Eur J Cancer, Vol. 28A, No. 10, pp. 1719–1720, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Phase II Study of Interferon Alfa-2a and Dacarbazine in Advanced Melanoma

Biological Response Modifiers in Melanoma (BREMIM) Italian Cooperative Group

In phase II, the tolerance and activity of dacarbazine and recombinant interferon alfa-2a (rIFN) was studied in 79 patients with metastatic melanoma. The regimen was well tolerated. Response rate was 25%, with 8% having a complete response. Response duration and survival after a follow-up of 39 months are reviewed. The mean durations of complete and partial responses are 13.7 months (range 1 to 31+) and 10 months (2 to 36+), respectively. Median time to progression is 3 months; median survival is 9 months. At present, 11% of treated patients are alive, thus addition of rIFN to dacarbazine may prolong response duration.
Eur J Cancer, Vol. 28A, No. 10, pp. 1719–1720, 1992.

INTRODUCTION

UP TO the present time, no medical treatment is available to substantially influence prognosis in advanced malignant melanoma [1]. It has been hypothesised that interferons (IFNs) may act as immuno-stimulating factors or as sensitisers to conventional chemotherapy [2, 3]. In our previous experience, dacarbazine plus recombinant interferon alfa-2a (rIFN α-2a) has given a response rate of 25.3%, 8% complete response (CR), with a mean duration of objective response of 8.2 months [4]. It is our intent to update these results in terms of response duration and survival, after that the median follow-up time for the entire series has been changed from 16 to 39 months. It is useful to perform such an evaluation in order to better define the evolution of responses duration and survival. These data are often lacking in other papers more involved in pointing out response rates and treatment toxicities.

PATIENTS AND METHODS

The methodology employed in this trial has been reported in an earlier paper [4]. Briefly, 79 patients were treated with dacarbazine 800 mg/m^2 intravenously every 3 weeks and rIFN-α-2a 9 MU intramuscularly daily for the first 2 months and 3 times a week thereafter. After 6 months of therapy, in patients with objective responses, treatment was continued with rIFN-α-2a for another 6 months. Thereafter, patients were followed-up every 2 months clinically and instrumentally.

During the follow-up time, any clinical situation correlating to delayed toxicity was also carefully reported. The duration of objective responses was evaluated from the time of the evidence to the time of progression or last follow-up. Time to progression was calculated from the onset of treatment to the moment in which disease progressed. Survival was calculated from the start of therapy. The survival curves were constructed using the Kaplan–Meier method and differences among curves were evaluated with the Mantel–Haenszel test.

RESULTS

The mean duration of CR is 13.7 months (range 1–31+), whereas the mean partial response (PR) duration is 10.0 months (range 2–36+). It is noteworthy that 2 out of 6 CR patients have a remission lasting more than 2 years. In particular, a 47-year-old female and a 45-year-old male, both with soft tissue lesions, have a CR duration of 29+ and 31+ months, respectively.

With regard to partial responders, 2 out of 13 patients have had a remission lasting more than 2 years. 1 patient is a male with bone and lymph node localisations (PR duration 36+ months), whilst the other one is a female with lung involvement and a response duration of 27 months. Overall the mean duration of objective responses has been changed from 8.2 to 11.1 months. The median time to progression for the total group is 3.0 months. The overall survival of the patients treated is 11% at 39 months. It is worth mentioning that after a median follow-up time of 39 months, 33% of responding patients are still alive, whereas all the patients who did not respond to therapy died. Overall, the median survival for the entire group is 9 months. Actuarial time to progression and survival of the whole group is depicted in Fig. 1. In Table 1 are summarised the data concerning response duration, time to progression and survival and

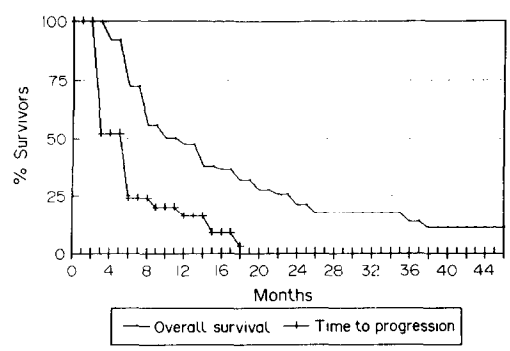

Fig. 1. Time to progression and overall survival.

Correspondence to E. Bajetta, Divisione di Oncologia Medica B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via Venezian 1, 20133 Milan, Italy.
The BREMIM group is Emilio Bajetta, Angelo Di Leo, Maria G. Zampino, Benvenuto Giannotti, Laura Brogelli, Andrea Ardizzoni, Mario R. Sertoli, Maria G. Bernengo, M. Barduagni, Giuseppe Maifredi, Giuseppe Zumiani, Giuseppe Comella, Roberto Buzzoni, Nicoletta Zilembo, Domenico Criscuolo, Giorgio Massimini and Natale Cascinelli.
Revised and accepted 28 Jan. 1992.

Table 1. Response duration, time to progression and survival

	Median follow-up	
	16 months	39 months
Mean duration (range)		
CR	6.2 (1–11)	13.7 (1–31+)
PR	7.2 (2–16)	10.0 (2–36+)
CR+PR	8.2	11.1
Median time to progression	1.5	3.0
Median survival (months)	8.0	9.0
Patients alive	38%	11%

their variation after a longer follow-up. No delayed toxicity has been detected.

DISCUSSION

The update of our original work seems to emphasise that some patients responding to chemotherapy for advanced malignant melanoma may have a prolongation of their response as a consequence of adding IFNs to the cytotoxic treatment.

Indeed, in our series we have observed 4/19 objective responses lasting for more than 2 years and this observation is confirmed by other authors, reporting with IFN with or without chemotherapy in malignant melanoma a disease stabilisation in 24% of cases for up to 12 months [5]. Furthermore, in other reports some long-term responses have been found similar to ours [5, 6].

Certainly, these observations need confirmation by ongoing clinical trials in which a treatment randomisation (dacarbazine vs. dacarbazine + IFNs) is proposed, in order to observe any advantage between the different treatment groups in terms of response rate, response duration and survival [5, 7].

1. McClay EF, Mastrangelo MJ. Systemic chemotherapy for metastatic melanoma. *Semin Oncol* 1988, **15**, 569–577.
2. Clemens MJ, McNurlan MA. Regulation of cell proliferation and differentiation by interferons. *Biochem J* 1985, **226**, 345–360.
3. McLeod GRC, Thomson DB, Herzey P. Recombinant interferon alpha-2a in advanced malignant melanoma. A phase I–II study in combination with DTIC. *Int J Cancer* 1987 (suppl. 1) 31–35.
4. Bajetta E, Negretti E, Giannotti B, *et al.* Phase II study of interferon alpha-2a and dacarbazine in advanced melanoma. *Am J Clin Oncol* 1990, **13**, 405–409.
5. Mickiewicz E, Estevez R, Rao F, *et al.* Interferon alpha-2b alone or in combination with DTIC in metastatic melanoma. Compiled data. *Proc ASCO* 1990, **9**, 281, Abstract.
6. Mulder NH, Willemse H, Schraffordt Koops H, de Vries EG, Slijfer DTh. Dacarbazine and human recombinant interferon alpha-2b in the treatment of disseminated malignant melanoma. *Br J Cancer* 1990, **62**, 1006–1007.
7. Falkson CI, Falkson G, Falkson HC. Improved results with addition of interferon alpha-2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. *J Clin Oncol* 1991, **9**, 1403–1408.

Eur J Cancer, Vol. 28A, No. 10, pp. 1720–1727, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Additional Ecological Evidence: Lipids and Breast Cancer Mortality Among Women Aged 55 and over in China

James R. Marshall, Qu Yinsheng, Chen Junshi, Banoo Parpia and T. Colin Campbell

That dietary fat increases breast cancer risk has been strongly supported by international data collected among developed countries during the past few decades. Population aggregates with elevated lipid intake have tended to report elevated breast cancer incidence and mortality. This study is an ecological analysis of the association of various indicators of lipid intake with breast cancer mortality in 65 county-wide population aggregates in the People's Republic of China. Although the result is consistent with a positive association between lipid intake and breast cancer risk, the observed association is weaker than the association previously observed. This finding provides only modest support for the possibility of a diet–breast cancer link.
Eur J Cancer, Vol. 28A, No. 10, pp. 1720–1727, 1992.

INTRODUCTION

WHETHER WOMEN in the USA might materially alter their risk of breast cancer by lessening their lipid intake has proven an elusive question, and one that continues to provoke sharp debate. Any proposed answer must address the problem of the ambiguous evidence derived from different research arenas. International variation in fat intake and in breast cancer risk tend to coincide; countries with higher per capita fat intake report higher breast cancer incidence and mortality [1, 2]. As the fat intake of countries increases, the breast cancer rate of those countries tends to increase [3]. Animal experiments are said to consistently indicate that dietary fat increases breast cancer risk [4]. Individual-based human data are less consistent, several well-designed and executed case–control studies apparently failing to show any association [5, 6]. Although Howe *et al.*'s sophisticated meta analysis suggests that the weight of the