

Systemic treatments for metastatic cutaneous melanoma (Review)

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[Intervention Review]

Systemic treatments for metastatic cutaneous melanoma

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ABSTRACT

Background

Systemic therapies for metastatic cutaneous melanoma, the most aggressive of all skin cancers, remain disappointing. Few lasting remissions are achieved and the therapeutic aim remains one of palliation.

Many agents are used alone or in combination with varying degrees of toxicity and cost. It is unclear whether evidence exists to support these complex regimens over best supportive care / placebo.

Objectives

To review the benefits from the use of systemic therapies in metastatic cutaneous melanoma compared to best supportive care/placebo, and to establish whether a 'standard' therapy exists which is superior to other treatments.

Search strategy

Randomised controlled trials were identified from the MEDLINE, EMBASE and CCTR/CENTRAL databases. References, conference proceedings, and Science Citation Index/Scisearch were also used to locate trials. Cancer registries and trialists were also contacted.

Selection criteria

Randomised controlled trials of adults with histologically proven metastatic cutaneous melanoma in which systemic anti-cancer therapy was compared with placebo or supportive care.

Data collection and analysis

Study selection was performed by two independent reviewers. Data extraction forms were used for studies which appeared to meet the selection criteria and, where appropriate, full text articles were retrieved and reviewed independently.

Main results

No randomised controlled trials were found comparing a systemic therapy with placebo or best supportive care in metastatic cutaneous melanoma.

Authors' conclusions

There is no evidence from randomised controlled clinical trials to show superiority of systemic therapy over best supportive care / placebo in the treatment of malignant cutaneous melanoma.

Given that patients with metastatic melanoma frequently receive systemic therapy, it is our pragmatic view that a future systematic review could compare any systemic treatment, or combination of treatments, to single agent dacarbazine.

PLAIN LANGUAGE SUMMARY

Treatments for melanoma (an aggressive type of skin cancer) that has spread to other tissues.

There are no randomised trials comparing the effects of systemic therapies for metastatic cutaneous melanoma with best supportive care or placebo. Cutaneous melanoma is the most aggressive form of skin cancer. When it has spread (metastatic cutaneous melanoma), the prognosis is very poor. Current practice, based upon the results of non comparative studies, is to use different forms of chemotherapy (anti cancer drugs) as well as drugs that try to affect the immune system's response to the cancer. Combinations of these two types of therapy have improved the outcome in some forms of cancers, and are used for melanoma. However the review found no trials which compared the outcome of treatments, used alone or in combination, with the outcome of best supportive care or placebo.

BACKGROUND

Description of the condition

Cutaneous melanoma, the most aggressive of all skin cancers, is increasing in incidence. In 1990 there were 3100 new cases in the UK. Although the mortality rates are rising less quickly, there are still 1200 deaths per year from disseminated disease (U.S. incidence 18000, mortality 5500). The diagnosis of metastatic melanoma carries a poor prognosis with a median survival of six months. Systemic therapy for advanced disease is unsatisfactory, with a variety of agents used alone or in combination, usually with disappointing outcomes. There are few lasting remissions achieved and treatment intent is usually one of palliation.

Description of the intervention

Dacarbazine (DTIC, di-methyl triazeno imidazole carboxamide) is the most tested single chemo-therapeutic agent. When used alone it has partial response rates (greater than 50% reduction in tumour size for a duration of more than 4 weeks) of approximately 15 to 28%, complete responses in 3 to 5% and long-term remissions of less than 2% (Skibba 1969; Burke 1970; Gottlieb 1971; Cowan 1971; Nathanson 1971; Vogel 1971; Costanza 1972; Luce 1972; Wagner 1972; Gerner 1973; Moon 1975). These Phase One and Two studies are remarkable for their consistency in the responses seen. With current anti-emetics, it is well tolerated and is considered by many to be the 'gold standard' if one exists, against which other therapies should be tested (Balch 1993; Cascinelli 1995; Taylor 1995; Pritchard 1980).

Many other drugs such as platinum agents, vinca alkaloids, nitrosureas and more recently taxanes have been tried alone and in various combination regimens. Higher response rates have been

claimed for some of these but it remains unclear whether they offer significant improvement in quality of life or survival over single agent therapy. Tamoxifen, an oestrogen receptor blocking agent widely used in the treatment of breast cancer, has also been used, usually in conjunction with cytotoxic agents and may modify the disease response to such drugs. Again, whether any additional benefit is conferred by this approach is uncertain.

The importance of the immune system in metastatic melanoma, as evidenced by lymphoid infiltration into tumour and surrounding tissues and reported spontaneous remissions, has long been known (Balch 1993; Cascinelli 1995; Taylor 1995). This has led to attempts to modulate the immunological environment of tumours, usually by the use of cytokines, especially interferon-alpha and interleukin-2, given directly or by gene therapy. This has improved the outcome in other tumours (Atzpodien 1997). For theoretical reasons of synergy and in an attempt to improve the efficacy of existing regimens, these agents have been combined with cytotoxic agents. Once again it is unclear whether such combinations offer a therapeutic advance over simpler and less toxic treatments.

Why it is important to do this review

In view of the many treatments available which vary in terms of complexity and cost, the purpose of this review was to ascertain whether a 'gold standard' therapy exists in this disease i.e. whether any therapy has been consistently shown to be better than best supportive care/placebo. It was our impression that for metastatic cutaneous melanoma few, if any, such randomised controlled trials (RCTs) had been undertaken. If this is the case we propose to perform a second review which is pragmatic, and perhaps more clinically relevant, of RCTs comparing any systemic agent (s) with dacarbazine (DTIC) alone.

A glossary of terminology can be found in Appendix 1.

OBJECTIVES

To review the benefits from the use of any systemic therapy compared with supportive care/placebo in metastatic cutaneous melanoma.

If possible to establish a 'gold standard' therapy in this disease, against which other agent(s) / treatment(s) can be compared in a future review.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomised studies, see: Locating and selecting studies. In: Cochrane Collaboration Handbook, Version 4 (Mulrow 1997)

Types of participants

Adults with histologically proven metastatic cutaneous melanoma (UICC staging: T any stage, N any stage, M 1a/b). Patients with non-cutaneous melanoma (e.g. ocular or mucosal melanoma) or where the primary site of origin was unknown, were excluded.

Types of interventions

Systemic therapy versus placebo/best supportive care. For these purposes systemic therapy was cytotoxic chemotherapy and immunotherapy, with or without hormone therapy.

Types of outcome measures

Primary outcomes

Survival:

- a) Overall survival (one, two or five years etc)
- b) Median survival
- c) Progression free survival

Secondary outcomes

1. Quality of life:

As measured by appropriate and valid QOL tool (EORTC 1994).

2. Response rates:

Modified WHO response criteria (EORTC 1994), as below:

Complete response = the disappearance of all known disease

Partial response = 50% or more reduction in tumour size

Stable disease = less than 50% tumour reduction or 25% tumour increase

Progressive disease = 25% or more increase in tumour size

3. Treatment morbidity:

Treatment related toxicity using common toxicity criteria (NCI/WHO/EORTC/MRC) (EORTC 1994):

Grade 0 - no toxicity,

Grade 1 - mild toxicity

Grade 2 - moderate toxicity

Grade 3 - severe toxicity requiring treatment

Grade 4 - life threatening toxicity

4. Health economics:

Financial and resource implications, where available, of treatments given.

5. Non pre-specified outcomes judged important when performing this review.

Search methods for identification of studies

Electronic searches

See: Locating and selecting studies. In: Cochrane Collaboration Handbook, Version 4 (Mulrow 1997). All searches were conducted without language restrictions, as follows:

On-line/electronic database searches

- a. Cochrane controlled Trials Register
- b. MEDLINE (1967-present)
- c. EMBASE (1974- present)

All searches were performed using subject headings (MeSH) and key words (Optimal Search Strategy for RCTs - Dickerson, Appendix 5c., Cochrane Collaboration Handbook) (Mulrow 1997).

All electronic searches were conducted independently by two reviewers, one clinician with subject knowledge and a librarian with subject-specific search experience.

Searching other resources

1. Hand searches are being performed of the following journals back to 1967:

Journal of Clinical Oncology

Cancer Research

British Journal of Cancer

Cancer

European Journal of Cancer

Journal of the National Cancer Institute

2. Reference lists were handsearched for eligible studies. The source of reference lists included:

Studies identified in 1 and 2 above
Systematic reviews, review articles and meta-analyses located from:

- a. Cochrane controlled Trials Register
 - b. Medline (1967-present)
 - c. The York Database of Abstracts of Reviews of Effectiveness (DARE)
- Relevant clinical textbooks

3. Science Citation index/Scisearch to locate where key articles had been cited.

4. The following registries and organisations were contacted and/or searched for relevant open and closed studies;

The UKCCCR Cancer Trials Register
The UK National Research Register
Current Controlled Trials Register (including Pharmaceutical Trials Registers)
The National Cancer Institute, America (PDQ and CancerNet)
The National Cancer Institute, Canada
The European Organisation for Research and Treatment of Cancer
The National Health and Medical Research Council of Australia
The WHO Collaborating Centres for Evaluation of Methods of Diagnosis and Treatment of Melanoma

5. Colleagues, known specialists within the subject area, and first name authors of retrieved studies were contacted regarding their knowledge of any other published/unpublished data.

Data collection and analysis

See: Critical Appraisal of Studies and Collecting Data. In: Cochrane Collaboration Handbook, Version 4 (Mulrow 1997) and Chalmers 1989.

All abstracts were examined by at least one reviewer. Where it was felt that the citation referred to a clinical trial, full text articles were obtained and scrutinised by two reviewers to determine whether the study design, participants and outcome measures enabled a satisfactory comparison of interventions. Where these details were not clear from the publication, authors were contacted to obtain further clarification.

RESULTS

Description of studies

No studies were found

Results of the search

944 abstracts were retrieved. The sources of the abstracts were:
MEDLINE 592

EMBASE 153

Cochrane trials register 156

Database for Reviews of Effectiveness 3

Science Citation index 60

These were mostly Phase One/Two Studies of systemic therapy in malignant melanoma, often in the adjuvant (curative) setting. There were some randomised controlled trials comparing two active treatment arms i.e. the comparative arm was not best supportive care/placebo. Some were reviews.

We retrieved full text articles in 56 cases. Fifteen of these were reviews and 41 were non-eligible trials (Phase One/Two or non placebo/best supportive care). International experts replied to requests for their knowledge of published/unpublished data or studies. These have been acknowledged below. No relevant RCTs were known. None of the other search strategies above revealed any appropriate RCTs.

The handsearching of the journals noted above is ongoing. Results will be used to update the findings of this review. We will also update this review with the results of handsearches of other journals such as The Lancet and The New England Journal of Medicine etc and of Proceedings of learned societies.

Risk of bias in included studies

Not applicable

Effects of interventions

No RCTs were retrieved, so no analysis of the effects of the interventions was carried out.

DISCUSSION

No randomised controlled trials were found comparing a systemic therapy with placebo or best supportive care in metastatic cutaneous melanoma. There is no evidence from randomised controlled clinical trials to support a single, tried and tested 'gold standard' therapy in the treatment of malignant cutaneous melanoma against which other treatments can be compared.

It is perhaps understandable that in a disseminated disease which is devastating and where there is a tolerable, convenient and possibly effective therapy such as dacarbazine (DTIC), that investigators and/or patients would be unwilling to randomise to receive no treatment.

Dacarbazine is given intravenously, usually on an outpatient basis, 250 mg/m² on days 1 to 4/5 every 3 to 4 weeks or 800 to 1000 mg/m² daily once every 3 to 4 weeks. It can cause nausea and vomiting, though with modern anti-emetic schedules including 5HT-3 antagonists such as granisetron and ondansetron it is usually well tolerated. It can also suppress the bone marrow's production of blood cells (dose limiting) and more rarely causes diarrhoea and a flu-like syndrome 7 to 14 days after administration.

Although no RCTs were found comparing DTIC with best supportive care/placebo, dacarbazine has been used as the 'control' arm in more than 20 prospective RCTs (Bellet 1976; Lopez 1984; Luikart 1984; Veronesi 1984; Ringborg 1989; Falkson 1991; Cocconi 1992; Thomson 1993; Bajetta 1994). It is of note that in these randomised studies the response rates to single agent DTIC were, although slightly more variable, of the same order (9.1% to 29%) as the Phase One and Two studies. We propose to systematically review these and other controlled trials found, to determine the difference, if any exists, in efficacy, tolerability and cost between single or combinations of agents versus DTIC alone.

AUTHORS' CONCLUSIONS

Implications for practice

For the majority of patients, the goal of systemic treatment must be to achieve palliation with a minimum of unwanted side effects, and with minimum disruption to their quality of life. Dacarbazine remains the most tested therapy; is probably, moderately effective and is reasonably well tolerated. In a routine treatment setting it should, therefore, remain the treatment of choice. Ongoing studies

with newer agents such as temozolamide might show them to be useful alternatives. Combination bio-chemotherapy should not be prescribed outside of a clinical study or clinical trial.

Implications for research

The most urgent priority is to develop more effective systemic treatments for patients with metastatic melanoma. Such treatments can only be evaluated properly within the context of a properly designed clinical trial, and the relevant bodies should support such clinical research. For patients with incurable disease, in whom palliation is the goal, there is still scope for research aimed at defining the best systemic treatment (for example, a randomised trial of temozolamide versus DTIC). Unfortunately, it seems unlikely that a randomised trial of simple chemotherapy (e.g. with DTIC) versus best supportive care, will ever be performed, but there is a clear scientific need for such a study.

Given the lack of evidence from randomised controlled studies for any systemic therapy versus best supportive care, it is our view that a pragmatic approach would be to perform a systematic review of any systemic treatment, or combination of treatments, compared to single agent DTIC.

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* Indicates the major publication for the study

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 21 February 2000.

17 July 2008	Amended	Converted to new review format.
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HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 2, 2000

22 February 2000	New citation required and conclusions have changed	Substantive amendment
28 September 1999	New search has been performed	Update and conclusions changed
28 September 1999	Amended	Minor update
28 September 1999	Amended	Reformatted
28 June 1999	Amended	New studies sought but none found
25 June 1999	New search has been performed	New studies found but not yet included or excluded

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Velindre NHS Trust, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Melanoma [*drug therapy; *secondary]; Skin Neoplasms [*drug therapy; pathology]

MeSH check words

Humans