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Adjuvant Chemotherapy with a Nitrosourea-based Protocol in Advanced Malignant Melanoma

C. Karakousis and L. Blumenson

173 patients with regional lymphatic metastases (n = 139) or distant disease (n = 34) were prospectively randomised, following resection of all clinically detectable tumour, to observation (n = 88) or adjuvant chemotherapy (n = 85). The treatment group received 1, 3-bis(2-chloroethyl)-1-nitrosourea (BCNU) 80 mg/m² intravenously (i.v.) every 4 weeks, and actinomycin-D 10 μg/kg, vincristine 1.0 mg/m² i.v. every 2 weeks for 6 months. The disease-free survival curves between the two groups were significantly different (P = 0.03). The estimated 5-year disease-free survival rate for the observation group was 9% and for the treatment group 29%. However, the overall survival curves were not significantly different for the two groups. Nitrosoureas may have a weak effect as adjuvant treatment in malignant melanoma.
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INTRODUCTION

PATIENTS WITH recurrent melanoma generally have a poor outlook. Those with regional node involvement attain a 5-year survival rate ranging from 10–13% [1, 2] to 37% [3] following therapeutic node dissection. The majority of these patients, however, manifest recurrence and die of progression of their disease.

Patients presenting with distant, haematogenous metastases generally have diffuse, non-resectable disease, although occasionally this may be limited to one or two sites and hence can be resected. Following resection this group of patients may be expected to have a worse prognosis when compared with prognoses of patients with clinical involvement limited to the regional nodes.

Table 1. Distribution of patients per stage and treatment

Treatment group	No. of patients IIIA	IIIB	IIIAB	IV	All stages
Observation	6	53	13	16	88
Chemotherapy	6	54	7	18	85

There are several staging systems in malignant melanoma. One of them, useful because it allows a detailed description of lymphatic involvement, distinguishes stages I as localised melanoma, stage II as local recurrence, stage IIIA as in-transit metastases, IIIB as regional node metastases, IIIAB as a combination of IIIA and IIIB, and stage IV as distant, haematogenous recurrence [4].

In the past, dacarbazine was studied extensively in prospective randomised studies as adjuvant treatment for high risk malignant melanoma without apparent benefit to the treated group [5, 6]. The nitrosoureas produce a response rate similar to that of dacarbazine in malignant melanoma and are reported to be less immunosuppressive [7], but have not been evaluated adequately as an adjuvant modality.

PATIENTS AND METHODS

173 patients with recurrent malignant melanoma indicative either of lymphogenous (n = 139) or haematogenous (n = 34) dissemination were prospectively randomised following resection of all gross tumour to either observation (n = 88) or adjuvant chemotherapy (n = 85) (Table 1). These patients were accrued in the period 1981–1990. Only patients with clinical, palpable involvement of the regional lymphatic system were included in this study, since microscopic node involvement revealed with an elective node dissection has a better prognosis.

Randomisation was instituted within 2 weeks from the operation which effected removal of all detectable tumour. Patients in the treatment group received 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) 80 mg/m^2 intravenously every 4 weeks, actinomycin-D 10 μg/kg and vincristine 1.0 mg/m^2 intravenously every 2 weeks, for six full cycles. This was given on an outpatient basis, patients receiving treatment every 2 weeks by alternating three drugs with two drugs. Treatment was withheld for white blood cell (WBC) count less than 3 000/mm^3 or platelet count less than 100 000/mm^3. Vincristine was discontinued at the first evidence of paresthesias.

6 of the patients (7%) randomised to receive chemotherapy refused this treatment, while 1 (1%) of the observation group requested and received treatment. With regard to recurrence and survival these patients were considered as belonging to the group into which they were randomised.

The mean age of the patients was 51, median 52 (range 16–82). There were 99 (57%) men and 74 (43%) women.

Survival time and time to recurrence were computed from the time of entry in the protocol, to the last follow-up or death. The method of Kaplan and Meier was used [8] in estimating survival and disease-free survival distributions. Tests of significance with respect to survival/disease-free survival distributions were based on the log-rank test [9].

In the estimation of the disease-free survival curves "death without recurrence" was not considered a censoring event. The joint effect of both treatment and dissemination (regional vs. distant) on both disease-free survival and overall survival was also tested using Cox proportional hazards modeling [10]. The variables were tested using stepwise regression for the Cox model.

RESULTS

The median interval from the placement in the protocol to the time of review is 56 months for the observation group and 57 months for the chemotherapy group.

Chemotherapy was tolerated well. There was no life-threatening toxicity. Vincristine was discontinued after a few doses in 25 patients (29%) due to development of paresthesias. The protocol was discontinued in 16 patients (19%) due to progression of the disease before completion of all courses. Finally, the protocol was discontinued in 7 (8%) due to inability to tolerate subjective side-effects and it was only in 2 patients (2%) that it was discontinued due to objective side-effects (prolonged myelosuppression). Thus, excepting the patients who progressed while on treatment, it was possible to complete all courses for BCNU and actinomycin-D in 87% of the remaining patients.

The 5-year disease-free survival in the observation group was 9%, and in the treatment group 29%. The median disease-free survival in the observation group was 8 months and in the treatment group 10 months. All patients who had recurrences in the observation group did so within the first 6 years. The latest recurrence for the chemotherapy group was at 60 months with 9 patients free of disease at 61, 69, 71, 71, 79, 83, 86, 87 and 91 months, respectively. The difference in the two disease-free survival curves was significant (Fig. 1, P = 0.03). At the time of the last review of this protocol, 18/88 (20%) in the observation group and 27/85 (32%) in the treatment group were disease-free. However, the overall 5-year survival rate in the observation group was 25%, and in the treatment group 30%, the difference in the two overall survival curves for the years 1–5 not being significant (Fig. 2, P = 0.59). This discrepancy in the results for disease-free survival and overall survival rates between the two groups appears to be due, partly, to a difference in survival times following first recurrence from entry in the protocol. The median survival of the patients who relapsed in the observation group (n = 54) was 10.3 months, whereas in the treatment

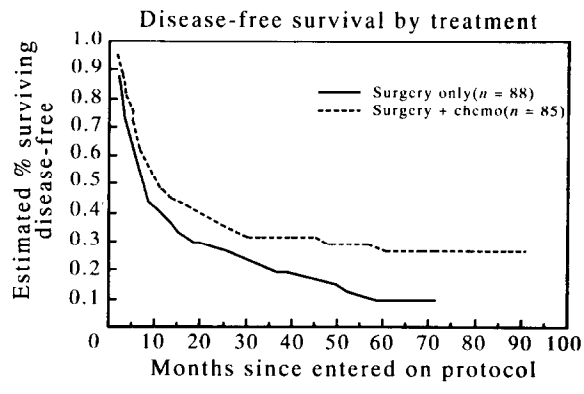

Fig. 1. Disease-free survival curves for the observation and treatment groups (P = 0.03).

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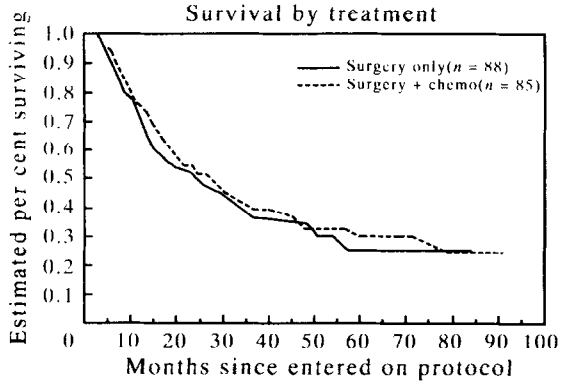

Fig. 2. Overall survival curves for the observation and treatment groups.

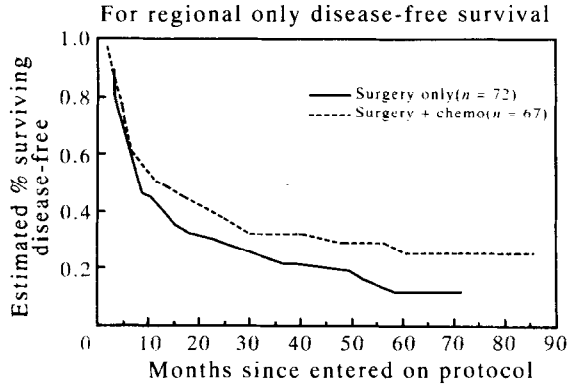

Fig. 3. Disease-free survival curves for patients with regional, lymphatic involvement according to treatment.

group (n = 50) it was 5.2 months (P = 0.03), following first recurrence on protocol.

When the patients with involvement only of the regional nodes were considered (n = 139), the disease-free survival curves for the observation and treatment groups were not significantly different (Fig. 3, P = 0.14). The median disease-free survival was 8 months in the former group and 13 months in the latter group. Considering the overall survival curves in these patients there was no significant difference between the observation and treatment groups. Their respective median survival was 26 and 27 months (Fig. 4, P = 0.83).

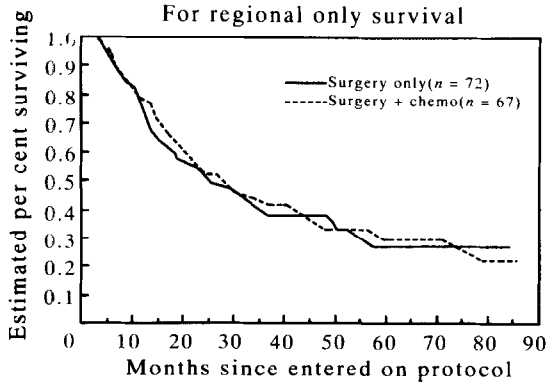

Fig. 4. Overall survival curves for patients with regional, lymphatic involvement according to treatment.

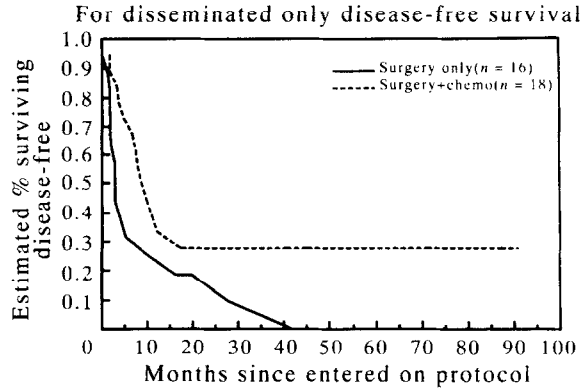

Fig. 5. Disease-free survival curves for patients with hematogenous metastases according to treatment (P = 0.05).

For patients with disseminated disease, the median disease-free survival was 3 months in the observation group and 9 months in the treatment group (Fig. 5, P = 0.05). The overall median survival rates were 14 months and 24.2 months, respectively (Fig. 6, P = 0.38).

Using Cox proportional hazards model the regression coefficient/standard error (RgCoeff/S.E.) estimated were −2.32 and 1.79 for treatment and dissemination, and the respective P-values 0.032 and 0.84, indicating that surgery + chemotherapy still exhibited a significant increase for disease-free survival after adjusting for the extent of dissemination.

The estimates of the RgCoeff/S.E. for overall survival were −0.59 and 0.82 for treatment and dissemination, respectively, with an overall P = 0.62, suggesting that neither treatment nor extent of dissemination had a significant effect on overall survival. Within each treatment group extent of dissemination had no significant effect on overall survival, and within each dissemination group (regional or distant) treatment had no significant effect on overall survival.

The comparison of time from recurrence to death in different treatment groups was also done by testing the joint effect of treatment and length of disease-free survival on the time from recurrence to death using the Cox's model with time-varying covariates. Only patients with recurrence were included in this analysis and patients still alive at the close of the study were censored at that time. When the stepwise regression was used only the treatment parameter entered the model with P = 0.032.

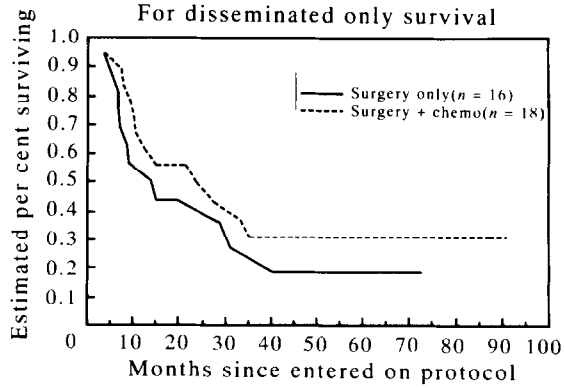

Fig. 6. Overall survival curves for patient with haematogenous metastases according to treatment.

When both parameters were forced into the model the RgCoeff/S.E. estimates were 2.04 and −1.33 for the treatment and disease-free survival variables, respectively, with overall $P = 0.04$, indicating that there was a significant decrease in time from recurrence to death in the surgery + chemotherapy group which was independent of the length of disease-free survival.

DISCUSSION

Previous attempts in prospective, randomised trials to identify an effective adjuvant treatment for malignant melanoma were unsuccessful. Among the chemotherapeutic agents dacarbazine (DTIC) either alone [5, 6] or in combination with other drugs [11] or BCG [12] has been evaluated extensively and was found to be ineffective in the adjuvant setting.

Non-specific adjuvant immunotherapy with BCG [13–16], *Corynebacterium parvum* alone [17, 18] or in combination with DTIC [19], and BCG in combination with a tumour vaccine [20] did not result in significant benefit in prospective randomised trials. Although in one study the combination of DTIC plus BCG increased the disease-free survival time compared with DTIC alone [21], other larger studies have shown no benefit with the use of this combination when compared against surgical controls [15, 22–23]. Non-specific immunotherapy with levamisole was also found to be ineffective in one study [24].

In a previous adjuvant study for stage I malignant melanoma in which one of the arms was methyl-*N*-(2-chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea (CCNU), it was observed that methyl-CCNU treated patients had slightly improved disease-free survival, but the number of patients in each group was small and the difference not significant [25].

Although the nitrosoureas produce similar rates of objective response in measurable disease as dacarbazine and are reputed to be less immunosuppressive they have not been evaluated adequately.

The adopted combination of BCNU, actinomycin-D and vincristine was selected empirically in an effort to test a combination of three drugs having some activity in patients with measurable disease, which had not been evaluated before. Among the three drugs BCNU is clearly the most effective agent and, in retrospect, the study might have been more definitive had only this drug been selected for adjuvant use. Considering the dosage used for each drug it appears also that BCNU was the drug employed at a level closer to a therapeutic one. Therefore, if one had to surmise as to which of the three drugs caused the observed difference in the treatment group, if the difference was not indeed the result of the combination, one would be inclined to think of BCNU. However, the observed improvement in the 5-year disease-free survival of about 20% using this adjuvant protocol did not result in significant improvement in the overall survival.

The above series of patients was analysed at various intervals as they were accrued in the protocol [26, 27] and always an improved disease-free survival was noted consistently in the treatment group. Evaluating separately the two major subgroups in the study, i.e. that of lymphogenous and that of haematogenous metastases it is clear that significant improvement in disease-free survival for the treated group was approached only in patients with hematogenous metastasis ($P = 0.05$, Fig. 5). In these patients the overall survival curves for the treated and observation patients are not superimposed, although the improvement in overall survival for the treated group did not reach statistical significance.

With the Cox proportional hazards model the surgery + chemotherapy group still exhibited a significant increase in disease-free survival after adjusting for the extent of dissemination. However, treatment or stage of dissemination had no significant impact on overall survival, which may be partly accounted for by the observed significant decrease in time from recurrence to death in the surgery + chemotherapy group which was independent of the length of the disease-free survival.

The above adjuvant protocol was administered on an outpatient basis and was free from any serious myelosuppression or other complications requiring hospitalisation. Further studies will be needed to elucidate the above findings. One might select to use BCNU only at a slightly higher dose. It appears that the adjuvant chemotherapy given in this study reduced significantly the amount of extant microscopic disease in the patients treated so, but progression was faster after relapse. An immunological component in the treatment may possibly avert this sequence of events. Given the recent success of levamisole with 5-fluorouracil in reducing the recurrence rate in Dukes-C colorectal carcinoma [28], a plausible adjuvant protocol to be studied in melanoma might be the combination of BCNU with levamisole.

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Folinic Acid, 5-Fluorouracil Bolus and Infusion and Mitoxantrone with or without Cyclophosphamide in Metastatic Breast Cancer

Christophe Louvet, Aimery de Gramont, Bénédicte Demuynck, Karine Beerblock, Charles Varette, Dominique Soubrane, Loïc Marpeau, Alain Pigné, Thierry Guillot and Marcel Krulik

60 patients with metastatic breast cancer were entered in a phase II study using folinic acid, 5-fluorouracil bolus and infusion and mitoxantrone with or without cyclophosphamide. 47 had measurable visceral metastases and 13 had exclusively bone metastases. 36 had received previous adjuvant or metastatic treatment (33/36 with anthracycline-based regimens). Overall response rate in visceral metastatic patients was 57.1% [95% confidence interval (CI) 35.4–78.8%]; 45.5% and 70% in previously and non-previously treated patients, respectively; duration of response was 9 and 13 months, respectively. 10 out 13 patients with exclusive bone metastases improved for a median time of 18 months. Median survival was 22 months for the 60 patients; 18 and 31 months for previously and non-previously treated patients, respectively. Cyclophosphamide was scheduled only in the absence of nadir grade 4 neutropenia. However, this toxicity occurred in the first 7 patients. For this reason, we chose to avoid cyclophosphamide in patients over 60 years, or with a performance status of 1–2, or who had received previous chemotherapy. Overall, cyclophosphamide was stopped due to nadir grade 4 neutropenia in 17/24 patients for whom this drug was planned. When mitoxantrone, 5-fluorouracil and folinic acid were used at the doses scheduled, the addition of cyclophosphamide appeared feasible in only about 25% of the patients. Furthermore, survival was identical for patients receiving or not receiving cyclophosphamide. Therefore, cyclophosphamide does not contribute substantially to this regimen. This study confirms the value of folinic acid, 5-fluorouracil and mitoxantrone in metastatic breast cancer.
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INTRODUCTION

METASTATIC BREAST cancer remains a frequently chemosensitive non-curable disease. First-line regimens can provide up to 50 to 70% objective response rates, with 10–20% complete responses [1]. For most patients, duration of response is relatively brief. Cyclophosphamide is commonly used in advanced breast carcinoma with a 34% objective response rate when used as a single agent [2]. Mitoxantrone is an active antineoplastic agent, considered as a substitute for doxorubicin with less non-haematological toxicity in advanced breast cancer [3], resulting in up to 35% response rate in non-pretreated patients [4]. 5-fluorouracil (5FU) bolus modulated with folinic acid bolus (FUFOL) or other 5FU–folinic acid combinations have been studied in gastrointestinal malignancies with increased response rates compared to 5FU alone [5]. We previously reported that high-dose folinic acid, 5FU bolus and infusion provided a greater