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[Intervention Review]

Systemic treatments for metastatic cutaneous melanoma

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ABSTRACT

Background

The prognosis of people with metastatic cutaneous melanoma, a skin cancer, is generally poor. Recently, new classes of drugs (e.g. immune checkpoint inhibitors and small-molecule targeted drugs) have significantly improved patient prognosis, which has drastically changed the landscape of melanoma therapeutic management. This is an update of a Cochrane Review published in 2000.

Objectives

To assess the beneficial and harmful effects of systemic treatments for metastatic cutaneous melanoma.

Search methods

We searched the following databases up to October 2017: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase and LILACS. We also searched five trials registers and the ASCO database in February 2017, and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs).

Selection criteria

We considered RCTs of systemic therapies for people with unresectable lymph node metastasis and distant metastatic cutaneous melanoma compared to any other treatment. We checked the reference lists of selected articles to identify further references to relevant trials.

Data collection and analysis

Two review authors extracted data, and a third review author independently verified extracted data. We implemented a network metaanalysis approach to make indirect comparisons and rank treatments according to their effectiveness (as measured by the impact on survival) and harm (as measured by occurrence of high-grade toxicity). The same two review authors independently assessed the risk of bias of eligible studies according to Cochrane standards and assessed evidence quality based on the GRADE criteria.

Main results

We included 122 RCTs (28,561 participants). Of these, 83 RCTs, encompassing 21 different comparisons, were included in meta-analyses. Included participants were men and women with a mean age of 57.5 years who were recruited from hospital settings. Twenty-nine studies included people whose cancer had spread to their brains. Interventions were categorised into five groups: conventional chemotherapy (including single agent and polychemotherapy), biochemotherapy (combining chemotherapy with cytokines such as interleukin-2 and interferon-alpha), immune checkpoint inhibitors (such as anti-CTLA4 and anti-PD1 monoclonal antibodies), small-molecule targeted drugs



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used for melanomas with specific gene changes (such as BRAF inhibitors and MEK inhibitors), and other agents (such as anti-angiogenic drugs). Most interventions were compared with chemotherapy. In many cases, trials were sponsored by pharmaceutical companies producing the tested drug: this was especially true for new classes of drugs, such as immune checkpoint inhibitors and small-molecule targeted drugs.

When compared to single agent chemotherapy, the combination of multiple chemotherapeutic agents (polychemotherapy) did not translate into significantly better survival (overall survival: HR 0.99, 95% CI 0.85 to 1.16, 6 studies, 594 participants; high-quality evidence; progression-free survival: HR 1.07, 95% CI 0.91 to 1.25, 5 studies, 398 participants; high-quality evidence. Those who received combined treatment are probably burdened by higher toxicity rates (RR 1.97, 95% CI 1.44 to 2.71, 3 studies, 390 participants; moderate-quality evidence). (We defined toxicity as the occurrence of grade 3 (G3) or higher adverse events according to the World Health Organization scale.)

Compared to chemotherapy, biochemotherapy (chemotherapy combined with both interferon-alpha and interleukin-2) improved progression-free survival (HR 0.90, 95% CI 0.83 to 0.99, 6 studies, 964 participants; high-quality evidence), but did not significantly improve overall survival (HR 0.94, 95% CI 0.84 to 1.06, 7 studies, 1317 participants; high-quality evidence). Biochemotherapy had higher toxicity rates (RR 1.35, 95% CI 1.14 to 1.61, 2 studies, 631 participants; high-quality evidence).

With regard to immune checkpoint inhibitors, anti-CTLA4 monoclonal antibodies plus chemotherapy probably increased the chance of progression-free survival compared to chemotherapy alone (HR 0.76, 95% CI 0.63 to 0.92, 1 study, 502 participants; moderate-quality evidence), but may not significantly improve overall survival (HR 0.81, 95% CI 0.65 to 1.01, 2 studies, 1157 participants; low-quality evidence). Compared to chemotherapy alone, anti-CTLA4 monoclonal antibodies is likely to be associated with higher toxicity rates (RR 1.69, 95% CI 1.19 to 2.42, 2 studies, 1142 participants; moderate-quality evidence).

Compared to chemotherapy, anti-PD1 monoclonal antibodies (immune checkpoint inhibitors) improved overall survival (HR 0.42, 95% CI 0.37 to 0.48, 1 study, 418 participants; high-quality evidence) and probably improved progression-free survival (HR 0.49, 95% CI 0.39 to 0.61, 2 studies, 957 participants; moderate-quality evidence). Anti-PD1 monoclonal antibodies may also result in less toxicity than chemotherapy (RR 0.55, 95% CI 0.31 to 0.97, 3 studies, 1360 participants; low-quality evidence).

Anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies in terms of overall survival (HR 0.63, 95% CI 0.60 to 0.66, 1 study, 764 participants; high-quality evidence) and progression-free survival (HR 0.54, 95% CI 0.50 to 0.60, 2 studies, 1465 participants; high-quality evidence). Anti-PD1 monoclonal antibodies may result in better toxicity outcomes than anti-CTLA4 monoclonal antibodies (RR 0.70, 95% CI 0.54 to 0.91, 2 studies, 1465 participants; low-quality evidence).

Compared to anti-CTLA4 monoclonal antibodies alone, the combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies was associated with better progression-free survival (HR 0.40, 95% CI 0.35 to 0.46, 2 studies, 738 participants; high-quality evidence). There may be no significant difference in toxicity outcomes (RR 1.57, 95% CI 0.85 to 2.92, 2 studies, 764 participants; low-quality evidence) (no data for overall survival were available).

The class of small-molecule targeted drugs, BRAF inhibitors (which are active exclusively against BRAF-mutated melanoma), performed better than chemotherapy in terms of overall survival (HR 0.40, 95% CI 0.28 to 0.57, 2 studies, 925 participants; high-quality evidence) and progression-free survival (HR 0.27, 95% CI 0.21 to 0.34, 2 studies, 925 participants; high-quality evidence), and there may be no significant difference in toxicity (RR 1.27, 95% CI 0.48 to 3.33, 2 studies, 408 participants; low-quality evidence).

Compared to chemotherapy, MEK inhibitors (which are active exclusively against BRAF-mutated melanoma) may not significantly improve overall survival (HR 0.85, 95% CI 0.58 to 1.25, 3 studies, 496 participants; low-quality evidence), but they probably lead to better progression-free survival (HR 0.58, 95% CI 0.42 to 0.80, 3 studies, 496 participants; moderate-quality evidence). However, MEK inhibitors probably have higher toxicity rates (RR 1.61, 95% CI 1.08 to 2.41, 1 study, 91 participants; moderate-quality evidence).

Compared to BRAF inhibitors, the combination of BRAF plus MEK inhibitors was associated with better overall survival (HR 0.70, 95% CI 0.59 to 0.82, 4 studies, 1784 participants; high-quality evidence). BRAF plus MEK inhibitors was also probably better in terms of progression-free survival (HR 0.56, 95% CI 0.44 to 0.71, 4 studies, 1784 participants; moderate-quality evidence), and there appears likely to be no significant difference in toxicity (RR 1.01, 95% CI 0.85 to 1.20, 4 studies, 1774 participants; moderate-quality evidence).

Compared to chemotherapy, the combination of chemotherapy plus anti-angiogenic drugs was probably associated with better overall survival (HR 0.60, 95% CI 0.45 to 0.81; moderate-quality evidence) and progression-free survival (HR 0.69, 95% CI 0.52 to 0.92; moderate-quality evidence). There may be no difference in terms of toxicity (RR 0.68, 95% CI 0.09 to 5.32; low-quality evidence). All results for this comparison were based on 324 participants from 2 studies.

Network meta-analysis focused on chemotherapy as the common comparator and currently approved treatments for which high- to moderate-quality evidence of efficacy (as represented by treatment effect on progression-free survival) was available (based on the above results) for: biochemotherapy (with both interferon-alpha and interleukin-2); anti-CTLA4 monoclonal antibodies; anti-PD1 monoclonal antibodies; BRAF inhibitors; MEK inhibitors, and BRAF plus MEK inhibitors. Analysis (which included 19 RCTs and 7632 participants) generated 21 indirect comparisons.

The best evidence (moderate-quality evidence) for progression-free survival was found for the following indirect comparisons:



• both combinations of immune checkpoint inhibitors (HR 0.30, 95% CI 0.17 to 0.51) and small-molecule targeted drugs (HR 0.17, 95% CI 0.11 to 0.26) probably improved progression-free survival compared to chemotherapy;

• both BRAF inhibitors (HR 0.40, 95% CI 0.23 to 0.68) and combinations of small-molecule targeted drugs (HR 0.22, 95% CI 0.12 to 0.39) were probably associated with better progression-free survival compared to anti-CTLA4 monoclonal antibodies;

• biochemotherapy (HR 2.81, 95% CI 1.76 to 4.51) probably lead to worse progression-free survival compared to BRAF inhibitors;

• the combination of small-molecule targeted drugs probably improved progression-free survival (HR 0.38, 95% CI 0.21 to 0.68) compared to anti-PD1 monoclonal antibodies;

• both biochemotherapy (HR 5.05, 95% CI 3.01 to 8.45) and MEK inhibitors (HR 3.16, 95% CI 1.77 to 5.65) were probably associated with worse progression-free survival compared to the combination of small-molecule targeted drugs; and

• biochemotherapy was probably associated with worse progression-free survival (HR 2.81, 95% CI 1.54 to 5.11) compared to the combination of immune checkpoint inhibitors.

The best evidence (moderate-quality evidence) for toxicity was found for the following indirect comparisons:

- combination of immune checkpoint inhibitors (RR 3.49, 95% CI 2.12 to 5.77) probably increased toxicity compared to chemotherapy;
- combination of immune checkpoint inhibitors probably increased toxicity (RR 2.50, 95% CI 1.20 to 5.20) compared to BRAF inhibitors;
- the combination of immune checkpoint inhibitors probably increased toxicity (RR 3.83, 95% CI 2.59 to 5.68) compared to anti-PD1 monoclonal antibodies; and

• biochemotherapy was probably associated with lower toxicity (RR 0.41, 95% CI 0.24 to 0.71) compared to the combination of immune checkpoint inhibitors.

Network meta-analysis-based ranking suggested that the combination of BRAF plus MEK inhibitors is the most effective strategy in terms of progression-free survival, whereas anti-PD1 monoclonal antibodies are associated with the lowest toxicity.

Overall, the risk of bias of the included trials can be considered as limited. When considering the 122 trials included in this review and the seven types of bias we assessed, we performed 854 evaluations only seven of which (< 1%) assigned high risk to six trials.

Authors' conclusions

We found high-quality evidence that many treatments offer better efficacy than chemotherapy, especially recently implemented treatments, such as small-molecule targeted drugs, which are used to treat melanoma with specific gene mutations. Compared with chemotherapy, biochemotherapy (in this case, chemotherapy combined with both interferon-alpha and interleukin-2) and BRAF inhibitors improved progression-free survival; BRAF inhibitors (for BRAF-mutated melanoma) and anti-PD1 monoclonal antibodies improved overall survival. However, there was no difference between polychemotherapy and monochemotherapy in terms of achieving progression-free survival. Biochemotherapy did not significantly improve overall survival and has higher toxicity rates compared with chemotherapy.

There was some evidence that combined treatments worked better than single treatments: anti-PD1 monoclonal antibodies, alone or with anti-CTLA4, improved progression-free survival compared with anti-CTLA4 monoclonal antibodies alone. Anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies in terms of overall survival, and a combination of BRAF plus MEK inhibitors was associated with better overall survival for BRAF-mutated melanoma, compared to BRAF inhibitors alone.

The combination of BRAF plus MEK inhibitors (which can only be administered to people with BRAF-mutated melanoma) appeared to be the most effective treatment (based on results for progression-free survival), whereas anti-PD1 monoclonal antibodies appeared to be the least toxic, and most acceptable, treatment.

Evidence quality was reduced due to imprecision, between-study heterogeneity, and substandard reporting of trials. Future research should ensure that those diminishing influences are addressed. Clinical areas of future investigation should include the longer-term effect of new therapeutic agents (i.e. immune checkpoint inhibitors and targeted therapies) on overall survival, as well as the combination of drugs used in melanoma treatment; research should also investigate the potential influence of biomarkers.

PLAIN LANGUAGE SUMMARY

Systemic treatments (tablets or injections) taken for metastatic melanoma (expanded from its starting point to other parts of the body)

Background

Melanoma is the most dangerous common skin cancer. Early diagnosis offers the best chance of cure. People affected by early stage melanoma represent about 70% to 80% of all those with melanoma and can be treated by surgical removal of the original tumour (known as the primary tumour). However, when a primary melanoma is detected at a later stage, there is a risk of disease spreading to the nearest lymph nodes (glands that are part of the body's immune system) and distant sites, such as the lungs, liver, bone and brain. In this case, systemic chemotherapy (giving drugs that kill cells throughout the body) and biochemotherapy (chemotherapy combined with substances that can improve the immune response, known as immunostimulating cytokines, such as interleukin-2 and interferon-alpha) have been



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the main treatments for over three decades. However, only few people experience spontaneous (i.e. not resulting from therapy) regression of the primary tumour.

Over the past few years, new classes of drugs have been used with promising results. We aimed to look at how new systemic treatments compare with older therapies, as well as with each other, in terms of survival, acceptability, tumour response, and quality of life. We assessed these outcomes in people with metastatic melanoma (AJCC TNM stage IV).

Review question

We aimed to assess the effects of systemic treatments for people with metastatic cutaneous melanoma (melanoma of skin tissue). We searched for relevant trials up to October 2017 and included 122 studies.

We summarised the results of melanoma treatments (delivered systemically), such as conventional chemotherapy, biochemotherapy, as well as newer drug classes, such as immune checkpoint inhibitors (anti-CTLA4 and anti-PD1 monoclonal antibodies, which increase the anti-tumour activity of the immune system), small-molecule targeted drugs (BRAF inhibitors, which are used only for melanomas containing specific BRAF gene mutations that promote tumour progression, and MEK inhibitors, which work on the same molecular pathway), and anti-angiogenic drugs (which reduce blood supply to cancer cells). We compared these treatments with conventional chemotherapy.

Study characteristics

All 122 studies were randomised controlled trials that enrolled participants with metastatic cutaneous melanoma and compared different systemic treatments (28,561 participants). Study participants were adults of either sex, with a mean age of 57.5 years. There were 29 studies that included people whose cancer had spread to the brain, which is important because the detection and treatment of brain metastases often present unique challenges. Most treatments were compared with chemotherapy, and all studies were set in hospitals. Frequently, the pharmaceutical company who produced a tested drug also sponsored the study in which it was assessed, especially in the case of new classes of drugs, such as immune checkpoint inhibitors and small-molecule targeted drugs.

Key results

Compared to conventional chemotherapy, several treatments can improve the progression-free survival of people with metastatic melanoma. These include biochemotherapy (high-quality evidence), anti-CTLA4 monoclonal antibodies plus chemotherapy (moderate-quality evidence), anti-PD1 monoclonal antibodies (moderate-quality evidence), BRAF inhibitors (high-quality evidence), MEK inhibitors (moderate-quality evidence), and anti-angiogenic drugs (moderate-quality evidence). However, no difference was found for use of a combination of several chemotherapy agents (polychemotherapy) (high-quality evidence). Moreover, the combination of immune checkpoint inhibitors (anti-PD1 plus anti-CTLA4 monoclonal antibodies) performed better than anti-CTLA4 monoclonal antibodies alone (high-quality evidence), but anti-PD1 monoclonal antibodies performed better than anti-CTLA4 monoclonal antibodies (high-quality evidence). The combination of small-molecule inhibitors (BRAF plus MEK inhibitors) lead to better results than BRAF inhibitors alone (moderate-quality evidence), for people with melanoma that has a BRAF gene change.

Anti-PD1 monoclonal antibodies improved patients' overall survival compared with either standard chemotherapy (high-quality evidence) or anti-CTLA4 monoclonal antibodies (high-quality evidence). Compared to chemotherapy alone, both BRAF inhibitors (high-quality evidence), and anti-angiogenic agents combined with chemotherapy (moderate-quality evidence) also prolong overall survival, but anti-CTLA4 monoclonal antibodies plus chemotherapy (low-quality evidence), MEK inhibitors (low-quality evidence), combined multiple chemotherapeutic agents (polychemotherapy) (high-quality evidence), or biochemotherapy (high-quality evidence) did not lead to significantly improved overall survival. WE also found that the combination of small-molecule inhibitors performed better than BRAF inhibitors alone (high-quality evidence). No data on overall survival were available for anti-CTLA4 monoclonal antibodies alone compared with the combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies.

In terms of toxicity (defined as occurrence of high-grade side effects), biochemotherapy (high-quality evidence), anti-CTLA4 monoclonal antibodies (moderate-quality evidence), polychemotherapy (moderate-quality evidence), and MEK inhibitors (moderate-quality evidence) were associated with worse toxicity compared to chemotherapy. In contrast, anti-PD1 monoclonal antibodies appear to be better tolerated than chemotherapy alone. Anti-PD1 monoclonal antibodies also appeared to be better tolerated than anti-CTLA4 monoclonal antibodies. However, evidence quality supporting these findings was assessed as low. Furthermore, the frequency of side effects did not differ significantly between anti-PD1 plus anti-CTLA4 monoclonal antibodies versus anti-CTLA4 monoclonal antibodies alone (low-quality evidence), anti-angiogenic drugs combined with chemotherapy versus chemotherapy (low-quality evidence), BRAF inhibitors versus chemotherapy (low-quality evidence).

We also conducted an analysis that compared treatments that had not been directly compared in a study. This is known as a network metaanalysis. For the outcome of progression-free survival, looking at only the best evidence available, we found the following results (please note that because the highest quality level was moderate, the following results can only be deemed probable):

• both combination of immune checkpoint inhibitors and combination of small-molecule targeted drugs were favoured compared to chemotherapy;

• both BRAF inhibitors and combination of small-molecule targeted drugs were favoured compared to anti-CTLA4 monoclonal antibodies;



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- biochemotherapy led to less favourable results than BRAF inhibitors;
- the combination of small-molecule targeted drugs was favoured compared to anti-PD1 monoclonal antibodies;
- both biochemotherapy and MEK inhibitors led to less favourable results than the combination of small-molecule targeted drugs; and
 biochemotherapy led to less favourable results than the combination of immune checkpoint inhibitors

For the outcome of toxicity, looking at only the best evidence available, we found the following results (again, evidence quality was no higher than moderate):

- combination of immune checkpoint inhibitors led to less favourable results than chemotherapy;
- combination of immune checkpoint inhibitors led to less favourable results than BRAF inhibitors;
- the combination of immune checkpoint inhibitors led to less favourable results than anti-PD1 monoclonal antibodies; and
- biochemotherapy was favoured compared to the combination of immune checkpoint inhibitors.

Our results suggest that the combination of small-molecule targeted drugs (BRAF plus MEK inhibitors) is the most effective treatment strategy, for people with melanoma that has a BRAF gene change, at least in terms of progression-free survival; however, this combination therapy is burdened by a higher rate of severe toxicity compared to effects observed among people treated with anti-PD1 monoclonal antibodies, which can be used in all melanoma types, and rank highest in terms of tolerability.

These results need long-term analysis from randomised trials to be confirmed, with special attention to effects on patients' overall survival.

Quality of the evidence

GRADE findings showed that most evidence was high- to moderate-quality for three (overall survival, progression-free survival and tumour response) out of four outcomes (toxicity). Evidence quality was reduced due to small numbers of participants in some comparisons, differences between the studies, and poor reporting of trials.