Review paper

WHAT'S NEW IN MALIGNANT MELANOMA - TREATMENT

F. Prignano, S. Moretti, P. Carli and B. Gianotti

ABSTRACT

The authors discuss biological markers which could make us better understand the function of biological response modifiers (BRMs) and their efficacy in the advanced melanoma treatment. The demonstration, that BRMs, in vitro, inhibit the growth of melanoma cell lines and that they modulate the expression of melanoma associated antigens (MAA) justify their therapeutic application. While the results obtained with chemotherapeuthical substances - alone or in combination - are substantially not very different from the past ones, but interesting progressions are coming from the active immunotherapy. The so called "adoptive immunotherapy" made of a combination of intratumoral T lymphocytes and interleukin 2, is feasible only for a fraction of patients.

KEY WORDS

melanoma, biologic response modifiers, chemotherapy, immunotherapy

Let us examine what's new in treatment and, in particular, how the recent advances in biology may improve our strategies.

Systemic chemotherapy remains unsatisfactory for treatment of disseminated (stage IV) disease. Dacarbazin (DTIC) remains the most active simple agent, with a response rate of about 20% (37). Patients with skin, subcutaneous tissue and lymphonode involvement respond more frequently. Lung metastases are also responsive - the median duration of responses is 5 to 6 months. In the widest case control study of 580 patients treated with DTIC 5% had a complete remission, but only 1-2% presented no relapses after 6 years follow-up (1). The Nitrosoureas are a second group of agents with defined activity against metastatic melanoma. Hematologic toxicity can be more severe than with DTIC. Carmustine and Lomustine are the best studied of this class, with a response rate of 10 to 20% (1). Fotoemustine is a new drug of this class. Its activity against disseminated melanoma has been demonstrated in a large - phase two-trial including 153 evaluable patients, with 37% responses (2).

Among the Alkylating Agents, Cyclophosphamide has a higher toxicity and is less effective than DTIC. Melphalan was used in high concentrations to induce bone marrow aplasia and therefore its administration was followed by autologous bone marrow transplantation. The response rate was 50-60%, but morbidity and mortality rates were too high in relation to efficacy. There has been considerable interest in the past few years in the dose-

response relation of Cisplatin in the treatment of melanoma. In general, response rates with high doses of this drug, either alone or in combination, are not discernibly better over standard doses. Regional administration of Cisplatin with hyperthermia produced responses in 67% of patients with in transit metastases of limbs. Alkaloids are used today only in combination regimens. The role of combination chemotherapy in treatment of advanced melanoma is not entirely clear. Several unconfirmed reports of high response rates were followed by randomized studies - or confirmatory trials - that found response rates that were similar to those of DTIC. Because toxicity of DTIC is minimal, it is important to demonstrate meaningful therapeutic gains of potentially more toxic combination regimens. High doses regimens have also been proposed. For example, high dose Carmustine (BCNU) has been added to varying combinations of Melphalan, Thiotepa, Ciclophosphamide or Cisplatin, with a 50% response rate (1).

High doses of DTIC+ Melphalan have produced responses in 49% of patients (1). However, toxicity of these regimens is substantial, and they are associated with fatalities in up to a third of cases at very high doses.

The introduction of Tamoxifen in some combination treatment of metastatic melanoma was due to demonstration (still controversial) of estrogen receptors in melanoma cells, and to the hypothesis that endocrine factors may influence the clinical course of melanoma. In particular, estrogens may suppress T-cell activity and modulate the activity of B-cells, macrophages and NK cells (3).

Cocconi et al. (4) support the therapeutic relevance of this drug; in a randomized study with DTIC alone versus DTIC + Tamoxifen, the overall response rate was higher (28% vs. 12%) and survival rate was longer (48 weeks vs. 29 weeks) among the patients who received DTIC + Tamoxifen. Women had better outcomes than men. Other data however (5) do not support the addition of Tamoxifen; disappointing results were obtained adding Tamoxifen both to DTIC and Cysplatin (5). These studies demonstrate a pattern often observed in clinical research studies involving melanoma: a small pilot trial of a new regimen is reported to have a high response rate, but subsequent larger studies fail to verify it. The point to keep in mind when evaluating studies in melanoma patients is that the likelihood of patients responding to treatment varies considerably with differences in performance status, time for recurrence, sites of involvement and prior treatment. A randomized trial helps to control these variables, but it must include enough patients stratified for known prognostic factors.

The biological approach to the treatment of melanoma is based mainly on biological response modifiers (BRMs). One of the most important effects of BRMs on melanoma cell lines is growth inhibition.

Table 1. Biological response modifiers' effect on melanoma cell lines

Growth inhibition
IFN-Beta
IFN-Alfa
IFN-Gamma
TNF-Alfa (Cytolysis)
TGF-Beta
IL-4

In Table 1 the BRM are listed according to their efficacy. TNF alpha is more cytolitic than cytostatic. In vivo it affects selectively melanoma cells with enhanced malignancy. In Table 2 are reported the effects of BRM on some melanoma progression markers (MPM) on cell lines. The action of IFN gamma is wider and stronger than that of other IFNs and TNF alpha. This modulation of MPM may influence the immune response of the host. Part of the effects of BRM working on MPM may justify their therapeutic application. IFN alpha is one of the most used BRM and as with other treatments, most responses have been partial and short-lived, and occurred mainly in skin, subcutaneous tissue, lymphonode and lung (1). The combined response rate on 380 patients is about 16%; complete responses have been observed in about 5% of patients (1). An optimal dose of IFN alpha has not been established, although there is a trend in favor of higher doses (1). In one of the widest protocols of the last two years performed by our Italian Cooperative Group, the response rate was 25%, with 8% having a complete response (6).

According to our results, the addition of IFN alpha to DTIC may prolong the response duration and is a well-tolerated regimen. Moreover, the comparison of different arms of the trial demonstrated that 3 000 000 of IFN alpha were as effective as 9 000 000.

A very rare example of systemic administration of TNF alpha is associated to BCNU but the results

Table 2. Biological response modifiers (BRMs), their effect on melanoma cell lines. The effects of each BRM on the corresponding melanoma progression markers (MPM) (listed above the line) is progressively decreasing from the top to the bottom.

BRM'S EFFECTS ON MELANOMA CELL LINES				
HLA-1	HLA-II	ICAM-1	LFA-3	VLA-2
IFN-Beta IFN-Alfa IFN-Gamma TNF-Alfa IL-4	IFN-Gamma IL-4 TNF-Alfa	IFN-Gamma TNF-Alfa IL-1	IFN-Gamma TNF-Alfa IL-1	IFN-Gamma TNF-Alfa

are very disappointing, while locally - in hyperthermia - TNF alpha works much better. The use of another BRM, IL-2, is becoming more and more widespread in the treatment of melanoma due to its activity against the tumor. Clinical trials with IL-2, by bolus injection or by continuous intravenous infusion with or without the addition of lymphokine-activated killer (LAK) cells, have demonstrated reproducible response rates of 10 to 25% using several doses and schedules (1). Another current therapeutical approach with IL-2 is the so called "adoptive immunotherapy". It has been claimed to yield superior response rates but is technically feasible for only a fraction of patients: T intratumoral lymphocytes (TIL) stimulated by IL-2 are infused into the patient and are about 20-30 times more effective than peripheral blood lymphocytes in killing target cells. In this case the T cytotoxic cells show the CD3+ CD8+ phenotype. Monoclonal antibodies (MoAb) can be used to activate the host immune response alone, or conjugated to cytotoxic agents. Anti gangliosyde GD3 MoAb mediates activation of complement and triggers killing of melanoma cells by peripheral blood mononuclear cells (7). Responses have been observed after treatment with several MoAbs against the gangliosides GD2 and GD3 and preliminary results indicate that a combination of II-2 and anti-GD3 results in higher response rate (8, 9). The search for effective methods to induce active immunity against melanoma has been difficult. Evidence is mounting that vaccination can induce immune response to melanoma. In a study of the American Joint Committee on Cancer, a new polivalent melanoma cell lines obtained from different melanoma cells was administered (10). Another approach to active immunotherapy was to give autologous cryopreserved irradiated tumor cells conjugated to dinitrophenyl (DNP) to metastatic patients previously sensitized to DNF (11).

Thermochemotherapy is mostly used in limbs perfusion; the drugs most commonly used are Cisplatin, Melphalan and TNF alpha (12). Recently, in a trial in which was used, Cyclophosphamide it emerged that the efficacy is related to termal tolerance and growth rate of the tumor (11). Randomized trials using adjuvants have not demonstrated any advantage for treatment of patients at high risk for recurrence or for development of systemic metastases.

In conclusion, we have to admit that there is no existing standard therapy for metastatic melanoma and physicians should seriously consider enrolling these patients on clinical trials.

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AUTHORS' ADDRESSES

Francesca Prignano MD, Institute of Dermatology, Via Alfani 37, 50121 Firenze, Italy
Silvia Moretti MD, II Department of Dermatology, Via della Pergola 58, 50121 Firenze, Italy
Paulo Carli MD, same address
Benvenuto Gianotti MD, Professor and Chairman, same address