Acta Radiologica Oncology 25 (1986) Fasc. 3

FROM THE DEPARTMENT OF RADIATION THERAPY, UNIVERSITY CENTRAL HOSPITAL OF TURKU, SF-20520 TURKU, FINLAND.

COMBINATION CHEMOTHERAPY WITH DACARBAZINE AND LOMUSTINE IN DISSEMINATED MALIGNANT MELANOMA

H. JOENSUU, R. ASOLA and H. MINN

Abstract

Thirty-eight patients with disseminated malignant melanoma (stage IV) who had not received previous chemotherapy were given lomustine 50 to 80 mg/m^2 orally on day 1 and dacarbazine 400 mg intravenously on days 1 to 3 with intervals of 6 weeks. Three of the 36 evaluable patients showed complete response (8%), 4 partial response (11%), and 5 had stable disease for at least 3 months (13%). The responding patients had metastases confined to cutaneous, nodal or pulmonary sites. None of the patients with liver, osseous or cerebral metastases, or patients with Karnofsky's status of less than 80, responded. Patients with more than two years from the diagnosis to the start of the chemotherapy were more likely to achieve objective response ($p<0.05$). Eighty-four per cent of the patients had nausea or vomiting, but otherwise toxicity was minimal.

Key words: Chemotherapy; malignant melanoma, dacarbazine, lomustine.

Treatment of disseminated malignant melanoma with single or combination cytotoxic chemotherapy has been unsatisfactory. Several cytostatics have shown activity against melanoma, but the response rates have been disappointingly low. The most effective single agent tested has been dacarbazine (DTIC) with an objective response rate of about 20 per cent. Several alkylating agents, antimetabolites, antibiotics, vinca alcaloids and miscellaneous agents like hydroxyurea and procarbazine have also been reported to have some activity against malignant melanoma, but objective responses have usually occurred in less than 20 per cent of evaluable patients (3).

In order to increase the low response rate obtained with single agents the combination of dacarbazine and lomustine (CCNU) in the treatment of disseminated malignant melanoma has been studied. As single agents, nitrosoureas have been reported to be almost as effective as dacarbazine against melanoma, with an objective response rate of about 15 per cent (3).

Material and Methods

Thirty-eight patients with histologically diagnosed malignant melanoma with distant metastases (stage IV) were given combination chemotherapy with dacarbazine, 400 mg intravenously on days 1 to 3, and lomustine, 50 to 80 mg/m^2 orally on day 1 with 6 weeks' intervals. An average of 4.0 complete courses were given (range 1–18). Eighteen patients were males and 20 females with a mean age of 53.0 years (range 21–72 years). Their Karnofsky's status ranged from 100 to 50, mean 81.9. Two patients refused to continue the chemotherapy after one course and were considered unevaluable. Previous chemotherapy had not been given, but 15 patients had been irradiated to small regional fields, 40 to 60 Gy, and 8 had received immunostimulatory treatment before starting chemotherapy.

In all cases the primary tumor, if known, had been treated surgically and dissemination of melanoma confirmed histologically, cytologically or at radiography. Fourteen patients had pulmonary metastases only, 7 patients metastases only in lymph nodes or subcutaneously, 3 patients had liver metastases only, and the rest were known to have metastases in more than one organ.

All patients had white blood cell and platelet counts within the normal limits when starting the chemotherapy. Toxicity was recorded by the method of MILLER et coll. (7). Chemotherapy was discontinued if the metastases progressed or if complete remission had lasted for 12 months. Objective responses were assessed according to the following criteria: complete response (CR)—complete disappearance of all known disease; partial response (PR)—decrease of at least 50 per cent in the sum of the longest perpendicular diameters of all measurable lesions; stable disease (SD)—a <50 per cent decrease or a <25 per

Accepted for publication 8 December 1985.

Table 1

Responses

	No. of patients	Per cent
Complete remission	3	8
Partial remission	4	11
Stable disease	5	14
Progressive disease	24	67
Total	36	

Table 2

Responses to chemotherapy correlated with metastatic site

Location	CR	PR	SD	PD	Total
Skin or nodes only	3	0	2	2	7
Pulmonary	0	4	3	7	14
Other visceral/osseous	0	0	0	15	15
Total	3	4	5	24	36

Table 3

Toxicity

Toxic effect	Percentage of patients with toxic effects on one or more occasions
Nausea or vomiting	
Grade 1	14
Grade 2	51
Grade 3	19
Grade 4	0
Total	84
Leucopenia $<4.0\times10^9$/l	16
Thrombocytopenia $<100\times10^9$/l	5
Anaemia <110 g/l	3
Local pain at injection site	5
Alopecia (partial)	3

cent increase in the size of measurable lesions lasting for at least 3 months; and progressive disease (PD)—an increase of >25 per cent in the size of measurable lesions or appearance of new lesions. Patients with CR or PR were considered objective responders. The duration of response was calculated from the date of occurrence of remission until disease progression. Survival was calculated from the first cycle of chemotherapy to death or date of the last follow-up for patients still alive.

Results

Three patients (8%) achieved CR and 4 patients (11%) PR, the objective response rate thus being 19 per cent (Table 1). The duration of complete responses was 2 to 18 months and of partial responses 3 to 36+ months. All objective responses occurred during the first five months of chemotherapy, except in one case after nine months of chemotherapy.

Only patients with subcutaneous, nodal or pulmonary metastases responded (Table 2). None of the patients with metastases in the liver (n=8), bones (n=3), brain (n=2), or other visceral organs responded. The objective response rate with patients having a Karnofsky's status of 80 or more was 26 per cent, whereas none of the patients with a Karnofsky's status of less than 80 responded (n=9). The mean age of the responding patients was 58.9 years and that of the non-responding patients 52.3 years ($p>0.50$). Five of the responding patients were females and two males. All patients with CR had a small tumor burden at the beginning of chemotherapy.

The difference in survival was highly significant at 12 months ($p<0.001$), and very significant at 24 months ($p<0.01$), between the responding (CR+PR) and non-responding patients. However, patients whose chemotherapy had been started more than two years after the diagnosis had significantly more objective responses ($p<0.05$) than patients whose disease dissemination had been detected earlier, so the apparent increase in survival in responding patients may partly be due to a less aggressively growing melanoma in these patients. In the responding patients, chemotherapy was started on the average 61.4 months after the diagnosis of malignant melanoma, whereas in the non-responding patients the time interval was only 28.9 months.

There was no difference in the amount of lomustine and dacarbazine received by the responding and non-responding patients; the responding patients had received an average of 65.7 mg/m^2 lomustine and 659 mg/m^2 dacarbazine per cycle, whereas the non-responding patients had received 66.3 mg/m^2 lomustine and 676 mg/m^2 dacarbazine per cycle.

Patients whose metastases were confined to subcutaneous, nodal or pulmonary sites and whose Karnofsky's status was 80 or more had a response rate of 37 per cent. A response rate of 67 per cent (6/9) was achieved, if only patients with the following characteristics were considered: 1) only subcutaneous, nodal or pulmonary metastases, 2) a Karnofsky's status of 80 or more, and 3) a period of two or more years from the diagnosis to the start of the chemotherapy.

Eighty-four per cent of the patients had nausea of vomiting, which was generally not severe (mainly grade 2). Otherwise, toxicity appeared to be minimal (Table 3). Two patients refused to continue the therapy. In 5 cases (13%), dosage had to be reduced temporarily or permanently because of side effects.

Discussion

The overall response rate, 19 per cent, is about the same as has been obtained with dacarbazine alone (3).

Thus the addition of lomustine does not appear to increase the response rate.

The objective responses obtained lasted for 2 to 8 months except in 2 cases (18 months and 36+ months). It is thus likely that the combination of lomustine with dacarbazine does not improve the duration of the response. Dacarbazine has previously been given in combination with BCNU (4) and methyl-CCNU (5), and in these reports too, the addition of nitrosourea to dacarbazine did not increase the response rate when compared with dacarbazine alone. Similarly the response rates have not improved if actinomycin D (6), vincristine (1), vinblastine, cyclophosphamide or procarbazine (9) have been combined with dacarbazine.

Survival of the responding patients was significantly longer than in non-responders. However, the apparent increase in survival may not be real. Significantly more objective responses ($p<0.05$) were obtained if more than two years had elapsed from the diagnosis of melanoma to the start of chemotherapy, so the more slowly growing tumors responded more favourably to chemotherapy and the two groups are not comparable.

The combination of dacarbazine and lomustine is not curative in disseminated malignant melanoma. At the time of writing (July 1985), 89 per cent of the patients in this investigation have died of melanoma and the remaining 4 patients still alive all have active disease and are receiving chemotherapy. Although the toxicity was acceptable it must be remembered that no responses were achieved in symptomatic patients with large tumor burdens.

When selecting patients with malignant melanoma for chemotherapy it would be important to know what subgroup is likely to respond. Although the number of patients in this series is limited the results indicate that melanoma patients in good general condition and with slowly growing subcutaneous, lymph node or pulmonary metastases are more likely to respond to the combination of dacarbazine and lomustine. Recently, several reports with a combination of three or more cytostatic drugs yielding response rates of 40 to 50 per cent in malignant melanoma have appeared (2, 8, 10). However, if the patients included have mainly non-visceral or pulmonary metastases (2, 10) the response rate is likely to be high. When comparing chemotherapy results obtained in melanoma the distribution of the metastases, the growth rate of the tumors, and the general condition of the patients are important variables and should be taken into account. If patients who have received only one course of chemotherapy are not taken into analysis the most aggressive melanomas will be excluded. The real improvement with the three- or four-drug regimens in the treatment of disseminated melanoma remains to be confirmed in randomized trials.

The treatment of advanced malignant melanoma continues to be a growing problem in oncology. There is no conclusive evidence that any combination is superior to dacarbazine alone, in the chemotherapy of malignant melanoma, and the response rate with this agent is low and responses short-lived.

Request for reprints: Dr Heikki Joensuu, Department of Radiation Therapy, University Central Hospital of Turku, SF-20520 Turku, Finland.

REFERENCES

1. Ahmann D. L., Hahn R. G. and Bisel H. F.: Evaluation of 1-(2-chloroethyl-3-4-methylcyclohexyl)-1-nitrosourea (methyl-CCNU, NSC-95441 versus combined imidazole carboxamide (NSC-45388) and vincristine (NSC-67574) in palliation of disseminated malignant melanoma. Cancer 33 (1974), 615.
2. Carmo-Pereira J., Costa F. O. and Henriques E.: Combination cytotoxic chemotherapy with procarbazine, vincristine, and lomustine (POC) in disseminated malignant melanoma: 8 years' follow-up. Cancer Treat. Rep. 68 (1984) No. 10, 1211.
3. Comis R. L.: DTIC (NSC-45388) in malignant melanoma. A perspective. Cancer Treat. Rep. 60 (1976) No. 2, 165.
4. Costanza M. E., Nathason L., Lenhard R. et coll.: Therapy of malignant melanoma with an imidazole carboxamide and bis-chloroethyl nitrosourea. Cancer 30 (1972), 1457.
5. — — Schoenfeld D. et coll.: Results with methyl-CCNU and DTIC in metastatic melanoma. Cancer 40 (1977), 1010.
6. Gerner R. E., Moore G. E. and Didolkar M. S.: Chemotherapy of disseminated malignant melanoma with dimetyl triazeno imidazole carboxamide and dactinomycin. Cancer 32 (1973), 756.
7. Miller A. B., Hoogstraten B., Staquet M. and Winkler A.: Reporting results of cancer treatment. Cancer 47 (1981), 207.
8. Voigt H. and Kleeberg U. R.: PALA, vindesine and cisplatin combination chemotherapy in advanced malignant melanoma. A pilot study. Cancer 53 (1984), 2058.
9. Wittes R. E., Wittes J. T. and Golbey R. B.: Combination chemotherapy in metastatic malignant melanoma. Cancer 41 (1978), 415.
10. Young D. W., Lever R. S., English J. S. C. and MacKie R. M.: The use of BELD (bleomycin, vindesine, CCNU and DTIC) in advanced malignant melanoma. Cancer 55 (1985), 1879.