From the Cochrane Library: Systemic Treatments for Metastatic Cutaneous Melanoma

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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 chemotherapies 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: Summary of Significant Findings from the Cochrane Review

| Drug Combination | Overall Survival (HR) | Progression-Free Survival (HR) |
|------------------|-----------------------|-------------------------------|
| BRAF + MEK       | 0.59 (0.47-0.74)      | 0.24 (0.19-0.3)               |
| BRAF             |                       |                               |
| MEK              |                       |                               |
| Conventional     |                       |                               |
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<sup>a</sup> | Toxicity rate<sup>b</sup> |
|--------------------------------------------------------------|------------------|---------------------------------------|--------------------------|
| **Antiprogrammed cell death protein 1 (anti-PD1) vs conventional chemotherapy<sup>c</sup>** |                  |                                       |                          |
| Outcome                                                      | Improved         | Improved                               | Decreased               |
| Corresponding risk<sup>d</sup> vs assumed risk<sup>e</sup>   |                  |                                       |                          |
| 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<sup>f</sup> 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<sup>g</sup> 0.55, 95% CI 0.31-0.97, 3 studies, N=1360 |
| Evidence quality<sup>h</sup>                                 | High             | Moderate                               | Low                      |
| **Anti-PD1 vs anticytotoxic T-lymphocyte–associated protein 4 (anti-CTLA4)** |                  |                                       |                          |
| Outcome                                                      | Improved         | Improved                               | Decreased               |
| Corresponding risk vs assumed risk<sup>e</sup>               |                  |                                       |                          |
| 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<sup>h</sup>                                 | High             | High                                   | Low                      |
| **Anti-PD1 and anti-CTLA4 vs anti-CTLA4 alone**               |                  |                                       |                          |
| Outcome                                                      | Improved         | Improved                               | No significant difference |
| Corresponding risk vs assumed risk<sup>e</sup>               |                  |                                       |                          |
| 425 (95% CI 375-478) per 1000 vs 750 per 1000, respectively   |                  | 401 (95% CI 328-475) per 1000 vs 600 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<sup>h</sup>                                 | —                | High                                   | Low                      |
| **BRAF inhibitors vs conventional chemotherapy<sup>c</sup>**   |                  |                                       |                          |
| Outcome                                                      | Improved         | Improved                               | No significant difference |
| Corresponding risk vs assumed risk<sup>e</sup>               |                  |                                       |                          |
| 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<sup>h</sup>                                 | High             | High                                   | Low                      |
| **Mitogen-activated protein kinase (MEK) inhibitors vs conventional chemotheray<sup>c</sup>** |                  |                                       |                          |
| Outcome                                                      | No significant difference | Improved | Increased |
| Corresponding risk vs assumed risk<sup>e</sup>               |                  |                                       |                          |
| 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<sup>h</sup>                                 | Low              | Moderate                               | Moderate                 |
| **BRAF inhibitors + MEK inhibitors vs BRAF inhibitors alone**  |                  |                                       |                          |
| Outcome                                                      | Improved         | Improved                               | Increased               |
| Corresponding risk vs assumed risk<sup>k</sup>               |                  |                                       |                          |
| 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 |

https://derma.jmir.org/2021/2/e30270
Drug therapy comparison          Overall survival          Progression-free survival          Toxicity rate
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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 vs conventional chemotherapy
Outcome          Improved          Improved          No significant difference
Corresponding risk vs assumed risk          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 vs conventional chemotherapy
Outcome          None          None          Increased
Corresponding risk vs assumed risk          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

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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].

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

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

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

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.

HR: hazard ratio.

RR: risk ratio.

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.

No data available.

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.

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.

Bevacizumab and endostar.

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

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