹). The median number of metastatic sites was 3 (1–5). The sites of metastases were the lungs in 24 patients, lymph nodes in 24, skin/subcutaneous in 22, liver in 17, brain in 9, bone in 5 and other sites in ten patients. Visceral metastases were present in 81% of patients. Seven patients had received prior systemic treatment, eight had received prior radiotherapy and nine had had surgery for metastases. Patients received a median number of two (range 1–8) cycles.

**Anti-tumour responses**

Two patients were not evaluable for response. One patient died suddenly on the fifth day of treatment and one patient refused treatment after one cycle and was subsequently lost to follow-up. Thus, 41 patients were evaluable for response. The overall response rate was 27% (95% CI 14–43%) with one CR and ten PRs. No responses occurred in the seven patients who had been systemically pretreated. Of the nine patients with brain metastases,
one PR occurred in a patient who had received prior cranial irradiation, whereas all four patients with asymptomatic brain metastases who were not previously irradiated progressed at this site. The response rate in 25 previously systemically untreated patients without brain metastases was 40% (95% CI 21–61%). A 72-year-old man with a partial response of lung metastases and a complete response of liver, subcutaneous and lymph node metastases developed pulmonary fibrosis with dyspnoea at rest after the third chemotherapy cycle. Treatment was discontinued and treatment with corticosteroids was instituted, after which his condition remained stable. He died 6 months later of brain metastases. A 59-year-old female patient with a partial response of lung metastases experienced a severe depression, which was quickly reversible after discontinuation of IFN-α. BOLD was continued for a total of six cycles. She died after 20 months of tumour progression. A 67-year-old man died suddenly at home on the fifth day of the first chemotherapy cycle before treatment with IFN-α was initiated. A tentative diagnosis of a myocardial infarction was made, and a definite causal relationship with treatment could not be established. Toxicity necessitated dose reductions or discontinuation of BOLD chemotherapy in 16 out of 134 cycles (12%) in eight patients (19%), and chemotherapy was delayed in 12 out of 134 cycles (9%) in ten patients (24%). The dose of IFN-α was reduced or discontinued in six patients (14%).

DISCUSSION

The mechanisms underlying the supposed synergistic interaction between chemotherapy and immunotherapy are still speculative. Arguments for the enhancement of the anti-tumour activity of immunotherapy by chemotherapy as well as vice versa have been postulated. Clinical support for an interaction between these treatment modalities appears to be increasing CD4/CD8 ratios during chemoimmunotherapy with IFN-α is uncertain.

In conclusion, we confirm that BOLD plus IFN-α is an active regimen in patients with metastatic melanoma. The previous reported high response rate of 62% in 48 patients is probably related to a selection of patients with good prognosis. The median survival of 6 months in this group of patients is disappointing but may be related to poor prognostic parameters.
IL-2 and IFN-α significantly increases the response rate without prolonging survival (Kellholz et al., 1996). In order to provide patients with metastatic melanoma with the best possible care, further randomized phase III trials are warranted to establish the value of combination treatments vs less intensive and therefore less toxic regimens.

ACKNOWLEDGEMENTS

The following investigators also collaborated in this study: P van Luijster, Department of Internal Medicine, Carolus Hospital’s Hertogenbosch, E Bulk, Department of Internal Medicine, Streekziekenhuis Gelderse Vallei Beunnekem, and VA Derley, Department of Internal Medicine, Eikerkieck Hospital Helmond, The Netherlands. The assistance in data management of M Huider, Bajetta E, Dileo A, Zampino MG, Sertoli MR, Cornelia G, Barduagni M, Giannotti Atkins MB, Oboyle KR, Sosman JA, Weiss GR, Margolin KA, Ernest ML, Kappler Liessum, Department of Internal Medicine, Carolus Hospital’s

REFERENCES

Atkins MB, Obholz KR, Sosman JA, Weiss GR, Margolin KA, Ernest ML, Kappler K, Mier JW, Sperano JA, Fischer RI, Eckardt JR, Pereira C and Arosen FR (1994) Multinstitutional phase II trial of intensive combination chemoinmunotherapy for metastatic melanoma. J Clin Oncol 12: 1553–1560

Bajetta E, Dileo A, Zampino MG, Sertoli MR, Cornelia G, Barduagni M, Giannotti E, Tertemini P, Berghofer M, Storkenberg M, Menichetti ET, Palmeri S, Russo A, Cristofolini M, Erbuzzi A, Fossot C, Criscuolo D, Bufalino R, Zilemba N and Cascinelli N (1994) Multicenter randomized trial of dacarbazine alone or in combination with two different doses and schedules of interferon α2a in the treatment of advanced melanoma. J Clin Oncol 12: 806–811

Balch CM, Soong SJ, Shaw HM, Urist MM and McCarthy WH (1992) An analysis of prognostic factors in 8500 patients with cutaneous melanoma. In Cutaneous Melanoma, Balch CM, Houghton AN, Milton GW, Sober AJ and Soong SJ (eds), pp. 165–187. JB Lippincott: Philadelphia

Bureaud AC and Legha SS (1994) Combination of chemotherapy with interleukin-2 and interferon-α for the treatment of advanced melanoma. Semin Oncol 21: 23–28

Cantell K, Hirvonen S and Koistinen V (1981) Partial purification of human leucocyte interferon on a large scale. Methods Enzymol 78: 499–505

Del Prete SA, Maurer L, D’Oro Neto J, Fietscher RI and Lenamander P (1984) Combination chemotherapy with cisplatin, carbustine, dacarbazine, and tamoxifen in metastatic melanoma. Cancer Treat Rep 68: 1403–1405

Falkson CI, Falkson G and Falkson HC (1991) Improved results with the addition of interferon α2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. J Clin Oncol 9: 1403–1408

Falkson CI, Ibrahim J, Kirkwood J and Hum R (1996) A randomized phase III trial of dacarbazine (DTIC) versus DTIC + interferon α2b (IFN) versus DTIC + tamoxifen (TMX) versus DTIC + IFN + TMX in metastatic malignant melanoma: an EORTC trial (abstract). Proc Am Soc Clin Oncol 15: 435

Fiellér W, Jasmin C, Del Mulder PHM, Pyrhönen S, Palmero PA, Franks CR, Oskam and Hossfeld DK (1992) A phase II study of sequential recombinant interleukin-2 followed by dacarbazine in metastatic melanoma. Eur J Cancer 28: 443–446

Hernberg M, Muhonen T, Turtunen JP, Halaka-Kennepinen M and Pyrhönen S (1996) The CD4+CD8+ ratio as a prognostic factor in patients with metastatic melanoma receiving chemoinmunotherapy. J Clin Oncol 14: 1690–1696

Houghton AN, Legha S and Bajotin DF (1992) Chemotherapy for metastatic melanoma. In Cutaneous Melanoma, Balch CM (ed.), pp. 499–508. JB Lippincott: Philadelphia

Karakousis CP, Enrich LJ and Rao U (1986) Gruin dissemination in malignant melanoma. Am J Surg 152: 491–497

Kellholz U, Goey SH, Pani CJA, Proebstle T, Salzmann R, Schauendorf D, Lienard D, Scheibenbug C and Eggemert AAM (1996) A randomized trial of IFNα2b-IFN2 with or without CDDP in advanced melanoma: an EORTC Melanoma Cooperative Group trial (abstract). Proc Am Soc Clin Oncol 15: 435

Khayat D, Boed D, Tounini JM, Beznathmoua A, Antoine E, Rixe O, Vullienin E, Bazes PA, Thill L, Frank J, Audibet C, Barzin P and Weil M (1993) Sequential chemoinmunotherapy with cisplatin, interleukin-2 and interferon α2a for metastatic melanoma. J Clin Oncol 11: 2173–2180

Kirkwood JM (1995) Melanoma. In Biologic Therapy of Cancer: Principles and Practice, DeVita VT, Jr, Hellman S and Rosenberg SA (eds), pp. 388–411 JB Lippincott: Philadelphia

Kruit WH, Pani CJA, Goey SH, Demolder PH, Vanhoogenhuyze DC, Henzenlogmans SC and Stoter G (1994) Cardiotoxicity as a dose-limiting factor in a schedule of high dose bolus therapy with interleukin-2 and alpha-interferon – An unexpectedly frequent complication. Cancer 74: 2850–2856

Kruit WHJ, Pani CJA, Goey SH, DE Mulder PHM, Grinstead JW, Eggemert AMM, Bollius RLH and Stoter G (1996) Dose-efficacy study of two schedules of high-dose bolus administration of interleukin-2 and alpha-interferon in patients with metastatic melanoma. Br J Cancer 74: 951–955

Legha SS, Sieg S, Papadopoulou N, Plager C, Chowla S and Benjamin R (1989) A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. Cancer 64: 2024–2029

McCay EF, Mastrangelo MJ, Berd D and Bellet RE (1992) Effective combination chemo/hormonal therapy for malignant melanoma: experience with three consecutive trials. Int J Cancer 50: 553–556

Marincola FM, White DE, Wise AP and Rosenberg SA (1995) Combination therapy with interferon α2a and interleukin-2 for the treatment of metastatic melanoma. J Clin Oncol 13: 1110–1122

Marincola FM and Rosenberg SA (1995) Biologic therapy with interleukin-2: clinical applications. Melanoma. In Biologic Therapy of Cancer, DeVita VT, Jr, Hellman S and Rosenberg SA (eds), pp. 250–262. JB Lippincott: Philadelphia

Mulder NH, Vendergraaf WTA, Willemse PHS, Koops HS, Devries SG and Steijfer DT (1994) Dacarbazine (DTIC)-based chemotherapy or chemoinmunotherapy of patients with disseminated malignant melanoma. Br J Cancer 70: 681–683

Prudente Foundation Melanoma Study Group (1989) Chemotherapy of disseminated melanoma with bleomycin, vincristine, CCNU, and DTIC (BOLD regimen). Cancer 63: 1676–1680

Pyrhönen S, Halaka-Kennepinen M and Muhonen T (1992) A promising interferon plus four-drug chemotherapy regimen for metastatic melanoma. J Clin Oncol 10: 1919–1926

Richards JM, Mehta N, Ramming K and Skopec P (1992) Sequential chemoinmunotherapy in the treatment of metastatic melanoma. J Clin Oncol 10: 1338–1343

Sciglar HE, Lucas VS, Pickett NJ and Huang AT (1980) DTIC, CCNU, bleomycin and vincristine (BOLD) in metastatic melanoma. Cancer 46: 2346–2348

Singletary SE and Balch CM (1992) Recurrent regional metastases and their management. In Cutaneous Melanoma, Balch CM, Houghton AN, Milton GW, Sober AJ and Soong SJ (eds), pp. 427–435. JB Lippincott: Philadelphia

Stoter G, Amdahl S, Rodenhuis S, Clerton FJ, Iacobelli S, Franks CR, Oskam R and Shiloni E (1991) Sequential administration of recombinant human interleukin-2 and dacarbazine in metastatic melanoma: a multicenter study. J Clin Oncol 9: 1687–1691

Thompson DB, Adena M, McLeod GRC, Haney P, Gill PG, Costes AS, Oliver IN, Keffer LF and Lowenthal BM, Brdelle GF, Wilpols ET, Bolund K and Kingston D (1993) Interferon-α2a does not improve response or survival when combined with dacarbazine in metastatic malignant melanoma: results of a multi-institutional Australian randomized trial. Melanoma Res 3: 133–138

York M and Foltz AT (1988) Bleomycin, vincristine, lornustine, and DTIC chemotherapy for metastatic melanoma. Cancer 61: 2183–2186

© Cancer Research Campaign 1997

British Journal of Cancer (1997) 76(2), 266-269