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Review paper

Treatment of metastatic malignant melanoma

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The incidence of malignant melanoma continues to rise exponentially and it is estimated that 7000 people will die of metastatic malignant melanoma annually. Conventional chemotherapy, immunological and/or biological therapies and novel combinations are being studied intensively in an effort to improve the dismal outcome for patients with this disease. This review deals with recently published studies and the state of the art of the treatment available for metastatic malignant melanoma.

Key words: Metastatic malignant melanoma, treatment.

Conventional chemotherapy

Conventional chemotherapy for metastatic malignant melanoma is an established form of therapy with predictable outcome. Dacarbazine (DTIC) forms the cornerstone of this conventional therapy and is usually employed in multidrug regimens against melanoma. A number of new cytotoxic drugs have been investigated in advanced melanoma and a few of these hold some promise. Examples include the new nitrosourea, fotemustine, and the oral derivative of DTIC, temozolamide. Other agents such as didemnin B and taxol have given disappointing results. These drugs are briefly discussed in the following section.

Single agents

DTIC. Early clinical trials showed activity to metastatic malignant melanoma with DTIC.[1,2] Subsequently DTIC has remained the most reliably active single agent in this disease. When studied in prospectively randomized trials, no other agent, either alone or in combination, has proven superior to single-agent DTIC. Unfortunately the response rate of 20% (ranging from 10 to 30%) and few complete responses (4%) with an overall median survival of 4–6 months, and very few long-term remissions, is not ideal.[3–23] Only a third of patients who achieve complete remission are disease free at 6 years and only about 2% of these sustain long-term remissions.[24]

Temozolamide. Temozolamide is related to the active metabolite of DTIC, and has the distinct advantages over DTIC of being active in the oral form and of not being light sensitive. Its mechanism of action is similar to DTIC and early trials showed activity in melanoma. In a recent phase II trial, Bleehen *et al.*[25] reported a 21% overall response rate (including three complete responses in 56 previously untreated patients) with minimal toxicity. Further trials with this drug are warranted.

Nitrosoureas. As single agents, the older nitrosoureas, methyl-CCNU, CCNU and BCNU (Carmustine), have consistently given response rates of less than 18%.[26–28] In a series of controlled trials the ECOG documented an overall response rate of 11–15%.[8,29] BCNU continues, nevertheless, to play a role both as second-line therapy and, in combination with other drugs, in the treatment of advanced melanoma.

Fotemustine. This novel chloroethyl nitrosourea that readily penetrates the blood–brain barrier has considerable activity in metastatic malignant melanoma, which is probably at least equivalent to DTIC. The overall response rates obtained with fotemustine range from 16.7 to 47%. Especially significant is the overall response rate of 24.3% (range 8.3–60%) in 140 patients with cerebral metastases.[30] In view of the fact that no other agent has shown significant activity in cerebral melanoma, these results warrant further study with fotemustine. To date, combinations of fotemustine and DTIC have, unfortunately,

been disappointing, resulting in augmentation of toxicity and no significant benefit in response.[31–36]

Cisplatin and other platinum analogs. As single agent, cisplatin has given response rates of 0–69%,[37,38] usually accompanied by severe toxicity. Carboplatinum also gave disappointing results.[39] Zeniplatin, a third generation platinum analog, has shown only modest activity in metastatic malignant melanoma (two partial responses in 21 patients), also in the wake of considerable toxicity.[40]

Didemnin B. This cyclic peptide, isolated from the marine tunicate *Tridemnin cyanophorum*, does not have significant antimelanoma activity. The SWOG recently reported no responses in 11 evaluable patients with metastatic malignant melanoma treated on a phase II trial with didemnin B.[41]

Gemcitabine. A water soluble analog of deoxycytidine, gemcitabine has no relevant antitumor activity in metastatic malignant melanoma. In the phase II trial conducted by the EORTC Early Clinical Trials Group, only one partial response was seen in 33 patients with advanced melanoma.[42]

Plant alkaloids (taxol, taxotere and docetaxel). Trials with taxol in melanoma have been reviewed.[43] Modest activity has been reported with taxotere[44] and more recently also with docetaxel.[45]

Piroxantrone. An anthrapyrazole derivative, showed activity against melanoma in phase I trials, but in a recent phase II trial SWOG reported an overall response rate of only 5% in the face of cardiac toxicity.[46]

Merbarone. An investigational anticancer drug with activity against experimental tumors including melanoma, merbarone had only minimal activity against melanoma in a phase II trial (SWOG) but significant renal toxicity.[47]

Combination chemotherapy

The majority of combination chemotherapies used in advanced melanoma rely heavily on a cytokine component and as such are discussed in the subsequent section dealing with immunotherapy. The most important combination employing only conventional chemotherapy is the regimen originally described by Del Prete *et al.*, employing DTIC, cisplatin, carmustine and tamoxifen.[48] Overall response rates of more than 50% were also subsequently reported by others.[49–51] An intergroup, prospectively randomized trial, comparing this combination to single-agent DTIC is underway and should help place this combination in perspective.

While tamoxifen as a single agent is minimally active (0–14%)[52–56] in metastatic malignant melanoma, it is postulated that when combined with other chemotherapeutic drugs, it enhances therapeutic activity and may even delay development of platinum resistance.[57] While some investigators report that tamoxifen is an essential component,[58–61] other investigators are omitting tamoxifen from their combinations as more and more randomized trials show its addition does not the enhance antimelanoma effect of chemotherapy.[62,63] An ECOG trial, E3690, which recently completed accrual, addressed this question (DTIC plus tamoxifen) in part. These randomized trials will help, with finality, to clarify whether the hypothesis of modulation holds true and whether combining relatively inactive single agents in the optimal manner is the answer to obtaining superior results in advanced melanoma.

It is interesting that in a small phase II study, Nathanson *et al.*[64] showed that megesterol acetate may contribute to a high objective response rate and objective survival when used in combination with a regimen of DTIC, carmustine and cisplatin.

Immunological and/or biological therapy

During the past decade various immunological and/or biological therapies have been under intensive scrutiny in an attempt to improve the outcome of patients with malignant melanoma. Cytokines such as interferon (IFN)-α, the interleukins (IL), IL-4, -6, -10, -11, -12, and various vaccines and antibodies have been evaluated. The regimens have ranged from cytokine/IFN monotherapy, cytokine-chemotherapy combinations to adoptive immunotherapy, humoral immunotherapy and specific immunization.

Interleukin and IFN. The role of IFN and IL monotherapy has been extensively reviewed elsewhere.[65–67] Their overall response rates range from 10 to 30%. Complete responses of about 5% are reported, with some long-term durable remissions. The IL-2 Working Group reported a response rate of only 5% with single-agent IL-2.[68] The combination of IFN-α plus IL-2 also does not appear particularly promising, even though Keilholtz *et*

al.[69] demonstrated an apparently large difference in outcome using different dosing schedules in 54 patients. In a randomized trial, the IL-2 Working Group reported a response rate of only 5% with single-agent IL-2 and 10% with IL-2 combined with IFN-α in 85 patients. This combination therefore does not appear to warrant further pursuit.[68] The results with IL-2 alone, IL-2 plus LAK cells and adoptive immunotherapy, reported by Rosenberg *et al.*,[70–72] have not been duplicated. The overall results with IL-2 alone, IL-2 with adoptive IL-2 effector cell transfer and IL-2 with tumor infiltrating lymphocyte transfer show a drop in response rates from 20–25 to 10–15%.[73]

Chemoimmunotherapy. A plethora of trials employing chemotherapeutic agents and IFN and/or IL-2 have been published. The rationale for combining immunotherapy, and especially IFN, with conventional chemotherapy, is sound. IFN has both a dose-dependent antiproliferative effect as well as the potential ability to improve the cytotoxicity of chemotherapy. Its *in vitro* additive effect have been proven[74] and the possibility of true synergism exists. Cytokines act in cascades, thus both their direct effects and their indirect effects mediated through the induction of other cytokines or second messengers may be of importance. Their modulation of the host immune system, possibly by increasing tumor sensitivity by normalization of the malignant phenotype, regulating oncogene expression and increasing host defences, by means of natural killer cell activation and enhanced class I and II antigen expression, are some of the antitumor effects of IFN which may theoretically enhance the antimelanoma effects of conventional chemotherapy.

The most important recent chemoimmunotherapy trials are summarized in Tables 1 and 2. Overall it appears as if chemoimmunotherapy gives better overall response rates than either chemotherapy or immunotherapy by themselves. These are, however, preliminary observations. The results of these phase II studies need to be investigated in large prospectively randomized trials. An ECOG trial (E3690) comparing DTIC versus DTIC plus IFN versus DTIC plus IFN plus TMX versus DTIC plus TMX recently completed accrual of 271 patients. This trial

Table 1. Combination chemoimmunotherapy

	Response rate (%)
Carboplatin, DTIC, IL2, IFN-α[99]	35
Cisplatin, DTIC, IL-2, IFN-α[100]	83
DTIC, 5-FU, IFN-α[101]	38
DTIC, vincristine, bleomycin, CCNU, IFN-α[102]	62(13)
Cisplatin, DTIC, BCNU, TMX, IL-2, IFN-α[103]	54
Cisplatin, DTIC, BCNU, TMX, IFN-α[104]	29
Cisplatin, DTIC, BCNU, TMX, IFN-α[105]	53
Cisplatin, DTIC, BCNU, TMX, IFN-α[106]	26
Cisplatin, VBL, DTIC, IL-2, INF-α[107]	63
Cisplatin, IL-2, IFN-α[108]	26
Cisplatin, IL-2, IFN-α, TMX[62]	52
DTIC, carboplatin, IFN-α IL-2[109]	37.5
Cisplatin, BCNU, DTIC, TMX, IL-6[110]	31.5

Table 2. IFN-α plus DTIC non-randomized trials

Reference	No. of patients	Response rate (%)
Kerr *et al.*, 1989[111]	19	5
Avril *et al.*, 1990[112]	44	23
Mulder *et al.*, 1990[113]	31	35
Mulder *et al.*, 1994[114]	136	32
Gundersen and Flokkmann, 1991[115]	15	7
Sertoli *et al.*, 1992[116]	62	27

Table 3. IFN-α plus DTIC (randomized trials)

	DTIC plus IFN	DTIC alone
Kirkwood *et al.*, 1990[117]	4/21 (19%)	5/24 (21%)
Falkson *et al.*, 1991[118]	17/34 (50%)	7/34 (20%)
Thomson *et al.*, 1993[119]	18/87 (21%)	14/83 (17%)
Bajetta *et al.*, 1994 (266 patients)[120]	20%	28%, 23%[a]
ECOG E3690 (271 patients)	Results await maturation	

[a] Two different schedules of DTIC.

has a 2 x 2 factorial design, which has increased statistical power to detect a difference in outcome between the different treatment arms. It was designed to detect a 50% prolongation of survival by either the modulating agents, interferon and/or tamoxifen combined with DTIC. Results of this trial should be available within the near future and will no doubt help resolve this issue. Other randomized trials comparing DTIC to DTIC plus IFN are summarized in Table 3.

Melanoma vaccines. A number of early clinical trials with various melanoma vaccines have been conducted and are being studied further. The targets for these vaccines are varied and include, amongst others, gangliosides and peptides. The recent trials show evidence of immune response to these vaccines, tumor responses (both visceral and non-visceral) and even improved survival.[75–81] The responses have all been correlated with certain HLA phenotypes, suggesting the possibility of involvement of a shared antigen in the context of a given MHC class I molecule.[82]

Ganglioside vaccines. Normal melanocytes express GM3 as their major ganglioside, whereas melanoma gangliosides are GD3, GD2 and GM2. The detection of antibodies against these gangliosides in melanoma patients sera subsequently led to the development of monoclonal antibodies to melanoma. Since the responses reported in the phase I trial[83] with R24 (a monoclonal antibody against GD3), other trials reported responses of 8–20%.[84,85] Although responses have been reported, dose-limiting neurotoxicity with monoclonal antibody 14.18 against GD2 has been severe. Studies with the chimeric antibody ch.14.18 are in progress. Animal models suggest this antibody might be useful for treating human melanoma.[86,87] Bernhard *et al.*[88] classified patterns of ganglioside recognition with a series of 10 monoclonal antibodies and antibody reactivity can be grouped into five categories, which will, in all probability, prove different therapeutic values.

Peptide vaccines. A number of CTL-determined melanoma antigens have been structurally defined and epitomes delineated. Although preliminary reports with peptide vaccines have been disappointing, results from the majority of trials that have been initiated with peptide vaccines, including MAGE-1, MAGE-3, EADPTGHSY and MART-1, are still awaited.

Future directions

Gene transfer technology

Gene transfer technology, or 'genetic therapy', has advanced significantly during the past few years and therapeutic applications to melanoma may soon be possible.[89–91] Various approaches have been described,[92–94] especially the introduction of cytokine genes, IFN and growth factors into host effector cells, and the transfer of genes for histocompatibility antigens into tumor cells where the gene products may augment immunogenicity.

Oncogene-targeted antisense oligodeoxynucleotides may possibly prove to be a highly effective method of treating advanced melanoma in the future and techniques employing antisense oligodeoxynucleotides targeted against human growth factors (e.g. FGFR-1) also warrant further study.[95]

Alternative strategies (e.g. pigment producing pathway)

Studies done in the 1960s suggested quinonoid melanin precursors may potentially be toxic. Subsequently, the pigment producing pathway has been targeted as a strategy against melanoma. Several melanocytotoxic phenolic pro-drugs have been

developed and some of them have reached the preclinical stage. These have been reviewed elsewhere.[96]

Camptothecin

In vitro results suggest the plant alkaloid camptothecin (CPT) and its derivatives 9-nitro-CPT and 9-amino-CPT may have antimelanoma effects.[97] The clinical application of these agents needs to be evaluated.

Others

Quinocarmycin monicitrate (KW2152) and its analog, DX-52-1, demonstrated specificity for melanomas in the National Cancer Institute *in vitro* human tumor cell line drug screen. Because of statistically significant growth inhibition DX-52-1 has been selected by the NCI for development to clinical trial especially against melanoma.[98]

Conclusion

While our knowledge of melanoma tumor biology has increased dramatically, the list of drugs which have insignificant activity against melanoma has also increased. Our application of the new knowledge needs to be defined in the clinical setting. The challenge for the future is to develop clinically applicable therapeutic strategies which significantly improve both the survival and the quality of life for patients with metastatic malignant melanoma.

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