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ANTI-TUMOUR TREATMENT

Treatments for metastatic melanoma: Synthesis of evidence from randomized trials

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Data pooling

Summary *Background:* Advanced melanomas (non-resectable Stage-III/IV) are fatal, with few effective treatments. It remains unclear if other drugs offer improvements over the standard, dacarbazine.
Purpose: We quantified objective response rates (Complete + Partial response) of dacarbazine versus comparators for advanced cutaneous melanoma.
Methods: We retrieved all head-to-head randomized controlled trials involving dacarbazine and other drugs/combinations. Two reviewers searched MEDLINE (1966–Jan 2006), EMBASE (1980–2006), CINAHL (1982–2006) and Cochrane library, then compared results. Differences were resolved through consensus. Rates were combined using random effects meta-analysis. χ^2 tested heterogeneity; points from Jadad's method were assessed to examine study quality.
Results: We found 48 studies having 111 active treatment arms [24 with dacarbazine monotherapy ($n = 1390$), 75 with dacarbazine combinations ($n = 4962$), and 12 with non-dacarbazine treatments ($n = 783$)] treating 7135 patients. Overall, study quality was poor. Response to dacarbazine monotherapy ranged between 5.3% and 28.0% (average 15.3%), OR = 1.31, $CI_{95\%}$: 1.06–1.61; $N = 3356$. Partial responses comprised 73% of successes. Only adding interferons improved response rates (OR = 1.69, $CI_{95\%}$: 1.07–2.68, $N = 778$) but survival duration was not significantly longer ($P = 0.32$), and trials with larger sample sizes found lower success rates. All other treatments alone or in combination were ineffective $P > 0.05$.

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Conclusions: Dacarbazine generally produces poor outcomes. Adding other therapies offers minimal clinical advantages (possibly with interferons). In general, study quality was poor and sample sizes were small. This meta-analysis highlights the unmet need for effective treatment options for advanced melanoma.

Introduction

The worldwide incidence of melanoma is rising rapidly with an annual increase by 3–7%.[1] In the United States, the incidence almost tripled among males and more than doubled among females between 1973 and 1997.[2] The incidence is approximately 22 per 100,000 for males and 14 for females.[2] This translates to approximately 59,580 new diagnoses and 7770 deaths from melanoma in 2005.[2]

In the early stages of melanoma, surgery represents a potential curative modality. However, in non-resectable Stage III or IV malignant melanoma, the prognosis remains very poor. The median survival of Stage IV disease is approximately 6–10 months with only about 4–6% surviving to 5 years.[3,4]

Systemic chemotherapy is the mainstay of treatment, but it is generally considered palliative rather than curative. In the absence of placebo-controlled trials, dacarbazine (also known as DTIC) is currently considered the treatment of choice.[5] Unfortunately, the response rate remains low and duration of response is short. Other treatment options include alkylating agents, antineoplastic antibiotics (anthracyclines), platinum agents, vinca alkaloids, nitrosoureas, tamoxifen, biological response modifiers and immunotherapies. Some have shown promising results, but it is unclear which treatments offer substantial survival improvements in treating malignant melanoma. To further add to the complexity, much effort has been made to combine various single active agents for potential additive or synergistic effect. Some of these studies have claimed higher response rates than with monotherapy. However, many did not include a reference treatment arm making it difficult to compare their relative efficacies across different studies, so the situation remains unclear.

Several reviews have been published on this topic. Some have been narrative reviews that were concerned only with the clinical diagnosis and medical management of the disease.[6–8] Others have had a narrow focus, such as metastases to the brain[9,10] or the effects of biochemotherapy.[11] A number of systematic reviews have been done, but have not quantitatively combined the data.[12,13] At least two meta-analyses have been published during the present decade. One by Lens et al.[14] was restricted to an examination of tamoxifen. Finally, a meta-analysis by Huncharek et al.[15] compared dacarbazine alone versus dacarbazine in combinations in Stage IV patients, however, they included trials only until 1999. Much has changed since that time, so an update at this time would be appropriate.

We undertook the current study to characterize the efficacy and safety of dacarbazine alone and in combinations in treatment of non-resectable Stage-III and Stage-IV cutaneous melanoma. We sought to answer the following research questions by reviewing the published literature on the topic:

(a) Primary analyses
   1. Does the addition of any other drug therapy provide a clinical advantage over dacarbazine monotherapy in these patients?
   2. Are there treatment regimens that have ecacy superior to dacarbazine monotherapy?

(b) Secondary analyses
   3. What are the reported rates of serious (i.e., Grades 3 and 4) side eects of treatments for malignant melanoma?
   4. What is the quality of randomized controlled trials of treatments of this disease?

Methods

We included any phase II or III randomized controlled trials (RCTs) published in any language in peer-reviewed journals. Patients were adults with non-resectable Stage III or IV cutaneous malignant melanoma, staged according to the system of the American Joint Committee on Cancer (AJCC).[16] Studies must have contained at least one treatment arm with dacarbazine either as monotherapy or in combinations. The comparator arm could include any other systemic chemotherapy, such as:, biologic response modifier (such as interferon or interleukin), immunostimulating therapy (such as bacillus Calmette-Guerin or *Corynebacterium parvum*), combinations of agents or standard care/placebo. Studies were excluded if they involved local therapies such as surgery, radiation, or if they included patients having non-cutaneous melanoma. The outcomes of interest were success rate (i.e., objective response rate, which is the sum of complete response plus partial response) and median survival.

The following databases were searched: MEDLINE (1966–2006), EMBASE (1980–2006), CINAHL (1982–2006) and Cochrane library. We used the search term ''melanoma'' as Medical Subject Heading (MeSH) (if not available then as keyword) and combined with ''metastases'', ''metastatic'', or ''disseminated'' as keywords. The references of relevant articles were also searched to identify other relevant articles. No language restriction was applied. All possible articles were screened by two independent investigators and relevant articles were retrieved.

Two investigators independently extracted the data from accepted articles using a standardized data collection form. The following information was extracted: year of publication, inclusion and exclusion criteria, number of patients randomized (if not available, number of evaluable patients, i.e., eligible patients who were treated), number of patients lost to follow-up, drug regimens, median duration of survival, complete and partial responses, stable and progressive diseases, Grades 3 and 4 side effects including nausea, vomiting, neutropenia, anemia, thrombocytopenia,