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Advances in Systemic Treatment of Malignant Melanoma

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This paper reviews recent developments in the systemic treatment of advanced malignant melanoma. In the introduction emphasis is given to prevention and early detection of this disease. Metastatic malignant melanoma patients have a median survival of less than 1 year in the most favourable situation. Adjuvant chemotherapeutic treatment after initial surgery has not had an impact on prognosis, while immunological manipulations with interferon alfa or other agents may prove beneficial after primary surgery. In advanced disease which cannot be palliated by surgery, many approaches are under investigation. Modulation of the patient's immune response can be achieved with vaccines, monoclonal antibodies, interleukin-2 and interferons, as single agents or in combination between themselves or with peripheral blood mononuclear cells or with tumour infiltrating lymphocytes or even with chemotherapy. Immunological approaches yield a 20–30% response rate, with some possibly long-term responses. Chemotherapeutic agents have a 10–30% response rate, which is usually of short duration. Combinations of chemotherapeutic agents can increase the response rate to 50%, but an impact on ultimate survival seems unlikely. Randomised studies have shown that modulation of chemotherapy with interferon or tamoxifen improves response rates. Clinicians should be encouraged to enter their patients with malignant melanoma in therapeutic trials.
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INTRODUCTION

MALIGNANT MELANOMA has increased in incidence over most of Europe in the past 30 years to the extent that one may speak of a real epidemic. Although this is particularly true of northern countries where yearly rates were around 2/100 000 in the late fifties and now approach or are over 5/100 000, it is also true, especially for younger people, in southern Europe [1]. There is ample space for education of the medical, paramedical and lay public in order to detect early lesions, to follow carefully the high-risk population and possibly to modify attitudes towards sunbathing. A concerted European effort should be pursued [2] to obtain a decrease in the incidence of deep lesions and subsequently an overall incidence decrease, both of which would lead to a decrease in the mortality related to this cancer, which can touch 1 in 15 people in high-risk areas. Efforts towards early detection and prevention are encouraged by all those who have to treat advanced malignant melanoma, because, as this paper will once again demonstrate, treatment of metastatic malignant melanoma gives little real hope for these patients.

SYSTEMIC ADJUVANT TREATMENT OF MALIGNANT MELANOMA

After initial surgery, in view of the progressively worsening prognosis of malignant melanoma according to depth of invasion (10-year mortality of nearly 20% for lesions of 1 mm, and more than 80% in patients with a lesion of 8 mm [3]), one is tempted by the introduction of further treatment. This paper will not review the role, if any, of adjuvant lymph node dissection or of isolated perfusions. A recent publication [4] has suggested a role for adjuvant levamisole in the postsurgical treatment of malignant melanoma. There are, however, three other papers which do not show any advantage for levamisole-treated patients [5–7], whether in terms of delay before recurrence or of survival (Table 1), although a trend in delay of appearance of distant metastases favouring levamisole-treated patients is reported by one group [6]. Several arguments have been raised by the investigators reporting a positive result in their study. They argue that the negative result of alternative studies is due to a short follow-up, because the difference they observed is only seen after a long (greater than 5 years) follow-up. This argument does not hold for one of the other studies, which was reanalysed with a median of 10.5 years of follow-up [5]. The investigators also discuss differences in dosage of levamisole as a possible reason for their result, but 20% of their patients discontinued levamisole because of toxicity. It is difficult to conclude at present, and levamisole may have a small role in the adjuvant treatment of malignant melanoma.

There are several on-going or recently completed studies that investigate the possible role of adjuvant interferon alfa or gamma in malignant melanoma patients (Table 2). Because of a recent report from the Southwest Oncology Group (SWOG) and the

Table 1. Levamisole vs. placebo or control in malignant melanoma

Author	Patients	Levamisole dose/schedule	Result
Quirt, *et al.*	272	2.5 mg/kg days 1+2 every week for 2 years	74% 5 years survival (62% control)
Spitler	203	150 mg days 1+2+3 every 2 weeks for 3 years	No difference at 10 years
Loutfi, *et al.*	137	150 mg twice a week	No difference
Lejeune, *et al.*	197	150–250 mg days 1+2 every week	No difference

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Table 2. Adjuvant interferon in malignant melanoma

Group	Interferon type and administration	Patients
ECOG 1684	Alfa-2B iv then sc for 1 year	> 4.0 mm; stage II
ECOG 1690	Alfa-2B iv + im for 1 year Alfa-2B sc low dose for 2 years	> 4.0 mm; stage II
EORTC 18871	Alfa-2B sc low dose for 1 year Gamma sc low dose for 1 year	> 3.0 mm; stage II
NCCTG	Alfa-2A im for 3 months	> 4.0 mm; stage II
SWOG	Gamma sc low dose for 1 year	> 1.5 mm; stage II
WHO 16	Alfa-2A sc low dose for 2 years	stage II

NCCTG, North Central Cancer Treatment Group.
iv, Intravenously; sc, subcutaneously; im, intramuscularly.

discontinuation of their adjuvant interferon gamma study [8], the European Organization for Research and Treatment of Cancer (EORTC) has conducted a safety analysis of its own adjuvant study, and has found no reason to close the interferon gamma arm. Results of these adjuvant studies should be available in the next few years, but early data from their prior study and possibly another study [9] have prompted the Eastern Cooperative Oncology Group (ECOG) to start a second study of adjuvant interferon alfa, comparing the original intensive regimen with a biologically active dosage vs. observation control [10].

Corynebacterium parvum has once again been reported as an agent which could prolong survival of patients with stage II malignant melanoma [11]. 210 patients from two separate studies have been reported together in an update of the original reports. *Corynebacterium parvum* prolonged the disease-free and overall survival rates of treated patients to 1062 and 1855 days, compared with 504 and 1034 days for patients treated with bacillus Calmette-Gérin (BCG). The authors have reviewed all studies where *Corynebacterium parvum* has been used on an adjuvant basis in malignant melanoma and indicate that stage II patients in one study (but not stage I patients) and patients with an initial tumour depth of more than 3.0 mm (but not those with thinner tumours) benefitted from the use of this agent in two of the four studies. It is quite perplexing that *Corynebacterium parvum* should have an effect only in those patients with the worst prognosis, and one wonders about confounding factors like subset analyses or imbalances in prognostic criteria, in these relatively small studies.

THE ROLE OF INTERFERON IN MALIGNANT MELANOMA

While interferon gamma [10, 12] and beta have been shown to have limited activity against advanced metastatic malignant melanoma, the alfa interferons do have some activity. A response rate of 3–25% (average 15.7%) has been reported in a series of 14 different studies, encompassing 439 patients. Of the 69 responding patients, 23 had a complete response and most responses were observed in soft tissue lesions. The dosages used in these studies have been quite variable, and there does not appear to be an advantage of high doses compared to more tolerable ones, such as 5–10 MU/m^2, three times a week [13].

This constituted a basis for the evaluation of the role of interferon alfa in situations of minimal tumour burden, and many groups decided to proceed with adjuvant studies, as described above. Combinations of interferon alfa and cytoxic agents have been shown to have additive or synergistic effects in preclinical models [14] and several reports of phase II studies have appeared in the literature. Three recent reports have evaluated those initial promising results in a randomised fashion. In the first study 64 patients were randomised to receive either dacarbazine 200 mg/m^2 for 5 days every 28 days or interferon alfa 2B for 5 days a week at an intravenous dose of 15 MU/m^2 for 3 weeks, followed by 10 MU/m^2 for 3 days a week and the same dose and schedule of the cytotoxic agent from the fourth week of therapy. The prognostic determinants seem to have been well balanced among patient groups, with some non-significant increase in the number of unfavourable metastases in the combination therapy group, which was, however, younger and contained more female patients. Objective responses were documented in 6 out of 30 evaluable patients on dacarbazine and in 16 of the 30 evaluable patients treated with the combination. Importantly, the median survival time on dacarbazine was 9.6 months, compared with 17.6 months on dacarbazine plus interferon alfa 2B. An international intergroup study has been started to confirm these data [15]. The two other papers were presented at the American Society for Clinical Oncology meeting in 1992. In one study from Italy 203 patients have been randomised to dacarbazine 800 mg/m^2 every 3 weeks, or the same plus interferon alfa 2A 9 MU intramuscularly daily for 6 months followed by subcutaneous interferon as in the third arm which combined dacarbazine to interferon 3 MU intramuscularly three times a week. Responses were seen in 16.3, 27.4 and 24.4% of patients, respectively. Mean durations of responses have been 2.6, 6.6 and 9 months, respectively [16]. The third paper comes from Australia and is not as encouraging. This group randomised 170 patients to dacarbazine 800 mg/m^2 every 3 weeks or to an escalating dosage of dacarbazine (200 to 400 to 800 mg/m^2 every 3 weeks) combined with subcutaneous interferon alfa 2A escalated after 3 days to 9 MU daily for 10 weeks and then decreased to the same dose 3 days a week. The response rate has been 17% for dacarbazine alone and 21% for the combination, with median durations of response reported as 286 and 256 days, respectively, with a median survival for all patients of 269 and 229 days. At the time of the reported analysis there was no clear advantage for the combination therapy [17]. This latter study is difficult to evaluate, as it is not clear how many patients progressed in the combination arm before dacarbazine was administered at a dose which is generally recognised as efficacious.

INTERLEUKIN-2 ALONE OR IN COMBINATION

Interleukin-2 alone or in combination with lymphokine-activated killer (LAK) cells are another means of treating advanced melanoma with biological agents. The response rates with and without LAK cells are similar and quite comparable to what can be achieved with interferons (18–24), and are depicted in Table 3. Another approach has been to utilise the lymphocytes which can be found in a metastasis as a target for *in vitro* interleukin-2 and subsequent infusion back into the patient. Many such studies have been published, and they indicate that it is possible to obtain tumour infiltrating lymphocytes (TIL) from the majority of the melanoma metastases; moreover, the response rate to TIL-interleukin-2 treatment seems better than that observed for interleukin-2 alone or with LAK cells [25]. As a further step forward, the National Cancer Institute (NCI) Surgery Branch Group has developed techniques which allow gene transfer into humans using TIL. This type of approach will eventually allow accumulation of transformed effector cells in

Table 3. Randomised studies of interferon and dacarbazine combinations

Author	Patients	Interferon type	% response CR	% response PR	Duration (months)
Falkson, *et al.*	31	—	6.7	13.3	S: 9.6
	31	Alfa 2B	40.0	13.3	S: 17.6
Sertoli, *et al.*	67	—	4.5	11.9	R: 2.6
	62	Alfa 2A	6.5	20.9	R: 6.6
	74	Alfa 2A	6.8	17.6	R: 9.0
Thomson, *et al.*	83	—	2	15	S: 8.9
	87	Alfa 2A	7	14	S: 7.6

CR, complete response; PR, partial response; S, survival; R, response.

the area around the tumour, which will be able to produce locally a potent cytotoxic cytokine [26].

Animal models have shown that interleukin-2 and interferon could have an increased antitumour effect when used in combination and initial clinical results have been promising in this respect [27]. Similarly, biomodulation of cytotoxic agents has been investigated preclinically; two cytotoxic chemotherapeutic agents, doxorubicin and cyclophosphamide could increase the antitumour efficacy of interleukin-2. This has led to clinical evaluations of complex combinations. Thus, interleukin-2, LAK cells and interferon-alfa 2A have been combined with doxorubicin and cyclophosphamide at low doses [28] and administered to 43 patients with malignant melanoma, 3 of whom died from toxicity. Partial responses were observed among 8 of the 40 survivors, one of whom has a single iliac adenopathy after 26+ months of observation, while the others relapsed after 2–4 months. Because the toxicities of interleukin-2 and interferon-alfa combinations are not overlapping with those of chemotherapy, another group has combined these biological agents with carmustine, cisplatin, dacarbazine and tamoxifen in a phase II study. 10 patients out of 42 achieved a complete response and a further 14 achieved a partial response, totalling a 57% response rate [29]. The authors admit that this response rate is comparable to that observed with similar combinations of chemotherapy alone. They suggest that the observation of a tail on the survival curve, at least after a short period of observation (the longest follow-up is less than 18 months), indicates a possible long-term benefit for some patients, achieved through the immune modulation.

Table 4. Biological response modifiers and melanoma

Agent	Patients	% response CR	% response PR	CR+PR (range)
Interferon alfa 2A	249	4.8	11.2	16.0 (8–25)
2B	190	5.8	9.4	15.2 (3–25)
Interleukin-2	135	1.5	16.3	17.8 (0–24)
Interleukin-2 + LAK cells	170	4.1	14.7	18.8 (14–22)
Interferon alfa + interleukin-2	63	6.3	22.2	28.5 (12–33)
Interleukin-2 + TIL	101	3.0	28.7	32.9 (20–40)

CR, Complete response; PR, partial response.

MONOCLONAL ANTIBODIES AND VACCINES

Clinical observations have linked melanoma and immune response, and cases of spontaneous regression of metastases or regression after non-specific immunostimulation have been documented. Many trials have been performed with monoclonal antibodies directed to diverse epitopes on the malignant melanoma cells, and some encouraging responses have been observed. One of the most promising avenues of research in this area lies with the monoclonal antibody R24 directed against the ganglioside GD3, which by itself is capable of eliciting responses [30]. As monoclonal antibodies which are not conjugated to cytotoxic agents require an immune response from the patient, a logical step was to combine R24 with interleukin-2. A preliminary report indicates a 43.5% response rate with such a combination in evaluable patients, a response rate which decreases to 35.7% if one accounts for all treated patients, 2 of whom died from interleukin-2 toxicity and 3 had severe side-effects which led to discontinuation before R24 was administered [31]. Studies with conjugated antibodies have produced minimal results until now.

There have been many trials of vaccinations, utilising tumour cell extracts, transformed tumour cells, or antigenic determinants like GD3 or GM2 [32]. Some reports have indicated not only the detection of an immune response, but also a clinical response in some patients. 4 out of 25 patients have, for example, responded to subcutaneous injections of melanoma cell lysates along with an adjuvant ("DETOX": detoxified endotoxin and mycobacterium cell wall skeleton) [33]. Using a similar approach another group has observed only one response among 16 evaluable patients [34].

CHEMOTHERAPY

A review performed for the 1989 European Winter Oncology Conference showed that three cytotoxic agents have a 20–24% response rate: dacarbazine, cisplatin and cyclophosphamide. Vinblastine, vindesine and actinomycin D have a 15–19% response rate, and all other agents have a lower activity (hydroxyurea, methotrexate, VP-16). The reported combinations have response rates between 11 and 47%, with a mean of 21% among 1484 patients [35].

Considerable interest lies in a new class of cytotoxic agents, derived from *Taxus brevifolia* or *Taxus baccata*. There are indications from phase I studies that taxotere may have activity in malignant melanoma and phase II studies have been started. Taxol has been investigated for a longer time, and seems to be a promising agent for treatment of cisplatin-refractory ovarian cancer. Two studies have evaluated its activity in malignant melanoma, and seven responses have been observed among 53 patients, most of whom were heavily pretreated [36, 37].

A new nitrosourea has been extensively studied in malignant melanoma patients. Nitrosoureas have a 15% response rate in malignant melanoma, and a large phase II study in 153 patient has shown a 24% response rate for fotemustine, with a higher response rate among non-pretreated patients (19 of 62 = 30%). Interestingly, there has been good documentation of a 25% response rate of cerebral metastases with this agent [38]. A second study has confirmed these observations [39], which may, however, depend on the choice of patients introduced in these studies. Combinations of dacarbazine and fotemustine have been reported to produce response rates around 30% [40–42] (Table 5). One of these papers has documented a 50% response rate in lung metastases when fotemustine was preceded by dacarbazine [40]. However, this combination sequence may be extremely

Table 5. New agents and combinations for metastatic malignant melanoma

Agent	Patients	% response		
		CR	PR	Total
Taxol	53	3.8	9.4	13.2
Fotemustine	183	2.7	20.8	23.5
Fotemustine + dacarbazine	146	12.3	15.8	28.1

CR, Complete response; PR, partial response.

toxic, as 1 patient who had a complete remission died from pulmonary toxicity after the third cycle of treatment. The authors point out that there is preclinical evidence for a restoration of sensitivity to nitrosoureas by pretreatment with a methylating agent, whose role is to deplete cells of O^6 alkylguanine alkyl transferase activity, and that such depletion has been documented in patients' lymphocytes. Studies are under way to elucidate if the lung toxicity may be related to this mechanism.

One should not forget that most of the responses observed with chemotherapy are of short duration and that their meaning for the patients' ultimate outcome is minimal. An overview of the Royal Marsden's experience shows that even though responses are minimal with single-agent vindesine and frequent (21–44%) with complex regimens (bleomycin-vincristine-lomustine-dacarbazine), there is no difference in survival, as only 10% of the patients survive beyond 1 year and 4% at 2 years [43].

With the above in mind, one has to consider the possible role of tamoxifen as an additive to chemotherapy. This antioestrogenic agent probably has a role in modulating the chemoresistance of melanoma cells and has been incorporated in therapeutic regimens for malignant melanoma for many years [44, 45], with remission rates of the magnitude of 50% being reported in these older studies. Two recent sets of data have revived the interest in this approach. There may be an advantage in using higher doses of tamoxifen (160 mg for 7 days prior to chemotherapy instead of 20–40 mg/day continuously), as a pilot study suggests an increase in the number of complete responses in a new group of patients, compared with historical data [46] (Table 6). More convincing is the randomised study reported from Italy, where 117 patients were randomised to dacarbazine alone vs. dacarbazine plus tamoxifen. This study confirms the low level of activity of single-agent dacarbazine (12% response rate) and indicates that the combination was very active, and especially in women (overall 28% response rate) [47] (Table 6). Unfortunately, this improvement in response rate translates only in a median time of survival advantage (48 vs. 29 weeks), with rare survivors at 3 years.

Table 6. Tamoxifen in melanoma: a chemopotentiator?

Author	Patients	Dose	Chemotherapy	% Response	
				CR	PR
Berd, *et al.*	*15	160 mg	Carmustine, dacarbazine, cisplatin	27	20
	43	40 mg	Same	9	33
Cocconi, *et al.*	32	none	Dacarbazine	6 (CR+PR: males 13%, females 10%)	6
	31	20 mg/m²	Same	7 (CR+PR: males 19%, females 38%)	22

*Non-randomised study. CR, Complete response; PR, partial response.

CONCLUSION

4 years have passed since the previous review of treatment of malignant melanoma at a European Winter Oncology Conference. There are several new approaches which are under investigation, and better response rates can be consistently achieved in metastatic disease. It is, therefore, time to start the investigation of length of response, and there is for the time being no clear indication as to an advantage of biological response modifiers with or without chemotherapy in this respect. Future studies should pay considerable attention to prognostic factors of these patients [48]. Phase III studies will make sense only once a carefully conducted phase II study shows a possible prolongation of patient survival beyond 3 years; meanwhile, comparison of response rates can be achieved by critical review of well-described patient populations. There is no standard therapy for inoperable malignant melanoma and there is no standard adjuvant treatment either [49].

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