Research Letter

From the Cochrane Library: Systemic Treatments for Metastatic Cutaneous Melanoma

Austin Hamp[1], BSc; Jarett Anderson[1], BSc; Torunn E Sivesind[2], MD; Mindy D Szeto[2], MSc; Andreas Hadjinicolaou[3,4], MPH, PhD

[1]Arizona College of Osteopathic Medicine, Midwestern University, Glendale, AZ, United States

[2]Department of Dermatology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

[3]Human Immunology Unit, Institute of Molecular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom

[4]Medical Research Council Cancer Unit, Hutchison/MRC Research Centre, University of Cambridge, Cambridge Biomedical Campus, Cambridge, United Kingdom

Corresponding Author:
Austin Hamp, BSc
Arizona College of Osteopathic Medicine
Midwestern University
19555 N 59th Ave, Room 2138
Glendale, AZ, 85308
United States
Phone: 1 8016470632
Email: ahamp79@midwestern.edu

(JMIR Dermatol 2021;4(2):e30270) doi: 10.2196/30270

KEYWORDS

melanoma; metastatic melanoma; skin neoplasms; angiogenesis inhibitors; monoclonal antibodies; antineoplastic agents; Cochrane reviews; systematic reviews; clinical trials; randomized controlled trials; dermatology

Melanoma is the most lethal type of skin cancer, with a 5-year survival rate of only 22.5% for stage IV (metastatic) disease [1]. Furthermore, with its steadily increasing incidence rate of 5% to 7% per year predicted through 2031, melanoma represents a significant health burden in the United States [1]. Treatment options for metastatic melanoma have changed dramatically with novel therapeutic strategies. However, a consensus on treatment and quality of evidence has yet to be established. “Systemic treatments for metastatic cutaneous melanoma,” a 2018 Cochrane review, assessed the beneficial and harmful effects of these new classes of drugs in treating unresectable metastatic melanoma, defined as stage IIIC or stage IV [2].

This review found high-quality evidence that many newer agents, such as immune checkpoint inhibitors and targeted therapies in the form of small-molecule inhibitors, were more effective than conventional chemotherapies (ie, dacarbazine and temozolomide) in treating unresectable metastatic melanoma. Table 1 summarizes significant findings of the Cochrane review on drug comparisons.

As noted in Table 1, BRAF inhibitors and BRAF inhibitors + mitogen-activated protein kinase (MAPK; MEK) inhibitors (both are MAPK pathway inhibitors) provide improved survival for patients with metastatic melanoma with BRAF gene mutations. These treatment options are of particular importance, as 40% to 60% of metastatic melanomas harbor the BRAF mutation [3]. A 2021 meta-analysis supported the findings of this Cochrane review, concluding improved overall survival (hazard ratio [HR] 0.59, 95% CI 0.47-0.74) and progression-free survival (HR 0.24, 95% CI 0.19-0.3) when comparing BRAF + MEK inhibitors against conventional chemotherapy for unresectable metastatic melanoma (TNM [tumor, node, metastasis] stage IIIc) [3]. While these data are encouraging, additional randomized controlled studies are warranted to further elucidate outcome differences between these combination treatment strategies.

Table 1. A Cochrane review of metastatic melanoma therapies for overall survival, progression-free survival, and toxicity rate.

Drug therapy comparison	Overall survival	Progression-free survival[a]	Toxicity rate[b]
Antiprogrammed cell death protein 1 (anti-PD1) vs conventional chemotherapy[c]			
Outcome	Improved	Improved	Decreased
Corresponding risk[d] vs assumed risk[e]	320 (95% CI 290-360) deaths per 1000 vs 600 deaths per 1000, respectively	610 (95% CI 520-690) per 1000 vs 850 per 1000, respectively	165 (95% CI 93-291) toxicities per 1000 vs 300 per 1000, respectively
Relative effect	HR[f] 0.42, 95% CI 0.37-0.48, 1 study, N=418	HR 0.49, 95% CI 0.39-0.61, 2 studies, N=957	RR[g] 0.55, 95% CI 0.31-0.97, 3 studies, N=1360
Evidence quality[h]	High	Moderate	Low
Anti-PD1 vs anticytotoxic T-lymphocyte–associated protein 4 (anti-CTLA4)			
Outcome	Improved	Improved	Decreased
Corresponding risk vs assumed risk[e]	428 (95% CI 423-454) deaths per 1000 vs 600 deaths per 1000, respectively	641 (95% CI 612-679) per 1000 vs 850 per 1000, respectively	278 (95% CI 215-362) toxicities per 1000 vs 398 per 1000, respectively
Relative effect	HR 0.63, 95% CI 0.60-0.66, 1 study, N=764	HR 0.54, 95% CI 0.50-0.60, 2 studies, N=1465	RR 0.70, 95% CI 0.54-0.91, 2 studies, N=1465
Evidence quality	High	High	Low
Anti-PD1 and anti-CTLA4 vs anti-CTLA4 alone			
Outcome	—[i]	Improved	No significant difference
Corresponding risk vs assumed risk[j]	—	425 (95% CI 375-478) per 1000 vs 750 per 1000, respectively	278 (95% CI 215-362) toxicities per 1000 vs 398 per 1000, respectively
Relative effect	—	HR 0.40, 95% CI 0.35-0.46, 2 studies, N=738	RR 1.57, 95% CI 0.85-2.92, 2 studies, N=764
Evidence quality	—	High	Low
BRAF inhibitors vs conventional chemotherapy[c]			
Outcome	Improved	Improved	No significant difference
Corresponding risk vs assumed risk[e]	307 (95% CI 226-407) deaths per 1000 vs 600 deaths per 1000, respectively	401 (95% CI 328-475) per 1000 vs 600 per 1000, respectively	433 (95% CI 163-1135) toxicities per 1000 vs 341 toxicities per 1000, respectively
Relative effect	HR 0.40, 95% CI 0.28-0.57, 2 studies, N=925	HR 0.27, 95% CI 0.21-0.31, 2 studies, N=925	RR 1.27, 95% CI 0.48-3.33, 2 studies, N=408
Evidence quality	High	High	Low
Mitogen-activated protein kinase (MEK) inhibitors vs conventional chemotherapy[c]			
Outcome	No significant difference	Improved	Increased
Corresponding risk vs assumed risk[e]	541 (95% CI 412-682) deaths per 1000 vs 600 deaths per 1000, respectively	667 (95% CI 549-781) per 1000 vs 850 per 1000, respectively	665 (95% CI 446-995) toxicities per 1000 vs 413 toxicities per 1000, respectively
Relative effect	HR 0.85, 95% CI 0.58-1.25, 3 studies, N=496	HR 0.58, 95% CI 0.42-0.80, 3 studies, N=496	RR 1.61, 95% CI 1.08-2.41, 1 study, N=91
Evidence quality	Low	Moderate	Moderate
BRAF inhibitors + MEK inhibitors vs BRAF inhibitors alone			
Outcome	Improved	Improved	Increased
Corresponding risk vs assumed risk[k]	260 (95% CI 204-321) deaths per 1000 vs 350 deaths per 1000, respectively	490 (95% CI 411-574) per 1000 vs 700 per 1000, respectively	500 (95% CI 421-594) toxicities per 1000 vs 495 toxicities per 1000, respectively

Drug therapy comparison	Overall survival	Progression-free survival[a]	Toxicity rate[b]
Relative effect	HR 0.70, 95% CI 0.59-0.82, 4 studies, N=1784	HR 0.56, 95% CI 0.44-0.71, 4 studies, N=1784	RR 1.01, 95% CI 0.85-1.20, 4 studies, N=1774
Evidence quality	High	Moderate	Moderate
Chemotherapy + antiangiogenic drugs[l] vs conventional chemotherapy[c]			
Outcome	Improved	Improved	No significant difference
Corresponding risk vs assumed risk[e]	423 (95% CI 338-524) deaths per 1000 vs 600 deaths per 1000, respectively	730 (95% CI 627-825) per 1000 vs 850 per 1000, respectively	185 (95% CI 25-1447) toxicities per 1000 vs 272 toxicities per 1000, respectively
Relative effect	HR 0.60, 95% CI 0.45-0.81, 2 studies, N=324	HR 0.69, 95% CI 0.52-0.92, 2 studies, N=324	RR 0.68, 95% CI 0.09-5.32, 2 studies, N=324
Evidence quality	Moderate	Moderate	Low
Polychemotherapy[m] vs conventional chemotherapy[c]			
Outcome	None	None	Increased
Corresponding risk vs assumed risk[e]	No significant difference	No significant difference	372 (95% CI 272-512) toxicities per 1000 vs 189 toxicities per 1000, respectively
Relative effect	HR 0.99, 95% CI 0.85-1.16, 6 studies, N=594	HR 1.07, 95% CI 0.91-1.25, 5 studies, N=398	RR 1.97, 95% CI 1.44- 2.71, 3 studies, N=390
Evidence quality	High	High	Moderate

[a]Progression-free survival is defined as the time from randomization until diagnosis of disease recurrence (local or distant/metastatic). The numbers listed refer to event rates (death rates and progression rates) [2].

[b]Toxicity is defined as the occurrence of grade 3 or higher adverse events according to the World Health Organization scale.

[c]Dacarbazine and its orally available derivative, temozolomide, both of which cross-link DNA, inhibiting transcription and replication [2].

[d]Corresponding risk is based on the assumed risk in the comparison group and the relative effect of the intervention.

[e]Assumed risk (which is defined as the median control group risk across all studies): 1-year overall survival rate (40%); assumed risk in the control population: 1-year progression-free survival rate (15%); assumed risk in the control population: toxicity rate across the control arms of the included trials.

[f]HR: hazard ratio.

[g]RR: risk ratio.

[h]High-quality evidence: further research is very unlikely to change the confidence in the estimate of effect; moderate-quality evidence: further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate; low-quality evidence: further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; very low-quality evidence: very uncertain about the estimate.

[i]No data available.

[j]Assumed risk in the control population: 1-year progression-free survival rate (15%); assumed risk in the control population: toxicity rate across the control arms of the included trials.

[k]Assumed risk in the control population: 1-year overall survival rate (65%); assumed risk in the control population: 1-year progression-free survival rate (30%); assumed risk in the control population: toxicity rate across the control arms of the included trials.

[l]Bevacizumab and endostar.

[m]Dacarbazine in combination with other chemotherapeutics.

Despite the efficacy of BRAF + MEK inhibitors in treating BRAF-mutated melanoma, about 20% of BRAF-mutated melanomas demonstrate resistance to this therapy [4]. Therefore, the pursuit of alternative treatments is necessary. New therapies, such as T-cell therapies, which include tumor-infiltrating lymphocytes (TILs), T-cell receptor therapy, and chimeric antigen receptor T-cell therapy, have shown promising results in treating metastatic melanoma. A recent study reported an objective response rate of 36% (95% CI 25%-49%) and a median duration of response that was not reached after an 18.7-month median follow-up (range 0.2-34.1 months) in patients with metastatic melanoma (stage IIIc or IV) treated with TILs [5]. These therapies present an exciting new avenue to treating metastatic melanoma in patients who have not responded to approved therapy, as there remain very few treatments to improve outcomes in these patients. Additional studies are underway to determine the efficacy of these T-cell therapies on metastatic melanoma and assess the duration of response.

In conclusion, this Cochrane review provides convincing evidence supporting the use of new therapeutics compared to

chemotherapy alone. Given recent evidence of resistance to older drugs, there is an ongoing and urgent need for alternative treatment options and approaches [4]. We encourage additional study and evaluation of evidence regarding novel therapies to accurately and comprehensively identify the most effective treatments for metastatic melanoma, especially the individualized treatment of specific melanoma subsets.

Conflicts of Interest

TS serves as a section editor for *JMIR Dermatology*. In addition, TS receives fellowship funding from the Pfizer Global Medical Grant (58858477) Dermatology Fellowship 2020 and fees for serving on the Medical Advisory Board of Antedotum Inc. JA and A Hamp serve as social media editors for Cochrane Skin. MS is a member of the Cochrane Collaboration.

Editorial Notice

The views expressed in this paper are those of the authors and in no way represent the Cochrane Library or Wiley.
This article is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2018, Issue 2, DOI: 10.1002/14651858.CD011123.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

References

1. Stage 4 Melanoma. Melanoma Research Alliance. URL: https://www.curemelanoma.org/about-melanoma/melanoma-staging/stage-4-melanoma/ [accessed 2021-07-06]
2. Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, Rossi CR, Mocellin S. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev 2018 Feb 06;2:CD011123 [FREE Full text] [doi: 10.1002/14651858.CD011123.pub2] [Medline: 29405038]
3. Wu J, Das J, Kalra M, Ratto B. J Comp Eff Res 2021 Mar;10(4):267-280 [FREE Full text] [doi: 10.2217/cer-2020-0249] [Medline: 33448878]
4. Czarnecka AM, Bartnik E, Fiedorowicz M, Rutkowski P. Targeted Therapy in Melanoma and Mechanisms of Resistance. Int J Mol Sci 2020 Jun 27;21(13) [FREE Full text] [doi: 10.3390/ijms21134576] [Medline: 32605090]
5. Sarnaik AA, Hamid O, Khushalani NI, Lewis KD, Medina T, Kluger HM, et al. Lifileucel, a Tumor-Infiltrating Lymphocyte Therapy, in Metastatic Melanoma. J Clin Oncol 2021 Aug 20;39(24):2656-2666. [doi: 10.1200/JCO.21.00612] [Medline: 33979178]

Abbreviations

HR: hazard ratio
MAPK: mitogen-activated protein kinase
TIL: tumor-infiltrating lymphocyte
TNM: tumor, node, metastasis

Edited by G Eysenbach; submitted 07.05.21; peer-reviewed by J Solomon, Y Li; comments to author 06.07.21; revised version received 23.07.21; accepted 12.09.21; published 23.09.21

Please cite as:
Hamp A, Anderson J, Sivesind TE, Szeto MD, Hadjinicolaou A
From the Cochrane Library: Systemic Treatments for Metastatic Cutaneous Melanoma
JMIR Dermatol 2021;4(2):e30270
URL: https://derma.jmir.org/2021/2/e30270
doi: 10.2196/30270
PMID: