Final report of a phase II study of interleukin 2 and interferon α in patients with metastatic melanoma

WHJ Kruit¹, SH Goey¹, F Calabresi², A Lindemann¹, RA Stahel⁴, H Poliwoda³, B Osterwalder⁵ and G Stoter¹

¹Department of Medical Oncology, Rotterdam Cancer Institute, PO Box 5201, 3008 AE Rotterdam, The Netherlands;
²Department of Medical Oncology, National Cancer Institute Regina Elena, Viale Regina Elena 291, 00161 Rome, Italy;
³Department of Hematology and Oncology, University Hospital, Hugstetter Str 55, D-79106 Freiburg, Germany; ⁴Division of Oncology, Department of Medicine, University Hospital, CH-8091 Zürich, Switzerland; ⁵Department of Hematology and Oncology, University Medical Center, D-3000 Hannover 61, Germany; *International Clinical Research Oncology, F Hoffmann-La Roche Ltd, Grenzacherstrasse 124, 4002 Basle, Switzerland.

Summary. Fifty-seven patients with metastatic melanoma were treated with interleukin 2 (IL-2) 7.8 MİU m⁻² day⁻¹ as a continuous infusion for 4 days combined with interferon α (IFN-α) 6 MİU m⁻² day⁻¹ subcutaneously on days 1 and 4. The cycle was repeated every 2 weeks for a maximum number of 13 cycles. Of the 51 evaluable patients, one (2%) achieved a complete and seven (14%) a partial response (total response rate 16%; CI 7–29%). Median time to progression and median survival were 2.5 and 11.3 months respectively. This regimen of IL-2 and IFN-α appeared to be only moderately active.

Keywords: interleukin 2; interferon α; immunotherapy; metastatic melanoma

Immunotherapy with recombinant interleukin 2 (IL-2) has been reported to yield a 5–27% response rate in metastatic melanoma (Rosenberg et al., 1989a, 1993; Parkinson et al., 1990; Whitehead et al., 1991; Sparano et al., 1993). Interferon α (IFN-α) alone in this group of patients has shown response rates of 12–22% (Robinson et al., 1986; Kirkwood, 1991).

Based on the synergistic activity of IL-2 and IFN-α in preclinical experiments (Brunda et al., 1987; Cameron et al., 1988; ligo et al., 1988) and on the encouraging results of early clinical trials with this combination (Budd et al., 1989; Lee et al., 1989; Rosenberg et al., 1989b), we decided to perform a phase II study. Here, we report the final analysis after a median follow-up period of 10.5 months (range 1.1–47+ months).

Materials and methods

Patients

Fifty-seven patients with metastatic melanoma were entered in the study. Eligibility criteria included: age 18–70 years, Karnofsky performance status 60–100, no metastases in the central nervous system, no significant cardiovascular history, normal pulmonary function, serum bilirubin and creatinine within normal range, normal bone marrow function (haematocrit> 30%, white blood count> 4000 ml⁻¹, platelets> 100 000 ml⁻¹), normal coagulation parameters, normal serum calcium and negative tests for HIV antibody and hepatitis B antigen.

Previous treatment with IL-2 or IFN-α was not allowed. Prior radiotherapy or chemotherapy had to be completed at least 4 weeks before entry into the study. Corticosteroids were prohibited.

The protocol was reviewed and approved by the institutional review board and the ethical committee of each participating centre.

Six patients were ineligible: three had non-measurable disease, two had brain metastases, one was pretreated with interferon 2b. Fifty-one patients were evaluable for response and toxicity. The patient characteristics are shown in Table 1. The median time from initial diagnosis to immunotherapy was 24 months (range 1–142 months).

| Table 1 | Patient characteristics |
|---------|-------------------------|
| Number of patients | 51 |
| Age (years) | Median 49, Range 21–72 |
| Sex | Male 29 (57%), Female 22 (43%) |
| Performance status (Karnofsky) | Median 90, Range 70–100 |
| Prior therapy | None 25 (49%), Chemotherapy 19 (37%), Radiotherapy 5 (10%), Hormone therapy 2 (4%) |
| Distribution of metastatic sites | Lung 20 (39%), Lymph nodes 29 (57%), Skin 16 (31%), Liver 17 (33%), Bone 10 (20%) |
| Number of metastatic sites | 1 15 (29%), 2 14 (27%), 3 10 (20%), 4 9 (18%), 5 2 (4%), 6 1 (2%) |

Correspondence: WHJ Kruit
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Monitoring
Toxicity was recorded and analysed using the WHO grading system (WHO, 1979). Side-effects not described in the WHO guidelines were graded from mild (grade 1) to life-threatening (grade 4).

Response was evaluated according to the WHO guidelines (WHO, 1979). A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks. A partial response (PR) was defined as a reduction in the sum of the products of the largest perpendicular diameters of the tumour lesions by at least 50% for more than 4 weeks. Stable disease (SD) denoted less than 50% tumour reduction and less than 25% tumour progression. Progressive disease (PD) was defined as the appearance of a new lesion or an increase in size of more than 25% in any lesion.

Results
Response
Of the 51 eligible patients, 24 (47%) received 2–4 treatment cycles, 12 (24%) 5–8 cycles, 13 (26%) 9–13 cycles, one patient 15 and one patient 16 cycles. Four patients were taken off study early, one because of intercurrent illness and three because of grade 4 toxicity.

The overall response rate was 16% (95% confidence interval 7–29%), including one CR (2%) and seven PRs (14%). Twenty patients (39%) had stable disease. In 23 (45%) patients progressive disease was documented. Three of the responders were male and five were female. Responses were seen in skin lesions (36%), lymph nodes (27%), lung (18%) and liver (18%). Of note, bone metastases did not respond. All responses occurred in the first 3 months of treatment.

The median duration of response was 8.2 months (range 4.5–39+ months). For all 51 patients the median time to progression was 2.5 months (range 0.5–39+ months). Time to progression for responding patients was 8.2 months (range 4.5–39+ months), for patients with stable disease 3.6 months (range 1.7–9.4 months) and for progressive disease patients 1.2 months (range 0.5–2.0 months). The median survival of all patients was 11.3 months (Figure 1), and of the responding patients 20.2 months.

Toxicity
An overview of the observed toxicity is presented in Table II. Frequently occurring side-effects were fever, skin rash, nausea, vomiting, diarrhoea and malaise. Two-thirds of patients had tachycardia and hypotension, mostly of mild to moderate grade. Life-threatening hypotension requiring vasopressors occurred in three patients, who were taken off study (see above). One patient developed ventricular extrasystoles and another patient atrial fibrillation. In a minority of patients neurological abnormalities and mental disturbances were seen. Neurotoxicity included aphasia, peripheral neuropathy, somnolence, confusion and agitation.

Two patients required dose reductions because of adverse events, and in eight patients short interruption of treatment was needed. Not toxic death occurred and all toxicities resolved after cessation of immunotherapy. Chronic cumulative fatigue occurred after about 3 months of treatment. Consequently, only two patients received more than 13 cycles.

The most frequent manifestation of haematological toxicity was anaemia (71%). Thrombocytopenia was seen in 18% of the patients. Moderate and reversible increases in serum creatinine and bilirubin occurred in a minority of patients.

Discussion
In this study the combined use of IL-2 and IFN-α in the treatment of metastatic melanoma resulted in a 16% response rate, including 2% complete responses. These results are disappointing and not better than can be expected of conventional chemotherapy or immunotherapy with IL-2 alone.

Response rates of 21–44% have been reported in some studies using the combination of both cytokines (Lee et al., 1989; Rosenberg et al., 1989b; Budd et al., 1992). However, low response rates of 10% or less were observed by others (Oldham et al., 1992; Dillman et al., 1993; Sparano et al., 1993). The median response duration in these trials varied between 2 and 11 months, and the median survival was approximately 10 months (Lee et al., 1989; Rosenberg et al., 1989b; Oldham et al., 1992; Dillman et al., 1993; Sparano et al., 1993). We achieved similar results.

We failed to confirm the ability of IFN-α to augment the effect of IL-2. This may have been due to suboptimal dose and schedule. Our patients received moderate doses of IL-2. In animal studies the efficacy of IL-2 is dose dependent without reaching a plateau below the maximum tolerated dose (Mule et al., 1984). However, in trials using high-dose IL-2 (18 MIU m⁻² day⁻¹) given by continuous infusion in patients with metastatic melanoma inferior response rates were reported (Oldham et al., 1992; Dillman et al., 1993). An NCI Surgery Branch Study, administering high-dose bolus IL-2 (>30 MIU m⁻² day⁻¹) and IFN-α found the highest response rates (Rosenberg et al., 1989b). On the other hand, the Extramural IL-2 Working Group, using identical dose, schedule and patient selection criteria, did not observe any evidence of enhanced response with the IL-2 IFN-α combination (Sparano et al., 1993). In summary, a dose–response effect for IL-2 in the treatment of metastatic melanoma is not clear.

The side-effects we observed were of similar incidence and severity as reported previously (Lee et al., 1989; Rosenberg et al., 1989b; Budd et al., 1992; Oldham et al., 1992; Sparano et
al., 1993). Toxicity was manageable and patients tolerated the therapeutic regimen relatively well. However, cumulative fatigue made it impossible to give patients more than 13 cycles of therapy.

In conclusion, combined therapy with IL-2 and IFN-α in the described regimen has only moderate activity in the treatment of patients with metastatic melanoma. Further clinical trials have to be designed to improve therapeutic results.

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