ONCODAILY MEDICAL JOURNAL

mini review

Evolution of the treatment of metastatic cutaneous melanoma over the past 5 decades

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Published: December 12, 2024

doi.org/10.69690/odmj-002-1224-315

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SUMMARY

Melanoma is a malignancy of melanocytes. Cutaneous melanoma is the deadliest skin cancer. Recent advances have made it possible the availability of targeted therapies and checkpoint inhibitors which significantly improved the prognosis of patients with metastatic cutaneous melanoma. The improvement in prognosis is based on identifying and matching patients to new therapies. The development of resistance after the initial response is a major problem. Studies are underway to understand the mechanisms of the resistance so that new strategies can be found to prevent the emergence of resistance.

CONVENTIONAL THERAPIES

For three decades, from the 1960s to the 1980s, the cornerstone of therapy for metastatic melanoma was dacarbazine (DTIC). It was used alone or in combination with cytotoxic agents or non-specific immunotherapy drugs. Dacarbazine had an overall response rate (ORR) of 5% to 15%. When used in combinations, such as CVD (which includes cisplatin, vinblastine, and DTIC), the response rate increased to 35%, but without a significant impact on survival. High doses of Interleukin-2 (IL-2), administered as intravenous boluses, produced an ORR of 10% to 16% in patients with metastatic melanoma, with about half achieving a complete response (CR) that lasted many years[1]. It was approved by the FDA in 1998. IL-2 therapy requires close monitoring of patients in the hospital due to the potential for multi-organ failure caused by uncontrolled hypotension. To reduce the toxicity of IL-2, we evaluated a lower dose administered via a 24-hour IV continuous infusion, given together with interferon alfa and CVD (referred to as biochemotherapy) at our institution[2]. Bedikian et al. reviewed the outcome of 616 patients treated with CVD alone or biochemotherapy in 8 Phase II/III clinical trials[3]. The ORR (,52% vs. 35%) median overall survival (MOS, 12.2 vs. 9.1 months,) and the 10-year survival rates (12.5% and 5%) respectively were significantly better for patients treated with biochemotherapy. Cox proportional-hazards regression analysis identified treatment with biochemotherapy as a favorable prognostic factor for long-term survival[4]. There was a causal relationship between complete response (CR) and sur-

vival, with half of the patients who achieved CR alive at 10 years. Since the CR rate was 2.5 times higher with biochemotherapy compared to CVD, it became the preferred treatment for young patients with rapidly progressive disease at our institution. However, a meta-analysis of 18 trials involving 2,621 patients failed to show overall survival (OS) benefits with biochemotherapy compared to chemotherapy, despite the higher response rate observed with it[5]. The availability of targeted therapies and drugs inhibiting checkpoint molecules in the late 1990s necessitated checking for BRAF mutations and expression of CTLA-4 and PD-1, PDL1 receptors on melanoma samples.

TARGETED THERAPIES

Targeted therapy is a class of drugs designed to halt the growth of cancer cells by inhibiting mutation-related abnormal molecules within them. Approximately half of skin melanomas harbor mutations in the BRAF gene, making it a key target for treatment. Other, less common mutations, such as those in MEK, NRAS, and KIT, are also addressed with newer, mutation-specific drugs.

BRAF inhibitors

Vemurafenib is a selective inhibitor of the BRAF kinase, specifically targeting the V600E-mutated form of the protein, which is present in 80% to 90% of patients with BRAF-mutated melanoma. In a phase III prospective, randomized trial conducted in chemo-naive melanoma patients with the BRAF V600 mutation, vemurafenib therapy was compared to dacarbazine (DTIC). Patients treated with vemurafenib demonstrated a significantly higher overall response rate (ORR) (48% vs. 5%) and median overall survival (MOS) (13.3 months vs. 10.0 months), respectively[6]. Other BRAF inhibitors with activity against metastatic melanoma include Dabrafenib and encorafenib. Although both Vemurafenib and Dabrafenib were active against metastatic BRAF V600E skin melanoma, virtually all patients eventually had disease progression[7].

At progression, nearly all tumors showed continued BRAF mutation, in addition to elevation of pERK at the time of resistance to Vemurafenib[8]. In some patients, new NRAS, MEK1, and E203 mutations were found. Both Vemurafenib and Dabrafenib are well tolerated and are active against BRAF V600E melanoma. The most frequent grade ≥ 2 toxicities were dermatologic. Other grade ≥ 2 toxicities included arthralgia, fatigue, headache, and fever.

MEK inhibitors

In a phase II multicenter clinical trial, patients with metastatic BRAF V600E or V600K positive skin melanoma were randomized to receive Trametinib or chemotherapy with dacarbazine or paclitaxel. The result showed superiority with Trametinib compared with chemotherapy, (median PFS of 4.8 vs. 1.4 months)[9], diarrhea and edema occurred in 43% and 26% of cases, respectively[9]. Less common toxicities of Trametinib included a decreased cardiac ejection fraction and interstitial lung disease. Other MEK I Inhibitors include Cobimetinib, Binimetinib and Selumetinib.

BRAF-MEK inhibitor combinations

Dabrafenib plus Trametinib

Trametinib has been combined with Dabrafenib to delay the development of resistance to Dabrafenib and to reduce the toxicities of BRAF inhibition. In a phase III trial, patients were randomized to receive either Dabrafenib plus Trametinib or Dabrafenib plus placebo[10] Survival was better with the combination (median 25.1 versus 18.7 months)[10]. The ORR and complete responses were significantly better with the combination compared with Dabrafenib alone.

In a second phase III trial, patients with previously untreated BRAF V600 mutation-positive metastatic melanoma were randomly assigned to either Dabrafenib plus Trametinib or Vemurafenib[11]. Survival, median PFS, and ORR were significantly better with the Dabrafenib plus Trametinib combination. The incidence of cutaneous squamous cell carcinoma and keratoacanthoma was significantly decreased

Table 1 - Phase 3 targeted studies in Metastatic melanoma					
Study Name	*Year last reported*	*Regimens*	*No. of pts*	*Resp. rate (%)*	*Median survival [months] (95% CI)*
COMBI-v [36]	2015	Dabrafenib plus Trametinib	352	64	NR
		Vemurafenib	352	51	17.2
COMBI-d [37,38]	2019	Dabrafenib plus Trametinib	211	67	25.1 (19.2-NR)
		Dabrafenib plus Placebo	212	51	18.7 (15.2-23.7)
COLUMBUS [39,40]	2020	Encorafenib plus Binimetinib	192	63	33.6 (24.4–39.2)
		Encorafenib			
		Vemurafenib	191	40	23.5 (19.6–33.6)
CoBRIM [41,42]	2921	Vemurafenib plus Cobimetinib	247	70	23.5 (19.6–33.6)
		Vemurafenib plus Placebo	248	50	23.5 (19.6–33.6)
NR=Not reached					

with the combination compared with Vemurafenib alone (1% versus 18%).

Vemurafenib plus Cobimetinib

Combination of Vemurafenib plus Cobimetinib was evaluated in a phase III trial in which patients with previously untreated advanced V600 mutation-positive melanoma were randomly assigned to Vemurafenib plus Cobimetinib or Vemurafenib plus placebo[12,13]. The ORR) and complete response rate were superior with the combination of cobimetinib and vemurafenib compared to vemurafenib alone. Additionally, the combination therapy resulted in a 30% reduction in the risk of death compared to vemurafenib monotherapy. Both Trametinib-Dabrafenib and Cobimetinib-Vemurafenib combinations were approved by the US Food and Drug Administration for use as the initial targeted therapy for patients whose melanoma contained a BRAF V600 mutation. The final results of these Phase III trials comparing BRAF-MEK inhibitor combinations to single agent therapy are summarized in (**Table 1)**[14-20]. These results confirm that the regimens combining BRAF and MEK inhibitors are superior to the BRAF or MEK inhibitor used alone with better response rates and overall survival. However, the adverse effects of the combination regimes were more frequent and more severe. While the onset of response was prompt and resulted in rapid clinical improvement, it was noticed that even the patients who achieved complete response with the combination therapy were at risk for tumor recurrence.

C-KIT INHIBITION

Curtin et al. reported c-KIT mutation and/or increase in copy number of c-KIT in mucosal (39%) melanoma, acral lentiginous melanoma (36%), and melanomas arising from chronically sun-damaged skin (28%)[14]. Pilot studies with Imatinib (c-KIT tyrosine kinase receptor inhibitor) failed to confirm clinical efficacy in a small number of patients. Other c-KIT inhibitors include dasatinib or nilotinib.

CHECKPOINT INHIBITORS

Anti-CTLA-4 Antibody

The immune system self-regulates by controlling the expression of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which

binds to the co-stimulatory molecules CD80 and CD86 on antigen-presenting cells. This interaction prevents these molecules from binding to CD28, a process required for full T-cell activation. Monoclonal antibodies targeting CTLA-4 disrupt this inhibitory mechanism, allowing T-cell activation. Ipilimumab, a fully human IgG1 monoclonal antibody, blocks CTLA-4 and enhances T-cell activity. In patients with previously treated stage III/IV melanoma, ipilimumab significantly improved overall survival (OS) compared to the gp100 peptide vaccine15. In another trial with chemo-naive melanoma patients, Ipilimumab plus DTIC demonstrated significant improvement in OS vs DTIC[16]. In these phase 3 studies, the ORR of Ipilimumab was 10 to 15%. The 2-year survival rates of Ipilimumab arms were 10% better than the control arms.

PD- 1 Blockers

PD-1 is an inhibitory cytotoxic T lymphocyte co-receptor that may result in the suppression of anti-tumor immunity.

Nivolumab

Nivolumab is a humanized, monoclonal IgG4 antibody against PD-1. In a dose-finding trial of 107 metastatic melanoma patients, cohorts of patients received Nivolumab 0.1 to 10mg/kg[17]. The MOS was 16.8 months across all doses and it was 20.3 months at the 3 mg/kg dose. The 3-year survival was 40%. Grade 3/4 adverse events occurred in 21% of patients and included diarrhea, endocrine disorders, and hepatitis[18]. A retrospective analysis of pooled results of 4 Novolumab trials in melanoma was performed. The ORR was 34.6% for BRAF- and 29.7% for BRAF+ patients. The ORR was not affected by prior BRAF inhibitor therapy, prior ipilimumab therapy, or PD-L1 status of the tumor. The median duration of objective response was 14.8 months for BRAF- and 11.2 months for BRAF+ patients. The median time to objective response was 2.2 months in both groups. The incidence of grade 3 or 4 treatment-related toxicity occurred at 11.7% and 2.8% of BRAF- and BRAF+ patients respectively[17]. Other PD-1 inhibitors were evaluated and included Lambrolizumab (Pambrolizumab), Cemiplimab (Libtayo). Pembrolizumab works by blocking the interaction between the (PD-1) receptor and its ligands PD-L1 and PD-L2. Atezolizumab is a humanized IgG antibody that binds to PD-L1, preventing it from interacting with PD-1 and B7-1. This removes inhibition of the anti-tumor immune response. Durvalumab stimulates the immune system by binding to PD-L1, preventing it from interacting with PD-1 and CD80 receptors. Cemiplimab works by promoting T cell-mediated immune response against tumors by blocking PD-1.

COMBINATION THERAPY

CTLA-4 Blockade and PD-l Blockade Combination

In a phase I trial, IV doses of Nivolumab and Ipilimumab were administered every 3 weeks for 4 doses, followed by Nivolumab alone every 3 weeks for 4 doses; the combined treatment was then administered every 12 weeks for up to 8 doses[19]. At the optimum doses of Nivolumab at 1 mg/kg of body weight and Ipilimumab at 3 mg per kilogram, 53% of patients had an objective response. Drug-related grade 3/4 adverse effects occurred in 53% of patients.

Several Phase 3 trials have been conducted to determine the best immunotherapy combination regimen. The results of five of these clinical trials are summarized in **(Table 2)**[20-28]. These results confirm that the combination regimes are superior to the single-agent therapies with better ORR and OS. However, the adverse effects of the combination regimes were more frequent and severe.

Special situations and considerations: Two effective regimens became available for therapy of patients with BRAF+ metastatic melanoma, To find out how to sequence them National Cancer Institute conducted DREAMseq trial[29]. The patients were randomly assigned to receive either ipilimumab plus nivolumab

Table 2 - Phase 3 immunotherapy trials in Metastatic melanoma					
Study Name	*Reported Year last*	*Regimens*	*No, of pts*	*Resp. rate (%)*	*median survival [months] (95% CI)*
KEYNOTE-006 [20,21]	2017	Pembrolizumab 10 mg/kg Q21d	185	36	32.7 (24.5–41.6)
		Pembrolizumab 10 mg/kg Q14d	183	37	
		Ipilimumab	181	13	16 (13.3–22.0)
CheckMate 066 [22,23]	2020	Nivolumab	210	40	37.3 (25.4-51.6)
		Dacarbazine	208	14	11.2 (9.6-13.0)
CheckMate 067 [24,25]	2022	Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg	314	57.6	72.1 (38.2 – NR)
		Nivolumab plus Placebo	316	43.7	36.9 (28.2 – 58.7)
		Ipilimumab plus Placebo	315	19	19.9 (16.8 – 24.6)
RELATIVITY-047 [26]	2022	Relatlimab plus Nivolumab	355	43.1	NR (34.2–NR)
		Nivolumab plus Placebo	359	32.6	34.1 (25.2–NR)
COMBI-i [27]	2022	Spartalizumab plus Dabrafenib plus Trametinib	267	69	NR (30.6-NR)
		Dabrafenib plus Trametinib plus Placebo	265	64	NR (28.3-NR)
Imspire150 [28]	2022	Atezolizumab plus Vemurafenib plus Cobimetinib	256	66.3	39
		Vemurafenib plus Cobimetinib plus Placebo	258	65	25.8
NR = Not reached					

or dabrafenib plus trametinib. After reviewing data from the first 265 patients, the safety board found that 2-year survival was significantly superior in the immunotherapy first group (72% vs. 52%). Serious side effects were more common in patients who received immunotherapy. It was recommended that patients with BRAF+ advanced melanoma should receive an immunotherapy combination first unless they have rapidly growing cancer that may cause their demise before immunotherapy benefit kicks in.

Those patients preferably should be treated initially with Targeted therapy. The latest combination immunotherapy regimen for metastatic melanoma approved by FDA includes Relatlimab (a human IgG4 monoclonal antibody that binds to LAG-3, a protein that inhibits T-cell proliferation and cytokine secretion) and nivolumab. The combination significantly improved progression free survival compared to nivolumab[26].

TREATMENT OF PATIENTS WITH BRAIN METASTASIS

Patients with BRAF 600E positive melanoma with brain metastases

In a multi-institutional study of 125 patients with melanoma brain metastases were treated with dabrafenib plus trametinib administered by mouth. The intracranial tumor response rate was about 58% and 44% in asymptomatic vs symptomatic brain metastases patients respectively confirming the activity of the dabrafenib-trametinib combination[30]. Multivariate analysis indicated that

treatment with corticosteroids was associated with poorer ORR (39% vs 63%, and good performance status was associated with better OS[31].

Patients with metastatic melanoma to the brain irrespective of BRAF mutation

This randomized phase 2 trial was done in immunotherapy-naive patients with melanoma brain metastases. Patients with asymptomatic brain metastases with no previous local brain therapy were randomly assigned to nivolumab plus ipilimumab or (nivolumab alone[32] Patients with symptomatic brain metastases or failed to local therapy were given Nivolumab alone. Intracranial ORR and CR rates were 46% vs 20%) and 17 vs 12%) with combination immunotherapy vs nivolumab treated asymptomatic patients respectively. No responses were seen in patients with symptomatic/locally recurrent brain metastases or leptomeningeal disease who were treated with Nivolumab alone.

OTHER THERAPIES FOR METASTATIC MELANOMA

Tumor-infiltrating lymphocyte (TIL) therapy

This therapy involves separating TIL cells from tumor tissue, culturing and expanding their number in the lab, and administering them IV, together with high dose bolus IL-2 after lymphodepletion chemotherapy. In a study, sponsored by by Iovance Biotherapeutics, 66 of 70 enrolled patients received the TIL cell (Lifileucel) therapy, the ORR was 36% with two CR and 22 partial responses. The median duration of response was not reached after an 18.7-month follow-up[33] In February 2024 the Food and Drug Administration (FDA) approved Lifileucel therapy for previously treated progressive melanoma patients[34]. However, persistent hurdles related to separating adequate TIL cells from the tumor and the prohibitive cost ($500.000) make this therapy out of reach of the patients.

CAR-T cell therapy

This therapy involves genetic modification of the patient's mono-nuclear cell-derived T cells collected from the bloodstream to give them the ability to recognize specific target molecules on the cancer cells and to increase their ability to kill them. The modified cells are expended and infused into the patient together with IL-2. Unfortunately, the ideal target molecule for melanoma cells has not been found to date. Of the dozen phase I /II CAR-T studies in melanoma the results of only one are available. More research is needed[35].

New studies

Multiple new studies directed to new immunotherapy targets are being investigated. The mechanisms of the emergence of resistance to checkpoint inhibitors and ways to prevent them. are being investigated New PD-1 inhibitors have been found and research to compare their efficacy to the ones already in use is underway. The results of studies combining targeted therapy with checkpoint inhibitors will be reported soon.

CONCLUSIONS

The treatment landscape for advanced cutaneous melanoma has witnessed remarkable progress in the past 2 decades. This progress was driven by the introduction of targeted therapies and checkpoint inhibitors into clinical practice. These new treatments of melanoma shifted to the outpatient clinic while significantly improving the survival of the patients. This review has provided a simplified overview of treatment strategies for BRAF+ and wild-type melanoma. Further research is needed to deal with the problem of the emergence of resistance given the limited availability of salvage therapies.

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