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Synchronous Cisplatin Infusion During Radiotherapy for the Treatment of Metastatic Melanoma

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In two pilot studies, 55 patients with symptomatic metastases from malignant melanoma were treated with irradiation and concurrent cisplatin. In the first group, cisplatin was given as a continuous intravenous infusion of 20 mg/m^2 per day on days 1–5 and 22–26, with irradiation on days 2, 5, 9, 16, 23 and 26. The second group received 20 mg cisplatin over 24 h commencing 1 h before each fraction of irradiation on days 1, 4, 8, 11, 15 and 18. The first series of 28 patients had 30 lesions treated. Nine (30%) of these lesions responded completely and 10 (33%) achieved partial response for an overall response rate of 63% (95% confidence interval 44–80%). Survival was not evaluated in this group. The second group was comprised of 27 patients, with one irradiated lesion each. 1 patient achieved a complete response and 13 (48%) a partial response for an overall response rate of 52% (32–71%). Median survival was 21 weeks (16–31 weeks). Treatment was well tolerated with nausea and vomiting being the most common toxicity. Synchronous cisplatin infusion with radiotherapy achieves high response rates in metastatic melanoma. Whether it is superior to radiotherapy alone will require evaluation in a randomised trial.
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INTRODUCTION

RADIOTHERAPY, FREQUENTLY in large dose fractions, has been used in the palliative treatment of metastatic malignant melanoma [1]. Its efficacy may be limited by the ability of melanoma cells to repair DNA damage induced by radiotherapy [2].

In vitro animal and human studies have indicated the potential for cisplatin to act as a radiosensitiser in a variety of tumours [3, 4]. Possible mechanisms include the activity of cisplatin as an hypoxic cell sensitizer [5], an inhibitor of DNA repair [6] and as a depletor of protein bound thiols [7]. Radiosensitisation appears to be maximal when cisplatin is given prior to radiotherapy [8] although the most effective schedule for combined treatment is yet to be established [3].

Two small studies have reported high response rates using

radiation with cisplatin [9, 10]. The present study examined the effect of cisplatin administered synchronously with radiotherapy in two schedules in the treatment of 55 patients with metastatic melanoma. We chose clinically convenient cisplatin regimens which ensured that cisplatin was present both prior to irradation and during the repair process.

PATIENTS AND METHODS

Between March 1986 and March 1990, 55 patients with evaluable or measurable metastatic melanoma were entered on the study after written, informed consent. The study was approved by the Ethics Committees of the participating institutions. Eligibility criteria required symptomatic disease in at least one anatomical site, a life expectancy of at least 3 months and no significant renal or hepatic dysfunction (serum creatinine and liver function tests up to 1.5 times the upper limit of normal). Patient characteristics are shown in Table 1.

Treatment of the first group of 28 patients consisted of cisplatin given in a dose of 20 mg/m^2/day by continuous intravenous infusion in 3 l of normal saline daily for 5 days commencing on days 1 and 22. Radiotherapy was given with 6 MeV photons except in three superficial cutaneous lesions where 250 kV X-rays were used. The dose was 5–6 Gy fractions on days 2, 5, 9, 16, 23 and 26 thus achieving tumour doses of 30–36 Gy. The fractionation of radiotherapy was therefore adapted to fit the chemotherapy cycles.

In the second group, the chemotherapy was fitted to a more regular hypofractionation, potentially more suitable for comparative trial against radiotherapy alone. Cisplatin was given in a dose of 20 mg by 24 h continuous intravenous infusion twice weekly for 3 weeks. Radiotherapy was given on the same day 1 h after the commencement of the cisplatin infusion, again using 5–6 Gy fractions with 6 MeV or Cobalt-60 photons.

Table 1. Patient characteristics

	First series	Second series
Total	28	27
Age (years)		
Median	50	56
Range	25–70	29–78
Sex		
Male	18	17
Female	10	10
Performance status		
0	11	8
1	5	10
2	0	5
Not documented	11	4
Treatment sites		
Brain	14	13
Mediastinum	2	5
Subcutaneous	4	4
Bone	1	1
Nodes	7	4
Renal	1	0
Pelvis	1	0

Table 2. Response according to site of treated lesion

	First series	Second series
Brain	4/14 (29%)	6/13 (46%)
Mediastinum	1/2	2/5
Subcutaneous	4/4	1/4
Lymph nodes	7/7	4/4
Bone	1/1	1/1
Renal	1/1	
Pelvic	1/1	

Standard WHO criteria for response and acute toxicity were used [11]. No formal assessment of chronic radiation toxicity was made. Response was assessed both in lesions in the irradiated field and, in the few patients in whom it was applicable, in other lesions exposed only to the cisplatin. Although survival is an indirect measure of efficacy, since many patients died of disease in non-irradiated areas, survival duration and time to treatment failure were recorded in the second series.

Statistics

Life-table estimates of survival and time to treatment failure were calculated only for the second group of patients using the method of Kaplan and Meier [12]. Confidence intervals (CI) for median estimates were calculated according to the simple reflected method [13]. Survival was measured from the first day of treatment to date of death or last patient contact. Time to treatment failure was defined as time from the commencement of treatment to the first observed progression in the treated field or death.

RESULTS

All patients were assessable for tumour response in the treated field and acute toxicity of chemotherapy. Response by metastatic site for both groups is shown in Table 2. In the first group of 28 patients with 30 treated sites there were 9 complete and 10 partial responses for an overall response rate of 63% (95% CI 44–80%). Seven lesions were classed as stable and four as progressive disease. Responses included complete response in four subcutaneous sites, four lymph node sites and one cerebral metastasis. Partial responses occurred in three cerebral metastases, three lymph node lesions and single lesions in bone, kidney, pelvis and mediastinum. 3 patients had partial responses outside the field of treatment. Evaluation of this group did not include long term follow up, and no reliable survival statistics are available. 2 patients who had responded at the treated site eventually developed progressive disease at that site. The median time to treatment failure in responders was 36 weeks.

In the second treatment group of 27 patients, each with a single treated site there was one complete response and 13 partial responses for an overall response rate of 52% (95% CI 32–71%). 9 patients were classed as having stable disease and 4 as having progressive disease. The responses included complete remission at a subcutaneous site and partial responses in 6 patients with cerebral metastases, 2 patients with mediastinal metastases, 4

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patients with nodal metastases and 1 patient with a bone metastasis. Responses to the cisplatin alone were rare. Metastases were present outside the radiation field in 20 patients. 1 patient (5%) had a partial response in a lung lesion and another had partial response in one lymph node site but progressed in other nodes.

1 patient, whose cerebral metastases had responded, eventually developed progressive disease at that site. Of the remaining 13 responders, 9 had no objective evidence of site progression and 4 patients with cerebral metastases had no clinical evidence of progressive intracranial disease at the time of death. The median time to treatment failure in this second group was 17 weeks (95% CI 15–21 weeks). The median survival was 21 weeks (95% CI 16–31 weeks).

Haematological toxicity in both groups of patients was minimal with the most significant toxicity being nausea and vomiting. In the second group, Grade 1 (nausea only) was recorded in 3 patients (11%), grade 2 (vomiting) in 5 (19%), and severe vomiting requiring hospitalization in only 1 patient. Although irradiation toxicity was not systematically recorded, there were no significant episodes of acute toxicity. Compliance was excellent, and all but 1 patient completed planned therapy.

DISCUSSION

Local control of metastatic melanoma has been attempted with a number of modalities. Radiotherapy alone has reported response rates of 50–60% in subcutaneous and lymph node disease [1, 14]. Although most studies show that response is superior with a high dose per fraction [1, 15], one recent randomized trial indicated that hypofractionation did not improve response rates [14].

High response rates to radiotherapy with cisplatin have been reported in some small studies [9, 10], but, in common with the present study, these did not compare the combination with radiotherapy alone.

This study examined the effect of combined radiotherapy and cisplatin in 55 patients with local problems from metastatic melanoma. Two treatment regimens were used. The second regimen used a more standard timing of radiotherapy fractionation, which we thought more suitable to a potential comparative trial against radiotherapy alone. The 24 h cisplatin infusion was given on an outpatient basis. We did not design the two series to be compared directly.

Both our series included patients with major visceral metastases. The first group had 14 (52%) patients with cerebral metastases while the second group had 13 (48%) such patients. The response rates in these patients were 29 and 46%, respectively. This compares favorably with reported response rates of less than 40% for radiotherapy alone for cerebral melanoma metastases [16].

This study demonstrates that combined radiotherapy and cisplatin is well tolerated acutely and achieves high response rates in the treatment of metastatic melanoma. Responses were seen in brain and bone, both are sites reported to respond poorly to conventional radiotherapy. The low complete response rate in the second series was disappointing, but may reflect the advanced nature of the lesions included. Only direct comparative studies would allow a proper perspective on this aspect of the results. Clinical control was encouraging, and only 3 of the responding patients developed recurrent disease at the treated site.

We believe that the results are encouraging, but radiotherapy alone has similar reported response rates. In view of the dangers of comparing response rates between series with potentially different inclusion and response criteria, proper definition of the place of cisplatin radiosensitization in malignant melanoma will require a randomized trial comparing radiotherapy alone with cisplatin plus radiotherapy.

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