Is There a Standard for the Palliative Treatment of Melanoma?

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Evidence-based medicine (EBM) is a thorough, explicit and rationale use of all the best available external scientific evidence in the medical care for individual patients (adapted from: Sackett DL, et al: Münch Med Wochenschr 1997;139:644–645).

Introduction

Melanoma continues to present a major therapeutic challenge to oncologists, oncological surgeons and dermatologists with rapidly rising incidence over recent decades. 10 melanomas per 100.000 inhabitants are newly diagnosed per year in Europe. Only early detection and adequate surgical excision of the primary tumor will prevent metastatic dissemination. Around 20% of affected patients will eventually develop metastases and die of melanoma. Current therapeutic concepts were recently reviewed [1]. No effective curative treatment is available in stage IV of this disease. In its metastatic stage, melanoma is highly resistant to standard forms of therapy (e.g. surgery, chemotherapy) [2, 3]. Polychemotherapy and/or combination with cytokines did not demonstrate superiority to single-agent dacarbazine (DTIC) which is still considered standard treatment in Europe. This paper reviews randomized-controlled clinical trials performed over the last 25 years that applied cytotoxic agents in advanced melanoma.

Randomized Trials with Cytotoxic Agents Only

Systemic therapies for metastatic cutaneous melanoma have achieved only a few lasting remissions and the therapeutic aim remains one of palliation. In a recent Cochrane review of melanoma treatment in stage IV no evidence from randomized controlled clinical trials was found to demonstrate superi-

ority of systemic therapy over best supportive care / placebo [4]. However, around 1.500 metastatic patients have been treated in 9 randomized trials comparing various DTIC-containing chemotherapy regimens with each other in studies accruing between 69 and up to 386 patients. 4 of the trials compared DTIC alone versus polychemotherapy regimens. Clinical response rates (RRs) of DTIC alone ranged between 9.9 and 18%, depending on the number of patients included in the treatment arm. RR were increased in several instances where chemotherapy combinations were used and which mostly included DTIC as well, however, median survival was not affected in all 9 randomized trials. RRs and overall survival were analyzed in a recent meta-analysis of 3,273 patients from 20 randomized trials that was performed comparing single-agent DTIC to combination chemotherapy with or without immunotherapy [5]. Although the analysis showed an increased odds ratio (OR) suggesting that combination drug therapies were associated with a certain increase in RR compared with single-agent DTIC, no survival benefit was detected. In a recently published report, the Dartmouth regimen, a treatment schedule widely used in the USA containing DTIC, BCNU, cisplatin and tamoxifen (TMX), was compared to DTIC alone in 240 patients by Chapman and co-workers [6]. Median survival time from randomization was 7 months and no difference in survival time between the two treatment arms was detected, however, bone marrow suppression, nausea/vomiting, and fatigue were significantly more common in the Dartmouth arm. In the recently reported trial DTIC was compared with temozolomide, a newly developed substance which can be given orally and has the capacity to penetrate the brain-blood barrier. 305 patients were randomized. RRs were around 13% and median survival times ranged around 7 months in both groups. Median progression-free survival time was significantly longer in the temozolomide-treated group (1.9 months) than in the DTIC-treated group (1.5 months) [7].

Randomized Trials with Cytotoxic Agents and Tamoxifen

At least 5 randomized studies were performed testing the beneficial effect of TMX. Based on the hypothesis that endocrine factors may affect the clinical course of melanoma and the response to the treatment of this disease a first randomized trial was initiated in 117 patients comparing DTIC with DTIC plus TMX by Cocconi et al. [8] demonstrating overall RR statistically higher (28 vs. 12%). Unfortunately, the effect of TMX was not reproducible in 3 subsequent trials. Rusthoven et al. [9] reported on a randomized, double-blind, placebo-controlled trial to compare the RR and survival of melanoma patients who had received the Dartmouth regimen (BCNU, DTIC, cisplatin, TMX) or the same triple chemotherapy with placebo. 211 patients were accrued, the overall RR were statistically not different in agreement with subsequent data reported by Chapman et al. [5]. In a randomized 2 × 2 factorial design to receive one of the 4 treatment arms [DTIC alone, DTIC plus interferon (IFN), DTIC plus TMX, and DTIC plus IFN plus TMX], 261 patients were included in a study performed by Falkson (1998) [10]. 9 complete remissions (CRs) and 18 partial remissions (PRs) were observed in the patients who received treatments that contained IFN compared with 4 CRs and 18 PRs in the patients who received treatments that did not contain IFN. 5 CRs and 20 PRs occurred in patients treated with TMX compared with 8 CRs and 16 PRs in those treated without TMX. Response differences were non-significant. There was no significant difference in survival time among any of the different groups. Significantly more severe and life-threatening toxic events occurred with treatments that contained IFN.

Randomized Trials with Cytotoxic Agents and Cytokines

Several randomized studies were performed testing the beneficial effect of IFN. A decade ago, Falkson et al. [11] reported on a two-arm study comparing DTIC versus DTIC plus IFN in only 64 patients suggesting a significant better RR in the IFN-treated patients (53%) than in the DTIC alone arm (20%). These results could not be reproduced in a number of controlled randomized trials including ones by Falkson and her group [10].

IFN was tested not only in combination with cytotoxic drugs but also in combination with high-dose intravenous bolus interleukin-2 (IL-2) versus high-dose IL-2 alone in 85 patients. There was no significant difference in the median survival duration (around 10 months). The authors concluded that IFN failed to enhance significantly the response rate to high-dose IL-2 in the treatment of patients with advanced melanoma. Adding cisplatin to both arms (as recently published) did not change overall survival time and RR significantly [12].

Whether a combination of IFN and high-dose IL-2 plus/minus cisplatin is active in metastatic melanoma was asked by Keilholz et al. [13]. 138 patients were accrued for the trial. The objective RR was 18% without and 33% with cisplatin ($p = 0.04$), but there was no statistically significant difference in survival between treatment arms. The effect of adding IFN and IL-2 to chemotherapy was also addressed by Rosenberg et al. [14]. 102 patients were prospectively randomized to receive chemotherapy composed of DTIC, TXM and cisplatin, or this same chemotherapy followed by IFN and IL-2. In patients randomized to receive chemotherapy, 14/52 objective responses (27%) were observed, in comparison to 22/50 objective responses (44%) in patients randomized to receive chemoimmunotherapy. In both treatment groups, the duration of partial responses was often short, and there was a trend toward a survival advantage for patients receiving chemotherapy alone. Treatment-related toxicities were greater in patients receiving chemoimmunotherapy. The German Melanoma Study Group (DeCoG) asked for the benefit of IL-2 in combination with DTIC and IFN [15]. 290 patients were randomized and no difference in terms of survival time from treatment onset between the two arms (median 11.0 months each) was detected. RR did not differ between both arms with 18.0% objective responses for DTIC plus IFN-alpha as compared to 16.1% for DTIC, IFN-alpha and IL-2.

The above quoted meta-analysis based on more than 3,500 patients came to the conclusion that the combination of DTIC plus IFN produced an increased RR than that observed with DTIC alone. This increase was greater than that seen with DTIC-containing multi-drug regimens. Unfortunately, no difference in overall survival was demonstrated.

Conclusion

A recent Cochrane review states that no trial has been performed to demonstrate the beneficial effect of chemotherapy in metastatic melanoma compared to best supportive care [4]. Since it is currently unclear whether any combination therapy for the treatment of metastatic melanoma is superior to standard single-agent DTIC in terms of RR and overall survival, single-agent DTIC remains the gold standard for advanced melanoma in first-line treatment.

Whether novel treatment approaches such as the modulation of drug resistance by infusing antisense oligonucleotides targeted against bcl-2 mRNA to increase melanoma cell apoptosis and subsequently leading to improve tumor responses and overall survival times in combination with DTIC, is currently under investigation in a worldwide prospective-randomized registration trial. Results are expected early in 2003. A second glimpse of hope in the palliative treatment of advanced melanoma is a recent multicenter study led by Agarwala [16] which suggests that histamine dihydrochloride exhibits unexpected clinical benefits in patients with metastatic

melanoma of the liver, thus achieving for the first time a significant survival advantage for metastatic melanoma patients using a combination of histamine and IL-2 in comparison to patients treated with IL-2 alone. Worldwide there is a confirmatory registration trial currently under preparation which is supposed to start in early 2002. Similar successes are also been expected by various vaccination approaches aiming at the induction of cellular (and humoral) immune response. However, most of these studies are still on a phase I/II level and industrial support is missing. Older vaccinations employing whole tumor vaccines have not been tested in prospective randomized fashion (reviewed in [17]). Only one prospective-randomized clinical phase II/III trial comparing DTIC alone versus

peptide-pulsed autologous dendritic cells is ongoing in Germany and supported by the German Cancer Aid. Results are expected in 2–3 years.

Last but not least, second-line chemotherapy in advanced melanoma is frequently performed, however, no randomized controlled phase II or III study has so far been performed.

Is there a standard for the palliative treatment of melanoma? Based on the evidence-based criteria outlined above, patients suffering from all stages of advanced melanoma should only be entered into controlled prospective (randomized) clinical protocols in the first- and second-line situation to improve the current situation in the long-term for the sake of our patients.

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