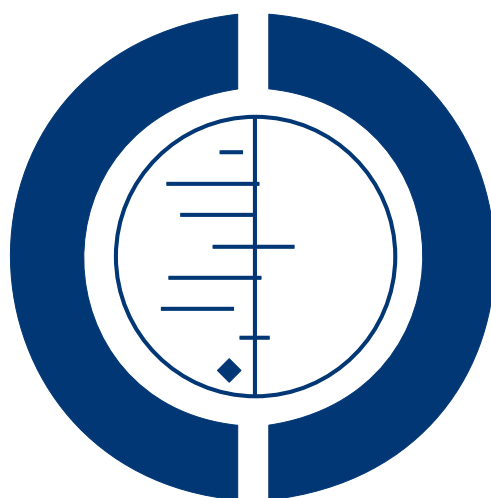


Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma (Review)

Sasse AD, Sasse EC, Clark LGO, Ulloa L, Clark OAC



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Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma (Review)
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[Intervention Review]

Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma

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ABSTRACT

Background

Malignant melanoma, one of the most aggressive of all skin cancers, is increasing in incidence throughout the world. Surgery remains the cornerstone of curative treatment in earlier stages. Metastatic disease is incurable in most affected people, because melanoma does not respond to most systemic treatments. A number of novel approaches are under evaluation and have shown promising results, but they are usually associated with increased toxicity and cost. The combination of chemotherapy and immunotherapy has been reported to improve treatment results, but it is still unclear whether evidence exists to support this choice, compared with chemotherapy alone. No language restrictions were imposed.

Objectives

To compare the effects of therapy with chemotherapy and immunotherapy (chemoimmunotherapy) versus chemotherapy alone in people with metastatic malignant melanoma.

Search strategy

We searched the Cochrane Skin Group Specialised Register (14 February 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 3, 2005), MEDLINE (2003 to 30 January 2006), EMBASE (2003 to 20 July 2005) and LILACS (1982 to 20 February 2006). References, conference proceedings, and databases of ongoing trials were also used to locate trials.

Selection criteria

All randomised controlled trials that compared the use of chemotherapy versus chemoimmunotherapy on people of any age, diagnosed with metastatic melanoma.

Data collection and analysis

Two authors independently assessed each study to determine whether it met the pre-defined selection criteria, with differences being resolved through discussion with the review team. Two authors independently extracted the data from the articles using data extraction

forms. Quality assessment included an evaluation of various components associated with biased estimates of treatment effect. Whenever possible, a meta-analysis was performed on the extracted data, in order to calculate a weighed treatment effect across trials.

Main results

Eighteen studies met our criteria and were included in the meta-analysis, with a total of 2625 participants. We found evidence of an increase of objective response rates in people treated with chemoimmunotherapy, in comparison with people treated with chemotherapy. Nevertheless, the impact of these increased response rates was not translated into a survival benefit. We found no difference in survival to support the addition of immunotherapy to chemotherapy in the systemic treatment of metastatic melanoma, with a hazard ratio of 0.89 (95% CI 0.72 to 1.11, $P = 0.31$). Additionally, we found increased hematological and non-hematological toxicities in people treated with chemoimmunotherapy.

Authors' conclusions

We failed to find any clear evidence that the addition of immunotherapy to chemotherapy increases survival of people with metastatic melanoma. Further use of combined immunotherapy and chemotherapy should only be done in the context of clinical trials.

PLAIN LANGUAGE SUMMARY

Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma

Malignant melanoma is one of the most aggressive of all skin cancers. If it is confined to the skin, it can often be cured by surgery. However if it has spread, melanoma is usually incurable because it does not respond to most treatments. Recently clinicians have been trying a combination of chemotherapy and immunotherapy in the hope of improving the outcome. The review of trials showed an increased response to treatment when immunotherapy was added to chemotherapy, but no difference was seen in survival rate and toxic effects were increased.

There is not enough evidence to support the use of a combination of combined immunotherapy and chemotherapy in treatment of metastatic malignant melanoma.

BACKGROUND

Description of the condition

Epidemiology and progress of melanoma

Malignant melanomas develop due to changes in the melanocytes cells that produce melanin pigment. Melanomas are most commonly found in the skin, but can also be found in the uveal tract (back of the eye), upper digestive tract, anal canal, rectum and vagina.

Malignant melanoma of the skin accounts for 1 to 3% of all malignant tumors and there has been an increase in its incidence of 6 to 7% each year since 1985 (La Vecchia 1999; Wingo 1995). However, the overall mortality rate has only slightly increased, probably due to an increase in the early diagnosis of lesions that have a better prognosis (Leong 2003).

As with other tumors, the stage (progress) of the disease is still an important determinant of survival. In the earlier stages, melanoma

is confined to the skin, where the disease is curable in a high percentage of cases through surgical removal of the tumor (Nathan 1998). The 5 year survival rate for melanoma that is confined to the skin is 80 to 100% (Nathan 1998), depending on the thickness of the primary tumor.

In people where the cancer has spread to the lymph nodes (nodal disease), three variables independently affect the prognosis:

1. the number of positive lymph nodes,
2. the presence of ulceration within the primary tumor,
3. whether the nodal disease is macroscopic (an enlarged lymph node can be felt by a doctor) or microscopic (the lymph node cannot be felt, but abnormal melanoma cells are present and can be seen when viewed under a microscope) (Balch 2001).

In people with macroscopic disease, more than one positive node, and an ulcerated primary tumor, the 5 year survival rate is only 16%. In people with one microscopically positive lymph node and without ulceration in the primary lesion, the 5 year survival rate is 71% (Balch 2001).

The detection of lymph node metastases previously relied on crude clinical or regional elective lymph node dissection (removal of a whole group of lymph nodes responsible for draining a particular area of the body), but several large randomised controlled trials have shown no improvement in survival using this technique. Currently, sentinel lymph node mapping and directed selective lymphadenectomy (i.e. only removing those nodes that show up as positive using the sentinel node imaging technique) has been shown to identify lymph node metastases more precisely and with less surgical morbidity than elective dissection (Gershenwald 1999).

Causes

Although the cause of melanoma is unknown, major risk factors have been identified (Koh 1991). Epidemiological studies suggest that sunlight (ultraviolet radiation) is the most common environmental factor. Pale skin, a tendency to sunburn, fair or red hair, large numbers of melanocytic nevi (moles) and multiple dysplastic nevi (atypical moles) have been shown to be independent risk factors for the development of melanoma. Fair skin that does not tan easily in combination with high sun exposure provides the largest cumulative risk factor for melanoma development (Rigel 1989).

Impact

Malignant melanoma that has spread to distant sites by dissemination is associated with extremely poor survival: median survival is approximately 8 months, and less than 5% of such people will survive for more than 5 years (Lee 2000).

There are large prospective, randomised, multicenter trials that have answered some basic management questions, improved the care of melanoma sufferers, and expanded our understanding of the disease. However, many aspects of treatment, such as the therapeutic role of cytotoxic chemotherapy and biologic therapy, alone or in combination, remain controversial and inconclusive (Crosby 2000; Leong 2003).

Description of the intervention

Systemic therapy

This has little or no impact on survival for advanced disease. There is no evidence derived from randomised controlled trials to show superiority of systemic therapy over supportive care (Crosby 2000). The minority of people with metastatic melanoma who do respond to systemic treatment have remissions which are generally of short duration (Nathan 1998). Few agents have demonstrated substantial anti-tumor activity against metastatic melanoma. The alkylating agent dacarbazine (DTIC) is considered to be the most active drug for the treatment of this disease, with a response rate of 20%, and a median duration of response of 4 to 5 months (Khayat

2002; Nathan 1998). Other cytotoxic compounds, such as temozolomide (a dacarbazine analogue) (Middleton 2000), cisplatin and carboplatin (Bajetta 2002), vinca alkaloids (Khayat 2002), taxanes (Bafaloukos 2002) and nitrosoureas (Cure 1999) have not improved these results. All of these treatments are associated with response rates of less than 15% and all are associated with significant adverse effects (Bafaloukos 2002; Bajetta 2002; Cure 1999; Khayat 2002; Middleton 2000).

Combination chemotherapy

The role of combination chemotherapy in advanced disease remains unclear. Prospective randomised studies have failed to demonstrate any significant benefit for combination chemotherapy when compared with single agents, except for a slight increase in response rates (Huncharek 2001).

Experimental treatments

Experimental treatments, such as vaccines, antibody treatments, and gene therapy are being developed and are of high scientific interest. However, their efficacy in advanced melanoma has so far been very limited, with overall response rates of less than 5% (Keilholz 2002; Stopeck 2001). Since the 1970s, immunostimulating agents such as Bacillus Calmette-Guerin (BCG) (Lokich 1979; Osborn 1977), *Corynebacterium parvum* (Osborn 1977), or isoprinosine (Tsang 1983) have been evaluated as local or systemic treatments. After some early hopes, all these treatments have also failed to demonstrate a significant and consistent effect in the clinical management of advanced melanoma (Khayat 2002).

Immunotherapy

Two points have driven the attention of researchers in the immunology field to melanoma. Firstly, the spontaneous regression of melanoma (i.e. the tumor occasionally appears to go away in some people). Spontaneous regression is much more frequent than in melanoma than with any other solid tumor and it is associated with a specific cellular immune response (Kadison 2003). Secondly, the fact that some people with melanoma also have tumor rejection antigen recognized by CD4 and CD8 T cells (immune cells that can help get rid of cancer cells) (Kadison 2003).

At least two types of immunotherapy have been used in advanced melanoma; interferon-alpha and interleukin-2.

Interferon-alpha (IFN- α) belongs to a group of proteins known to have antiproliferative and antitumor effects (Garbe 1990). In addition, IFN- α exhibits certain immunomodulatory effects - it upregulates the expression of major histocompatibility complex (MHC) class I antigens in melanoma cells and also the expression of co-stimulatory molecules, rendering the cells more susceptible to immunological defense mechanisms (Barth 1995). Phase II studies of IFN- α , as a single agent, have demonstrated response rates of approximately 20%, with a slightly more durable response

than the one found with dacarbazine (DTIC) (Creagan 1984; Dorval 1986; Sertoli 1989).

Interleukin-2 (IL-2) is a major growth factor for lymphoid cells, including T cells and natural killer (NK) cells (Hanninen 1991; Smith 1993). Clinical trials have demonstrated modest anti-tumor activity in people with metastatic melanoma (Rosenberg 1989); responses were seen in approximately 15% of people, with a small proportion of complete responses (Dutcher 1989; Rosenberg 1989).

Chemoimmunotherapy

As chemotherapy and immunotherapy have different and perhaps synergistic mechanisms of action, their combination of immunotherapy with chemotherapy (chemoimmunotherapy) has been studied since the early 1990s (Khayat 2002). Some reports have suggested that chemotherapeutic agents administered in combination with IL-2 or IFN, or both can improve response rates (Legha 1998; Richards 1992), with complete response rates in 10 to 20% of people, as well as increases in median survival (Falkson 1991). Based on these results, the use of chemoimmunotherapy is currently preferred in some institutions as a first-line treatment in advanced (stage IV) melanoma (Kadison 2003; Keilholz 2002), although it is still considered an experimental therapy by others (Crosby 2000).

Why it is important to do this review

There are substantial controversies about the real benefit of chemoimmunotherapy: some studies conclude that the combination of treatments did not improve survival (Rosenberg 1999; Young 2001) or even response rates (Falkson 1998; Gorbonova 2000; Johnston 1998; Thomson 1993) in people with metastatic melanoma. There is also concern that combined therapy may increase treatment-related toxicity (Falkson 1998; Johnston 1998). The lack of conclusive data, coming from seemingly conflicting studies about the impact of treatment, demands a systematic review. This will provide the most reliable assessment for supporting clinical decision-making with people who have advanced melanoma.

OBJECTIVES

To compare the effects of chemotherapy alone versus combined therapy with chemotherapy and immunotherapy (chemoimmunotherapy) in people with metastatic malignant melanoma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People of any age diagnosed with metastatic malignant melanoma that has spread to distant sites by systemic dissemination.

Types of interventions

1. Chemotherapy
2. Chemoimmunotherapy i.e. the combination of chemotherapy and immunotherapy with interferon-alpha or interleukin-2 or both

Types of outcome measures

Primary outcomes

Overall survival - number of participants alive at the end of the trial.

Secondary outcomes

1. One, two, and five-year survival rates - proportion of participants alive at one, two, and five year follow-up
2. Response rates (partial and complete) - proportion of participants that have achieved partial or complete responses, as defined by the trial authors
3. Progression-free survival - number of participants without progression of disease at the end of the trial
4. Treatment morbidity (treatment-related toxicity) - proportion of participants that have developed hematological or non-hematological toxicities
5. Treatment related mortality - proportion of participants that have died due to the treatment. This outcome was not described previously in the protocol and was added after discussion between the reviewers that considered it relevant. Mortality related to treatment is a great concern in oncology, when comparing treatments with potential differences in toxicity
6. Quality of life measures

Search methods for identification of studies

We searched electronic databases and other resources to locate reports of studies. No language restrictions were imposed.

Electronic searches

Electronic databases

We searched the following electronic databases:

1. MEDLINE (OVID) (Appendix 1)
2. The Cochrane Skin Group Specialised Register
3. The Cochrane Central Register of Controlled Trials
4. Medline (PubMed)
5. EMBASE
6. LILACS (Latin American and Caribbean Health Science Information Database).

Search strategies for databases 2 to 6 are located in Appendix 2.

Search of databases of ongoing trials (unpublished literature)

We asked trial authors and pharmaceutical companies about unpublished and ongoing trials. Databases of major research groups and registers of trials, in the following databases were also searched with the term 'MELANOMA':

- Current Controlled Trials Register ([http:// www.controlled- trials.com](http://www.controlled-trials.com)) on 30th January 2006
- European Organisation for Research and Treatment of Cancer ([http:// www.eortc.be](http://www.eortc.be)) on 20th February 2006
- National Cancer Institute, America ([http:// www.cancer.gov/ clinicaltrials/](http://www.cancer.gov/clinicaltrials/)) on 16th November 2005
- National Cancer Institute, Canada ([http:// www.ctg.queensu.ca/ public/ Clinical_Trials/ clinical_trials.html](http://www.ctg.queensu.ca/public/Clinical_Trials/clinical_trials.html)) on 30th January 2006
- Australian Clinical Trials Registry ([http:// www.actr.org.au/](http://www.actr.org.au/)) on 30th January 2006
- U.S. Food and Drug Administration ([http:// www.fda.gov/](http://www.fda.gov/)) on 30th January 2006
- ClinicalTrials.gov ([http:// www.clinicaltrials.gov](http://www.clinicaltrials.gov)) on 16th November 2005.

Searching other resources

References from unpublished studies

All bibliographies of selected studies were scanned for possible references to RCTs.

Conference proceedings

We handsearched the abstracts from conference proceedings of the ASCO (American Society of Clinical Oncology) and ESMO (European Society of Medical Oncology).

Data collection and analysis

Where there was uncertainty, we tried to contact trial authors for clarification.

A consumer (LU) was involved throughout the review process to ensure the readability of the final review. Updating will be done every two years.

Selection of studies

Two authors (ADS and ECS) checked the titles and abstracts identified from the searches. If it was clear that the study did not refer to a RCT on metastatic melanoma, we excluded it. Two authors (ADS and OAC) independently assessed each remaining study to determine whether it met the pre-defined selection criteria. Any differences were resolved through discussion with the review team. Excluded studies are listed in the Table of Excluded Studies.

Data extraction and management

Two authors (ADS and ECS) independently extracted the data from the studies. All data were extracted directly from the text or calculated according to the available information.

Any differences were resolved by discussion with one author (OAC). A data extraction form was developed and piloted in order to summarize the trials. One author (ADS) checked and entered the data. Two authors (ECS and LGC) independently checked the data entry.

Assessment of risk of bias in included studies

Assessment of methodological quality

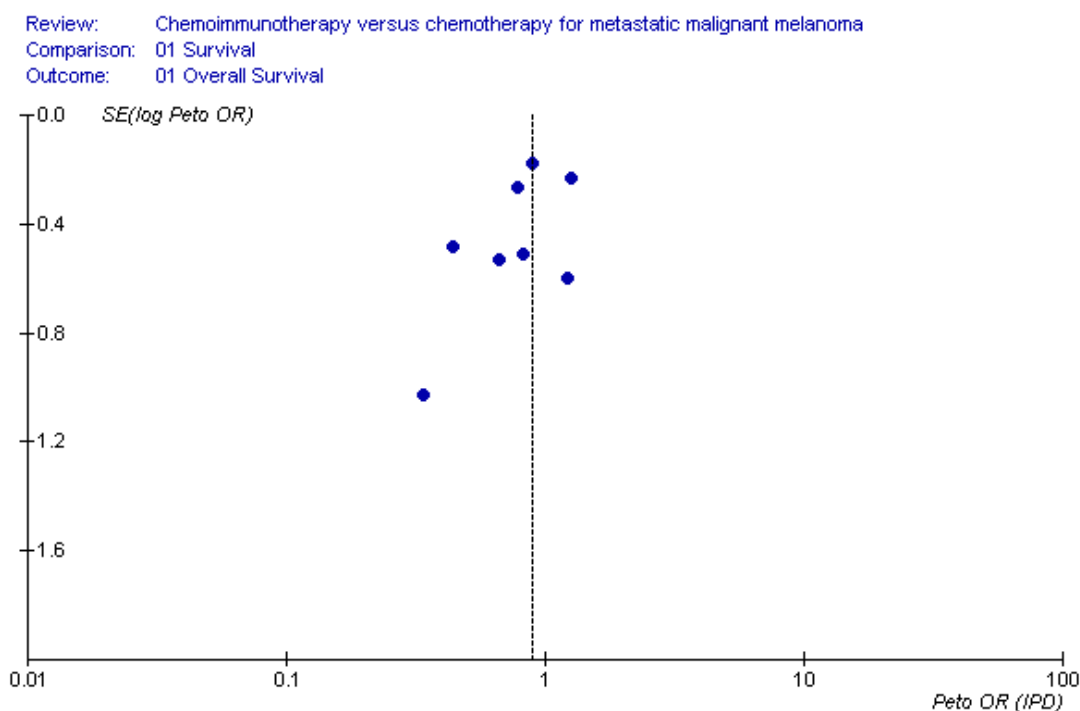
The quality assessment included an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect (Juni 2001):

- (a) the method of generation of the randomisation sequence;
 - (b) the method of allocation concealment - it was considered 'adequate' if the assignment could not be foreseen;
 - (c) who was blinded/not blinded (participants, clinicians, outcome assessors);
 - (d) how many participants were lost to follow up in each arm, and whether participants were analysed in the groups to which they were originally randomised (intention-to-treat).
- In addition the quality assessment also included:
- (e) the source of funding;
 - (f) if the participant had a biopsy proven melanoma;
 - (g) the baseline assessment of the participants for presence of liver and brain metastases, performance status;
 - (h) whether the aims, interventions (including drug doses and duration of treatment) and outcome measures were clearly defined;
 - (i) the use and appropriateness of statistical analyses.
- We recorded all the information in a table of quality criteria and gave a description of the quality of each study based on these characteristics.

Measures of treatment effect

Where possible, we performed a meta-analysis for the outcomes, in order to calculate a weighted treatment effect across trials, using a random-effects model. For binary endpoints, we calculated the risk ratio (RR) with 95% confidence intervals (Yusuf 1985). We also expressed the results as a number needed to treat (NNT) where appropriate, for a range of plausible control event rates. For overall survival, a time-to-event data, we calculated the Hazard Ratio (HR). When data were not available for direct extraction, we calculated indirectly (from different parameters using indirect calculation of the variance and the number of observed minus expected events) according to the method described by Parmar (Parmar 1998). In the funnel plot (Figure 1) and comparison 1 'Peto OR (IPD)' is a Hazard Ratio. For continuous data, such as quality of life, we planned to use standardised mean differences with 95% confidence intervals would have been used.

Figure 1. Funnel plot using overall survival as the outcome



Assessment of heterogeneity

Heterogeneity was assessed using I^2 . Where the heterogeneity was considerable ($I^2 > 50\%$), we explored possible reasons using the type (interleukin-2 or interferon) and dose (high or low) of immunotherapy used as subgroups. Where we were not able to find an explanation, we have recorded this along with appropriate caution in the interpretation of these data.

Data synthesis

Analysis and presentation

Once studies had been selected, critically appraised and the data extracted, we entered the data in the [Characteristics of included studies](#) table.

Three studies (Bajetta 1994; Kirkwood 1990; Vorobiof 1994) evaluated three arms of treatment, with one of them evaluating che-

motherapy alone and the two others using chemoimmunotherapy. One study (Falkson 1998) had four arms, two using chemotherapy and two using chemoimmunotherapy. The data from the similar arms were grouped, considered as one and then compared to the other arm.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

We scanned approximately 700 citations. Initially 28 studies were identified. Four studies (Arance 2000; Chiarion-Sileni 2003; Danson 2002; Falkson 1995) had data that overlapped with three included studies (Danson 2003; Falkson 1991; Ridolfi 2002).

Ongoing studies

No ongoing studies were available to be included in the meta-analysis.

Included studies

Eighteen studies, with a total of 2625 participants, met our criteria and were included in the meta-analysis (please see [Characteristics of included studies](#)). One study differed considerably from the others because vindesine was used as the chemotherapy control, a drug without evidence of response in metastatic melanoma (Vorobiof 1994). Another study differed considerably as lower dose treatment in the chemoimmunotherapy group was used (Middleton 2000). The first study was published in 1990, and the last studies were published in 2003.

Participants

The participants were between the ages of 16 and 88 years, and had an Eastern Cooperative Oncology Group performance status from 0 to 3. Only three studies included participants with brain metastasis (Atzpodien 2002; Danson 2003; Eton 2002).

Interventions

Seven studies compared chemotherapy to chemoimmunotherapy with IFN plus IL-2 (Atkins 2003; Atzpodien 2002; Del Vecchio 2003; Eton 2002; Johnston 1998; Ridolfi 2002; Rosenberg 1999). Eleven compared chemotherapy to chemoimmunotherapy with IFN (Bajetta 1994; Danson 2003; Falkson 1991; Falkson 1998;

Gorbonova 2000; Kirkwood 1990; Middleton 2000; Spieth 2003; Thomson 1993; Vorobiof 1994; Young 2001).

The drugs used in chemotherapeutic schemes varied between the trials. Seven trials evaluated DTIC combined with other drugs in both arms (Atkins 2003; Atzpodien 2002; Del Vecchio 2003; Eton 2002; Johnston 1998; Ridolfi 2002; Rosenberg 1999), and six evaluated DTIC alone as the control (Bajetta 1994; Falkson 1991; Falkson 1998; Kirkwood 1990; Thomson 1993; Young 2001).

Four studies evaluated other schemes without DTIC: two trials used temozolomide (Danson 2003; Spieth 2003), one trial used vindesine (Vorobiof 1994), and one trial used combined drugs based on cisplatin (Gorbonova 2000).

Only one study did not use the same scheme in both the arms, using combined drugs with DTIC as the chemotherapy control, and a lower dose for the chemoimmunotherapy group, with DTIC alone (Middleton 2000).

Setting

Ten studies were carried out in Europe, four in the United States, two in South Africa, and one was a multicentre worldwide trial. All trials were reported in the English language.

Outcomes

Response rates were the primary outcome measures in most trials, and were described in all included studies. Two studies did not evaluate survival rates (Gorbonova 2000; Kirkwood 1990). Three studies included quality of life analyses in the outcomes (Ridolfi 2002; Thomson 1993; Young 2001). The length of the follow-up varied widely between the trials, and sometimes it was not specified. We did not find a reasonable definition about what could be considered high or low doses of immunotherapy, and the influence of the immunotherapeutic doses on the outcomes could not be assessed.

Excluded studies

Six studies were excluded (see [Characteristics of excluded studies](#)). The reasons for exclusion were: that the study had immunotherapy on both arms (Bajetta 2001; Richtig 2004; Sertoli 1999; Sparano 1993; Vuoristo 2005) or the study was not randomised (Legha 1996).

Risk of bias in included studies

The quality assessment consisted of a basic methodological evaluation of each included study, and is shown in [Table 1](#). Additional quality assessment is shown in [Table 2](#). The criteria used for methodological quality analysis of the studies are listed in [Table 3](#) (Explanation of Quality Analysis Headings).

Table 1. Methodological quality analysis

Study ID	Randomization	Allocation Conceal	Blind pat/clin	Blind outcome	Lost to follow up	ITT	Funding
Atkins 2003	unclear	unclear	-	unclear	+	-	public
Atzpodien 2002	+	+	-	unclear	+	+	both
Bajetta 1994	+	+	-	unclear	+	+	pharm
Danson 2003	+	+	-	unclear	+	+	unclear
Del Vecchio 2003	unclear	unclear	-	unclear	+	+	unclear
Eton 2002	unclear	unclear	-	unclear	+	-	pharm
Falkson 1991	unclear	unclear	-	unclear	+	-	both
Falkson 1998	+	+	-	unclear	+	+	public
Gorbonova 2000	unclear	unclear	-	unclear	+	-	?
Johnston 1998	+	+	-	unclear	+	+	?
Kirkwood 1990	+	unclear	-	unclear	+	-	pharm
Middleton 2000	+	+	-	unclear	+	+	unclear
Ridolfi 2002	+	+	-	unclear	+	+	public
Rosenberg 1999	+	+	-	unclear	+	+	unclear
Spieth 2003	unclear	unclear	-	unclear	+	-	unclear
Thomson 1993	+	+	-	unclear	+	-	unclear
Vorobiof 1994	+	+	-	unclear	+	+	unclear

Table 1. Methodological quality analysis (Continued)

Young 2001	+	+	-	unclear	+	+	both
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Table 2. Additional Quality Analysis

Study ID	Biopsy	Baseline	Clearly defined	Statistics
Atkins 2003	-	-	-	+
Atzpodien 2002	+	+	+	+
Bajetta 1994	+	+	+	-
Danson 2003	+	-	+	-
Del Vecchio 2003	+	+	-	+
Eton 2002	+	-	+	+
Falkson 1991	+	+	+	-
Falkson 1998	+	+	+	+
Gorbonova 2000	+	-	-	-
Johnston 1998	-	+	+	+
Kirkwood 1990	-	-	-	-
Middleton 2000	-	+	+	+
Ridolfi 2002	+	+	+	+
Rosenberg 1999	+	+	+	+
Spieth 2003	+	-	-	-
Thompson 1993	+	+	-	+
Vorobiof 1994	+	+	+	-
Young 2001	+	+	+	+

Table 3. Content of Quality Analysis List

Abbreviation	Description
Randomization	Was an adequate method of randomisation performed?
Allocation Conceal	Was the method of allocation concealment adequate?
Blind pat/clin	Were participants and clinicians blinded?
Blind outcome	Was the outcome assessor blinded?

Table 3. Content of Quality Analysis List (Continued)

Lost to follow up	Was there a description of withdrawals and drop-outs? Was it adequate?
ITT	Did the analysis include an intention to treat analysis?
Funding	What was the source of funding? Public, pharmaceutical industry or both?
Biopsy	Was it described the necessity of a biopsy proven melanoma?
Baseline	Were there baseline assessments of the participants for presence of liver and brain metastasis, performance status?
Clear defined	Were the aims, interventions and outcome measures clearly defined?
Statistical	Were appropriate statistical analyses used? Were alpha and beta errors pre-defined?

Although blinding participants and clinicians is theoretically possible, it is difficult to plan a double-blind study with immunotherapy. This is due to the substantial acute and late toxicities associated with immunotherapy in one group. No study was described as double-blinded. The groups at baseline were in general similar, with a description of most prognostic factors related to metastatic melanoma (gender, performance status, age, prior therapy, liver metastasis).

In three studies almost all methodological aspects of the trials were described poorly (Gorbonova 2000; Kirkwood 1990; Spieth 2003).

Allocation

All the included studies were described as randomised, as this was a selection criterion. However, most papers did not describe the method of randomisation. The method of generation of the randomised sequence was described and considered adequate in only 6 out of 18 studies. Eleven of 18 studies provided information on allocation concealment, all of which were considered adequate.

Blinding

Blinding of outcome assessment and detection bias

We did not find information about blinding of the outcome assessors in any included study.

Follow up and exclusions

Handling of losses and attrition bias

In general, there were few participants lost to follow up in the studies. The highest number of people lost was 24 in a total of 262 participants (Bajetta 1994). Eleven studies included an intention-to-treat analysis.

Effects of interventions

Primary outcome

Overall survival (eight studies)

This was considered as the number of participants alive at the end of the trial. Sufficient data were available from 8 of the 18 studies. There was no statistically significant difference in survival between chemoimmunotherapy and chemotherapy, with a hazard ratio (HR) of improved survival of 0.89 (95% CI 0.72 to 1.11, $P = 0.31$; Analysis 1.1) in favour of chemoimmunotherapy. In other words, overall survival was slightly lower in the chemoimmunotherapy group, but this was not statistically significant. There was no heterogeneity across trials ($I^2 = 0\%$). The funnel plot method using overall survival as the outcome is presented in Figure 1. It shows that there was no evidence of substantial publication bias, but interpretation of the funnel plot is likely to be unreliable since only eight relatively large studies were found.

When we evaluated the influence of the type of immunotherapy used in the chemoimmunotherapy group (IL-2 plus IFN-alpha or IFN-alpha only) we found no statistically significant difference between the groups; with a HR of 0.96 (95% CI 0.74 to 1.24, $P = 0.76$; Analysis 1.1) for chemoimmunotherapy with IL-2 plus IFN-alpha, and a HR of 0.74 (95% CI 0.49 to 1.12, $P = 0.15$; Analysis 1.1) for chemoimmunotherapy associated with only IFN-alpha.

Secondary outcomes

One, two, and five-year survival rates (13 studies)

The number of participants alive at one, two, and five year follow-ups were analyzed. Data from 13 trials evaluating one year survival were pooled. There was no statistically significant difference in one year survival between the groups, with a risk ratio (RR) of 1.06 (95% CI 0.91 to 1.24, $P = 0.48$; Analysis 1.2), and no significant heterogeneity across trials ($I^2 = 36.3\%$).

Data from 11 trials evaluating 2 year survival were extracted and pooled. Again, there was no statistically significant difference between the groups, with a RR of 1.08 (95% CI 0.86 to 1.36, $P = 0.50$; Analysis 1.3), without heterogeneity across trials ($I^2 = 0\%$). Only two trials reported data about five year survival. The meta-analysis showed no statistically significant difference in 5 year survival between the groups, with a RR of survival of 2.34 (95% CI 0.97 to 5.65, $P = 0.06$; Analysis 1.4) favouring chemoimmunotherapy. There was no heterogeneity across trials ($I^2 = 0\%$).

Response rates (17 studies)

Data regarding the number of participants with partial or complete responses from 17 trials were used to evaluate objective response rates. The analysis detected a statistically significant difference in favor of chemoimmunotherapy in global response rates, with a RR of 1.40 (95% CI 1.20 to 1.63, $P < 0.0001$; Analysis 2.1). There was no heterogeneity across trials ($I^2 = 4.2\%$). We tried to evaluate the influence of the type of immunotherapeutic in the group of chemoimmunotherapy (IL-2 plus IFN-alpha or IFN-alpha only). We found similar results, with a RR of global response of 1.46 (95% CI 1.19 to 1.79, $p = 0.0002$; Analysis 2.1) in favor of chemoimmunotherapy with IL-2 plus IFN-alpha, and a RR of 1.32 (95% CI 1.02 to 1.71, $p = 0.04$; Analysis 2.1) in favor of chemoimmunotherapy with IFN-alpha. There was no heterogeneity across trials ($I^2 = 0\%$).

Data from 15 trials were used to evaluate partial and complete response rates. We found a statistically significant difference in favour of chemoimmunotherapy in both analyses, with an HR of 1.31 (95% CI 1.07 to 1.59, $p = 0.008$; Analysis 2.3) for partial response rates and an HR of 1.58 (95% CI 1.06 to 2.36, $p = 0.03$; Analysis 2.3) for complete response rates.

Progression-free survival (3 studies)

Only three studies had extractable data about the number of participants with no disease progression at the end of the trial. When pooled together, there was no statistically significant difference between the groups, with an HR of 0.76 (95% CI 0.57 to 1.02, $p = 0.07$; Analysis 3.1). There was no heterogeneity across these trials ($I^2 = 0\%$).

Treatment related toxicity (11 studies)

Data from 11 studies were collected, with the number of participants developing clinically significant hematological toxicity (defined as grade 3 or 4). Eight studies had estimated points that showed enhanced toxicities in the chemoimmunotherapy group. The meta-analysis of the studies showed extreme heterogeneity ($I^2 = 94.1\%$) across the trials. We performed a sensitivity analysis excluding the studies with relatively low doses of chemotherapeutic drugs in the chemoimmunotherapy group (Danson 2003; Middleton 2000), but we found similar heterogeneity ($I^2 = 97.8\%$).

When we analyzed data from the four studies with similar relative doses of chemotherapeutics associated with interferon-alpha, without interleukin-2, we found an increase of clinically significant hematological toxicities in the chemoimmunotherapy group, with a RR 4.54 (95% CI 2.35 to 8.79, $p < 0.00001$). There was no heterogeneity across these trials ($I^2 = 0\%$). When we analyzed data from studies with combination of interferon-alpha plus interleukin-2 in the chemoimmunotherapy group, we again found extreme heterogeneity across the trials ($I^2 = 97.9\%$).

Despite the heterogeneity in global meta-analysis, we concluded that it was not possible to quantify the differences in hematological toxicity in such different trials. In order to explore these differences, we noted that one study referred to hematological toxicity in 100% of participants treated with chemoimmunotherapy and in 96% of participants treated with chemotherapy (Eton 2002). Another study referred to hematological toxicity only in 2% and 1%, respectively (Bajetta 1994).

Non-hematological toxicities were described in almost all studies, and were mainly described as nausea, vomiting, flu-like syndrome, asthenia, hypotension, and fever. Data from six similar studies were extractable and were pooled in the meta-analysis, resulting in a statistically significant difference against the chemoimmunotherapy group, with a RR of 2.74 (95% CI 2.06 to 3.64, $p < 0.00001$; Analysis 4.2). There was no heterogeneity across trials ($I^2 = 0\%$). These results must be treated with caution, because of similar difficulties in pooling these data on hematological toxicities with different therapeutic schemes, and several trials described non-hematological toxicities, but we were not able to extract the data.

Data about treatment-related mortality were available in 11 studies. We found no significant difference between the groups, with a RR of 0.78 (95% CI 0.26 to 2.32, $p = 0.65$; Analysis 4.3). There was no heterogeneity across the trials ($I^2 = 0\%$).

Quality of life (three studies)

Only three studies reported data on quality of life (Ridolfi 2002; Thomson 1993; Young 2001), all using different methods. One trial described quality of life analysis in detail in an additional publication (Chiarion-Sileni 2003; Ridolfi 2002). This study found a significant decrease of overall quality of life in the chemoimmunotherapy group, in comparison to the chemotherapy group ($p = 0.03$). The other two studies did not find differences in global quality of life between the groups (Thomson 1993; Young 2001). Thomson did not report global quality of life (Thomson 1993). Young found no significant differences in quality of life for the change in scores over time ($z = -1.29$, $p = 0.20$) (Young 2001). It was not possible to pool the data as all three studies did not provide extractable data.

Sensitivity analyses on the influence of source of funding, baseline assessment, and allocation concealment on the survival analysis and response rate analyses revealed that there was no relation between these methodological aspects and the outcome. There was

no statistically significant difference in survival between the groups in all analyses, and the difference in response rates in favour of chemoimmunotherapy was found to be significant.

DISCUSSION

Metastatic melanoma is reputed as refractory to most systemic treatments, and little progress has been made in treatment of metastatic melanoma. These concepts are supported by results from previous systematic reviews. One review concluded that there is no evidence derived from RCTs that systemic treatment is better than best supportive care (Crosby 2000). Another review, of 20 randomised trials (involving 3273 participants) comparing single-agent DTIC with DTIC in combination with other drugs, with or without immunotherapy, concluded that combination of drugs increased response rates, but not overall survival (Huncharek 2001).

This systematic review summarises the evidence regarding the use of chemoimmunotherapy compared to chemotherapy alone to treat people with metastatic malignant melanoma. There are some important observations regarding the characteristics of the included studies in this systematic review. The ideal combination of drugs for an investigation is not well established. Seven studies evaluated chemoimmunotherapy with interferon-alpha plus interleukin-2, and 11 evaluated chemoimmunotherapy only with interferon-alpha. The treatment plans, with drugs and dosages used, differed between studies.

Most studies did not contribute in answering relevant questions about the impact of chemoimmunotherapy in the treatment of metastatic melanoma. The outcomes were not clearly described in several of the studies (Atkins 2003; Del Vecchio 2003; Gorbonova 2000; Kirkwood 1990; Spieth 2003; Thomson 1993). Two of them did not report survival rates, evaluating only response rates (Gorbonova 2000; Kirkwood 1990). All these aspects influenced the comparability of the trials and must be considered in the data interpretation.

On the basis of a meta-analysis of data coming from eight studies this review showed no evidence of a difference in overall survival to support the addition of immunotherapy to chemotherapy in the systemic treatment of metastatic melanoma (Atkins 2003; Danson 2003; Eton 2002; Falkson 1991; Johnston 1998; Ridolfi 2002; Spieth 2003; Young 2001). Evaluation of one, two and five-year survival, with data from other studies, again showed no survival advantage of the drug combination treatment.

We found higher clinical response rates in people treated with chemoimmunotherapy in comparison with people treated with chemotherapy, which was not translated into survival benefit. Additionally, we found higher toxicity rates in people treated with chemoimmunotherapy. Despite the importance of evaluating quality of life, there was no available data to perform the meta-

analysis in this systematic review. Only three studies reported data about quality of life, all with different methods. One trial described poorer quality of life in people treated with chemoimmunotherapy, related to more intense side effects (Ridolfi 2002). Two trials, however, showed no difference between groups (Thomson 1993; Young 2001). It is important that quality of life is included in all future studies.

Our meta-analysis did not find differences between treatment related mortality. Subgroup analysis comparing combinations with interferon-alpha and with interferon-alpha plus interleukin-2 did not show different results in survival or response rates.

The use of chemoimmunotherapy i.e a combination of chemotherapy with interferon-alpha or interleukin-2 or both, has not been shown to be beneficial in this review. Although short term response rates were better overall in the chemoimmunotherapy groups, survival was not improved, and drug-related toxicities were higher in the combined chemoimmunotherapy group. To date, no treatment regimen has shown efficiency in prolonging survival in people with metastatic melanoma. Little has changed in the systemic management of metastatic melanoma in the last few years. The standard of care remains single-agent DTIC, and the role of immunotherapy remains in doubt.

The use of chemoimmunotherapy in the treatment of melanoma is justified only in the context of clinical trials.

AUTHORS' CONCLUSIONS

Implications for practice

We failed to find any evidence to support the view that the use of chemoimmunotherapy prolongs survival in people with metastatic melanoma when compared to chemotherapy alone. Although short-term clinical responses were higher in the chemoimmunotherapy group, this was associated with a higher rate of serious adverse events, esp. haematological toxicity. Our review does not support the use of a combination of immunotherapy and chemotherapy in chemoimmunotherapy regimens outside of clinical trials. The standard of care for people with advanced melanoma remains chemotherapy with single-agent DTIC. Chemoimmunotherapy must not be recommended to people in daily practice.

Implications for research

Research related to the development of more effective treatments for people with metastatic melanoma is urgently needed.

For people with an incurable disease, the primary outcome needs to be overall survival and all studies should include a quality of life analysis.

Future trials should be designed to define the best systemic treatment, and should use chemotherapy with (DTIC) as a standard control group in order to permit comparisons to be made.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Atkins 2003

Methods	D: parallel group AC: unclear RS: unclear B: participant no, clinician no, outcome assessor no Size: yes ITT: no Placebo: no Funding: public	
Participants	PS <= 1 Brain mets: no info Age: 20 to 80 (median 50) Number of cycles: no info Randomised: 416; a: 206; b: 210 Evaluable: 405; a: 201; b: 204	
Interventions	a (CT): cisplatin 20mg/m ² D1 to 4; vinblastin 1.2 mg/m ² D1 to 4; DTIC 800 mg/m ² D1 b (ICT): cisplatin 20 mg/m ² D1-4; vimblastin 1.2 mg/m ² D1-4; DTIC 800 mg/m ² D1; IFN-alpha 5 mIU D1-5, D8, D10, D12; IL-2 9 mIU D1-4 (each 21 days)	
Outcomes	1. Overall survival 2. Response rates	
Notes	Multicentric : yes Withdrawals: a: five; b: six	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Atzpodien 2002

Methods	D: parallel group AC: independent allocation RS: centrally (unclear) B: participant no, clinician no, outcome assessor no Size: yes ITT: yes Placebo: no Funding: both (pharmaceutic and public)	
Participants	PS <= 1 Brain mets: yes Age: 28 to 77 (median 57) Number of cycles: no info Randomised: 124; a: 60; b: 64 Evaluable: 124; a: 60; b: 64	
Interventions	a (CT): cisplatin 35 mg/m ² D1 to 3, carmustine 150 mg/m ² D1 (cycles 1 and 3), DTIC 220 mg/m ² D1 to 3, tamoxifen 20 mg/m ² daily b (ICT): cisplatin 35 mg/m ² D1 to 3, carmustine 150 mg/m ² D1 (cycles 1 and 3), DTIC 220 mg/m ² D1 to 3, tamoxifen 20 mg/m ² daily, IFN-alpha 5 mIU/m ² D1 week4 and 5 mIU/m ² D1, D3, D5 week 5; IL-2 10 mIU/m ² D1, D3, D5 (each five weeks)	
Outcomes	1. Response rates 2. Overall survival 3. Progression free survival	
Notes	Multicentric : yes Withdrawals: a: 0; b: 0	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Bajetta 1994

Methods	D: parallel group (three groups) AC: independent allocation RS: centrally (unclear) B: participant no, clinician no, outcome assessor no Size: no ITT: yes Placebo: no Funding: pharmaceutical	
Participants	PS <= 2 Brain mets: no Age: 18 to 70 (median 53) Number of cycles: 8 Randomised: 266; a: 88; b: 86; c: 92 Evaluable: 242; a: 82; b: 76; c: 84	
Interventions	a (CT): DTIC 800 mg/m ² D1 b (ICT): DTIC 800 mg/m ² D1, IFN-alpha 3 mIU 3x/week c (ICT): DTIC 800 mg/m ² D1, IFN-alpha 3 mIU D1 to 3, 6 mIU D4 to 6, 9 mIU daily (each 21 days)	
Outcomes	1. Response rates 2. Response duration 3. Time to progression 4. Overall survival	
Notes	Multicentric : yes Withdrawals: a: six; b: ten; c: eight	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Danson 2003

Methods	D: parallel group AC: independent allocation RS: permuted blocks B: participant no, clinician no, outcome assessor no Size: no ITT: yes Placebo: no Funding: unknown	
Participants	PS <= 3 Brain mets: yes Age: 16 to 88 (median 58) Number of cycles: six Randomised: 125; a: 59; b: 62 Evaluable: 121; a: 55; b: 62	
Interventions	a (CT): temozolomide 200 mg/m ² 8/8 h (5 doses) b (ICT): Temozolomide 200 mg/m ² D1 to 5, IFN-alpha 5 mIU 3 x/week (each 28 days)	
Outcomes	1. Response rates 2. Overall survival	
Notes	Multicentric : no Withdrawals: a: 4; b: 0	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Del Vecchio 2003

Methods	D: parallel group AC: unclear RS: unclear B: participant no, clinician no, outcome assessor no Size: yes ITT: yes Placebo: no Funding: unknown	
Participants	PS <= 2 Brain mets: no Age: 19 to 70 (median 50) Number of cycles: no info Randomised: 151; a: 75; b: 76	

Del Vecchio 2003 (Continued)

	Evaluable: 145; a: 72; b: 73
Interventions	a (CT): cisplatin 30 mg/m ² D1 to 3; vindesine 2.5 mg/m ² D1; DTIC 250 mg/m ² D1 to 3 b (ICT): cisplatin 30 mg/m ² D1 to 3; vindesine 2.5 mg/m ² D1; DTIC 250 mg/m ² D1 to 3; IFN-alpha 5 mIU/m ² D1 to 5; IL-2 9 mIU/day x 5 days/week x 2 weeks with a week of rest (each 21 days)
Outcomes	1. Response rates 2. Time to Progression 2. Overall Survival
Notes	Multicentric : yes Withdrawals: a: three; b: three
Risk of bias	
Item	Authors' judgement Description
Allocation concealment?	Unclear B - Unclear

Eton 2002

Methods	D: parallel group AC: unclear RS: unclear B: participant no, clinician no, outcome assessor no Size: yes ITT: no Placebo: no Funding: pharm
Participants	PS <= 3 Brain mets: yes Age: median 49 Number of cycles: no info Randomised: 190; Evaluable: 183; a: 92; b: 91
Interventions	a (CT): cisplatin 20 mg/m ² D1 to 4; vimblastin 2 mg/m ² D1 to 4; DTIC 800 mg/m ² D1 b (ICT): cisplatin 20 mg/m ² D1 to 4; vinblastin 1.5 mg/m ² D1 to 4; DTIC 800 mg/m ² D1; IFN-alpha 5mIU/m ² D5 to 9, D17-21; IL-2 9 mIU/m ² D5 to 8, D17 to 20 (each 21 days)

Eton 2002 (Continued)

Outcomes	1. Response rates 2. Time to progression 3. Overall survival	
Notes	Multicentric : no Withdrawals not described	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Falkson 1991

Methods	D: parallel group AC: unclear RS: unclear B: participant no, clinician no, outcome assessor no Size: no ITT: no Placebo: no Funding: both	
Participants	PS <= 1 Brain mets: no Age: 22 to 79 (median 57) Number of cycles: at least two Randomised: 73; Evaluable: 68; a: 34; b: 34	
Interventions	a (CT): DTIC 200 mg/m ² D1 to 5 b (ICT): DTIC 200 mg/m ² D1 to 5; IFN-alpha 15 mIU/m ² 5 days/week for 3 weeks; IFN-alpha 10 mIU/m ² 3 x/week (each 28 days)	
Outcomes	1. Response rates 2. Time to treatment failure 3. Median survival 4. Toxicity	
Notes	Multicentric: no Withdrawals: a: three; b: two	
Risk of bias		

Falkson 1991 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Falkson 1998

Methods	D: 2 x 2 factorial design AC: independent allocation RS: permuted blocks B: participant N, clinician N, outcome assessor N Size: yes ITT: yes Placebo: no Funding: public	
Participants	PS <= 2 Brain mets: no Age: 18 to 84 Number of cycles: no info Randomised: 271; Evaluable: 263; a: 68; b: 65; c: 63; d: 67	
Interventions	a (CT): DTIC 200 mg/m ² D1 to 5 b (ICT): DTIC 200 mg/m ² D1 to 5; IFN-alpha 15 mIU/m ² 5 days/week for 3 weeks; IFN-alpha 10 mIU/m ² 3 x/week c (CT): DTIC 200m g/m ² D1 to 5; tamoxifen 20 mg/daily d (ICT): DTIC 200 mg/m ² D1 to 5; IFN-alpha 15 mIU/m ² 5 days/week for 3 weeks; IFN-alpha 10 mIU/m ² 3 x/week; tamoxifen 20 mg/daily (each 28 days)	
Outcomes	1. Response rates 2. Toxicity rates 3. Overall survival 4. Time to treatment failure	
Notes	Multicentric: yes Withdrawals: a: one; b: three; c: three; d: one	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gorbonova 2000

Methods	D: parallel group AC: unclear RS: unclear B: participant N, clinician N, outcome assessor N Size: no ITT: no Placebo: no Funding: unknown	
Participants	PS: no info Brain mets: no Age: 23 to 75 Number of cycles: no info Randomised: 30; Evaluable: 28; a: 14; b: 14	
Interventions	a (CT): cisplatin 100 mg/m ² D3; aranoza 600 mg/m ² D1 to 2 b (ICT): cisplatin 100 mg/m ² D3; aranoza 600 mg/m ² D1 to 2; IFN-alpha 3 mIU D5, 7, 9, 11, 13, 15, 17, 19 (each 28 days)	
Outcomes	1. Response rates	
Notes	Multicentric: no Withdrawals: a: two; b: two	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Johnston 1998

Methods	D: parallel group AC: independent allocation RS: centrally (unclear) B: participant N, clinician N, outcome assessor N Size: yes ITT: no Placebo: no Funding: unknown	
Participants	PS <= 1 Brain mets: no Age: 18 to 70	

Johnston 1998 (Continued)

	(median 45) Number of cycles: no info Randomised: 65; Evaluable: 65; a: 30; b: 35
Interventions	a (CT): BCNU 100 mg/m ² D1; cisplatin 25 mg/m ² D1 to 3; DTIC 220 mg/m ² D1 to 3; Tamoxifen 40 mg daily b (ICT): BCNU 100 mg/m ² D1; cisplatin 25 mg/m ² D1 to 3; DTIC 220 mg/m ² D1 to 3; Tamoxifen 40 mg daily; IFN-alpha 9 mIU D1 to 3; IL-2 18 mIU D-2, IL-2 9 mIU D-1 and 0 (each 28 days)
Outcomes	1. Response rates 2. Time to disease progression 3. Overall survival
Notes	Multicentric: no Withdrawals: a: 0; b: 0
Risk of bias	
Item	Authors' judgement Description
Allocation concealment?	Yes A - Adequate

Kirkwood 1990

Methods	D: parallel group AC: unclear RS: unclear B: participant N, clinician N, outcome assessor N Size: no ITT: no Placebo: no Funding: pharm
Participants	PS: no info Brain mets: no info Age: no info Number of cycles: no info Randomised: 74; Evaluable: 68; a: 24; b: 23; c: 21
Interventions	a (CT): DTIC 250 mg/m ² D1 to 5 (each 21 days) b (I): IFN-alpha 3 mIU d1 to 5 every week for 3 weeks, than 3 mIU/m ² 3 x/week c (ICT): DTIC 250 mg/m ² D1 to 5 (each 21 days); IFN-alpha 3 mIU d1 to 5 every week for 3 weeks, than 3 mIU/m ² 3 x/week

Kirkwood 1990 (Continued)

Outcomes	1. Response rates	
Notes	Multicentric: yes Withdrawals: not described	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Middleton 2000

Methods	D: parallel group AC: independent allocation RS: centrally (unclear) B: participant N, clinician N, outcome assessor N Size: yes ITT: yes Placebo: no Funding: unknown	
Participants	PS <= 3 Brain mets: no Age: 24 to 71 (median 51) Number of cycles: six Randomised: 105; Evaluable: 96; a: 46; b: 50	
Interventions	a (CT): DTIC 800 mg/m ² D1; cisplatin 25 mg/m ² D1 to 3; BCNU 150 mg/m ² D1; tamoxifen 20 mg/daily b (ICT): DTIC 800 mg/m ² D1; IFN-alpha 9 mIU 3 x/week (each 21 days)	
Outcomes	1. Response rates 2. One year survival 3. Median survival 4. Toxicity 4. Time spent in hospital	
Notes	Multicentric: no Withdrawals: a: seven; b: two	
Risk of bias		

Middleton 2000 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ridolfi 2002

Methods	D: parallel group AC: independent allocation by telephone RS: permuted blocks B: participant N, clinician N, outcome assessor N Size: yes ITT: yes Placebo: no Funding: public	
Participants	PS <= 2 Brain mets: no Age: 25 to 77 Number of cycles: six Randomised: 178; Evaluable: 176; a: 89; b: 87	
Interventions	a (CT): BCNU 100 mg/m ² D1; cisplatin 75 mg/m ² D1; DTIC 800 mg/m ² D1 b (ICT): BCNU 100 mg/m ² D1; cisplatin 75 mg/m ² D1; DTIC 800 mg/m ² D1; IFN-alpha 3 mIU 3 x/week; IL-2 4.5 mIU D3 to 5, D8 to 12 (each 21 days)	
Outcomes	1. Overall survival 2. Response rates 3. Time to progression 4. Toxicity	
Notes	Multicentric: yes Withdrawals: a: one; b: one	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rosenberg 1999

Methods	D: parallel group AC: independent allocation RS: centrally (unclear) B: participant N, clinician N, outcome assessor N Size: yes ITT: yes Placebo: no Funding: unknown	
Participants	PS <= 1 Brain mets: no Age: no info Number of cycles: four Randomised: 102; Evaluable: 102; a: 52; b: 50	
Interventions	a(CT): cisplatin 25 mg/m ² D2 to 4, D23 to 35; DTIC 220 mg/m ² D2 to 4, D23 to 25; tamoxifen 40 mg D1, 10 mg D2 to 29 b (ICT): cisplatin 25 mg/m ² D2 to 4, D23 to 35; DTIC 220 mg/m ² D2 to 4, D23 to 25; tamoxifen 40 mg D1, 10 mg D2 to 29; IFN-alpha 6 mIU/m ² D5 to 8, D 26 to 29; IL-2 720,000 IU/kg 8/8 hours to tolerance D5 to 8, D 26 to 29 (each 58 days)	
Outcomes	1. Response rate 2. Overall survival	
Notes	Multicentric: no Withdrawals: a: 0; b: 0	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Spieth 2003

Methods	D: parallel group AC: unclear RS: unclear B: participant N, clinician N, outcome assessor N Size: no ITT: no Placebo: no Funding: unknown	
Participants	PS: no info Brain mets: no info Age: no info Number of cycles: no info Randomised: 294; Evaluable: 280; a: 138; b: 142	
Interventions	a (CT): temozolomide 200 mg/m ² D1 to 5 b (ICT) temozolomide 200 mg/m ² D1 to 5; IFN-alpha 5 mIU/m ² daily for week 1, thereafter on D1, 3, 5 (each 28 days)	
Outcomes	1. Response rates 2. Overall survival 3. Toxicity	
Notes	Multicentric: yes Withdrawals: not described	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Thomson 1993

Methods	D: parallel group AC: independent allocation RS: centrally dynamic technique B: participant N, clinician N, outcome assessor N Size: yes ITT: no Placebo: no Funding: unknown	
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Thomson 1993 (Continued)

Participants	PS <= 2 Brain mets: no Age: 18 to 75 Number of cycles: no info Randomised: 176; Evaluable: 170; a: 83; b: 87
Interventions	a (CT): DTIC 800 mg/m ² D1 (each 21 days) b (ICT): DTIC 800 mg/m ² D1 (each 21 days); IFN-alpha 3 mIU D1 to 3, 9 mIU D4 to 67, thereafter 9 mIU 3 x/week
Outcomes	1. Response rates 2. Response duration 3. Time to progression 4. Quality of life 5. Toxicity 6. Overall survival
Notes	Multicentric: yes Withdrawals: a: five; b: one

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Vorobiof 1994

Methods	D: parallel group AC: closed envelope RS: closed envelope random number technique B: participant N, clinician N, outcome assessor N Size: no ITT: yes Placebo: no Funding: unknown
Participants	PS <= 2 Brain mets: no Age: no info Number of cycles: no info Randomised: 60; Evaluable: 60; a: 20; b: 20; c: 20

Vorobiof 1994 (Continued)

Interventions	a (CT): Vindesine 3 mg/m ² weekly for 3 weeks, followed by Vindesine 4 mg/m ² each 21 days b (I): IFN-alpha 6 mIU/m ² 3 x/week c (ICT): Vindesine 3 mg/m ² weekly for 3 weeks, followed by Vindesine 4 mg/m ² each 21 days; IFN-alpha 6 mIU/m ² 3 x/week	
Outcomes	1. Response rates 2. Overall Survival	
Notes	Multicentric: no Withdrawals: a: 0; b: 0; c: 0	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Young 2001

Methods	D: parallel group AC: independent allocation by telephone RS: centrally random permuted blocks B: participant N, clinician N, outcome assessor N Size: yes ITT: yes Placebo: no Funding: both	
Participants	PS <= 2 Brain mets: no Age: 31 to 80 (median 57) Number of cycles: 6 Randomised: 61; Evaluable: 59; a: 31; b: 28	
Interventions	a (CT): DTIC 950 mg/m ² D1 (each 28 days) b (ICT): DTIC 950 mg/m ² D1 (each 28 days), IFN-alpha 4.5 mIU 3 x/week	
Outcomes	1. Median survival 2. Response rates 3. Toxicity 4. Quality of life	
Notes	Multicentric: yes Withdrawals: a: 0; b: 2	

Young 2001 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

D = design; AC = allocation concealment; RS = randomization system; B = blindness; Size = population size calculated; ITT = intention to treat analysis; Funding = source of funding; PS = Eastern Cooperative Oncology Group definition of performance status; mets = metastasis; CT = chemotherapy; ICT - chemoimmunotherapy

Characteristics of excluded studies [ordered by study ID]

Bajetta 2001	Immunotherapy on both arms
Legha 1996	Not randomized
Richtig 2004	Immunotherapy on both arms
Sertoli 1999	Immunotherapy on three arms
Sparano 1993	Comparison of iFN with IL-2; immunotherapy on both arms
Vuoristo 2005	Immunotherapy on both arms

DATA AND ANALYSES

Comparison 1. Survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Survival	8	1355	Peto Odds Ratio (95% CI)	0.89 [0.72, 1.11]
1.1 ICT with interferon-alpha	4	526	Peto Odds Ratio (95% CI)	0.74 [0.49, 1.12]
1.2 ICT with interferon-alpha plus interleukin-2	4	829	Peto Odds Ratio (95% CI)	0.96 [0.74, 1.24]
2 1 year survival	13	1803	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.24]
2.1 ICT with interferon-alpha	7	1008	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.93, 1.50]
2.2 ICT with interferon-alpha plus interleukin-2	6	795	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.79, 1.20]
3 2 year survival	11	1677	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.36]
3.1 ICT with interferon-alpha	6	947	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.84, 1.67]
3.2 ICT with interferon-alpha plus interleukin-2	5	730	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.65, 1.43]
4 5 year survival	2	307	Risk Ratio (M-H, Random, 95% CI)	2.34 [0.97, 5.65]

Comparison 2. Response rates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall response rate	17	2434	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.20, 1.63]
1.1 ICT with interferon-alpha	10	1331	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.02, 1.71]
1.2 ICT with interferon-alpha plus interleukin-2	7	1103	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.19, 1.79]
2 Complete response rate	15	2109	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.06, 2.36]
3 Partial response rate	15	2110	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.07, 1.59]

Comparison 3. Progression free survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression free survival	3	424	Peto Odds Ratio (95% CI)	0.76 [0.57, 1.02]

Comparison 4. Toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hematological toxicity grade ≥ 3	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 ICT with interferon-alpha	6	842	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.42, 5.52]
1.2 ICT with interferon-alpha plus interleukin-2	5	892	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.82, 4.23]
2 Non-hematological toxicity grade ≥ 3	6	858	Risk Ratio (M-H, Random, 95% CI)	2.74 [2.06, 3.64]
2.1 ICT with interferon-alpha	2	332	Risk Ratio (M-H, Random, 95% CI)	2.89 [1.46, 5.73]
2.2 ICT with interferon-alpha plus interleukin-2	4	526	Risk Ratio (M-H, Random, 95% CI)	2.63 [1.78, 3.90]
3 Treatment related mortality	11	1883	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.26, 2.32]

FEEDBACK

Comment from Douglas Grindlay 09 July 07

Summary

Date of Submission: 09-Jul-2007

Name: Douglas Grindlay

Personal Description: Occupation NLH Dermatology Information Specialist

Feedback: In the context of my role compiling uncertainties for the Database of Uncertainties of Effects of Treatments (DUETs), I found it difficult to tell from this review whether the conclusion is that chemoimmunotherapy definitely has no advantage in terms of survival over chemotherapy, or whether there is still uncertainty over whether chemoimmunotherapy does work better. Given that 18 trials were found and the meta-analysis showed significant effect on survival, why would further research need to be done (see conclusion that "Further use of combined immunotherapy and chemotherapy should only be done in the context of clinical trials")? Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Dear Sir,

Thank you for your important comments. Our review found differences in response rates, but not in survival as described by Dr. Grindlay. Therefore, we concluded that there is not enough evidence that chemoimmunotherapy is more effective than chemotherapy alone in terms of survival. This conclusion is in conflict with some international guidelines recommendations (NCCN, NCI, etc), which include chemoimmunotherapy as a valid option to treat melanoma patients.

In addition to the need to demonstrate survival benefit for chemoimmunotherapy over chemotherapy, we also suggest that chemoimmunotherapy could be studied with different combinations of drugs and different doses, other than those used in existing trials included in the review. These are the main reasons why we concluded that there are still uncertainties that require new trials in the future.

Best wishes,

Andre Sasse

Contributors

Author of comments: Douglas Grindlay

Author responding: Andre Sasse

WHAT'S NEW

Last assessed as up-to-date: 14 November 2006.

6 September 2008	Amended	Converted to new review format.
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HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 1, 2007

CONTRIBUTIONS OF AUTHORS

draft the protocol: ADS, OAC, ECS

search for trials (2 people): ADS, ECS

obtain copies of trials: ADS

select which trials to include (2 + 1 arbiter): ADS, OAC, ECS

extract data from trials (2 people): ADS, ECS

enter data into RevMan: ADS

carry out the analysis: ADS, OAC, LGC

interpret the analysis: ADS, OAC, ECS

draft the final review: ADS, LGC, OAC

consumer review: LU

update the review: ADS

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Combined Modality Therapy [methods]; Immunotherapy [*methods]; Interferon-alpha [therapeutic use]; Interleukin-2 [therapeutic use]; Melanoma [drug therapy; secondary; *therapy]; Randomized Controlled Trials as Topic; Skin Neoplasms [drug therapy; *therapy]

MeSH check words

Humans