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BRAF inhibition: Bridge or boost to T cell therapy?

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Summary

The concept of treatment-refractory disease has evolved as checkpoint modulation has changed the therapeutic landscape for patients with metastatic melanoma. Developing meaningful salvage strategies will involve the exploration of combination therapies and new immunotherapeutics, including adoptive transfer of tumor infiltrating lymphocytes or other T-cell based therapy.

In this issue of Clinical Cancer Research, Atay and colleagues explore the relationship between mannose-6-phosphate receptor (M6PR) and inhibitors of the BRAF/MEK pathway in human melanoma(1). With a series of *in vitro* experiments, they demonstrate that M6PR is upregulated by PLX4720, a BRAF inhibitor, in a dose-dependent fashion in both BRAF-sensitive and BRAF-resistant melanoma. Treatment was associated with an increased susceptibility to lysis by HLA-matched tumor infiltrating lymphocytes (TILs). Treated cell lines also demonstrated increased intracellular GranzymeB, associated with M6PR overexpression and abrogated in M6PR knock-out lines. In models utilizing patient-derived xenografts, a combination of PLX4720 and TILs significantly slowed the growth of tumors when compared to either agent alone or no treatment.

While patients with tumors bearing the $BRAF^{V600E/K}$ mutation may experience initial clinical benefit, most will develop resistance to these targeted therapies. Previous observations in murine models of melanoma led the group to hypothesize that a combination of BRAF targeted therapy with adoptive transfer of TILs may be a feasible human clinical alternative. Using this strategy, this group demonstrated a 63% 12-week and 35% 12-month objective response rate (6 of 16 treated patients).

These interesting experiments by Atay et al reflect upon an earlier era, before the clinical translation of immune checkpoint modulation radically changed the course of patients with metastatic melanoma. The role of BRAF/MEK inhibition in an overall treatment strategy has been altered, and it is necessary to place these clinical findings within that context. The initial trials leading to the approval of vemurafenib, a BRAF inhibitor, and ipilimumab, a monoclonal antibody targeting cytotoxic T lymphocyte antigen 4 (CTLA-4), were being conducted concurrently. The first new drug for metastatic melanoma since interleukin-2 in 1998, ipilimumab was capable of mediating objective responses in 7% of patients(2). Vemurafenib was approved later the same year after demonstrating significant improvements

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in overall and progression free-survival (hazard ratio 0.37 and 0.26, respectively) when compared to dacarbazine(3).

While continuing to monitor progression and survival in those clinical trials, monoclonal antibodies targeting programmed death receptor 1 (PD-1) were developed. Nivolumab and pembrolizumab were both initially approved for patients with melanoma refractory to vemurafenib and/or ipilimumab. However, the difference between the strategies became clear over time as the survival curves matured. The checkpoint modulators were capable of "raising the tail" of the survival curves, signifying long-term durable survival benefit for patients, whereas BRAF/MEK targeted strategies demonstrated transient responses. Pembrolizumab, nivolumab, and nivolumab in combination with ipilimumab are now approved as first-line treatment regimens for patients with metastatic melanoma(4,5).

The translational challenge now is to develop meaningful therapeutic options for patients refractory to checkpoint blockade, and investigators have focused on the development of novel immunotherapeutics and combinations of reagents with known reactivity in melanoma. Unfortunately, attempts to combine vemurafenib with other approved treatments have met with little success. Two independent trials of vemurafenib with high dose interleukin-2 were stopped early for poor accrual in the era of checkpoint blockade and adding ipilimumab to vemurafenib induced dose-limiting hepatotoxicity.

An experimental strategy also capable of "raising the tail" is the adoptive transfer of TILs derived from freshly resected melanoma metastases. In trials with long-term follow-up, objective clinical responses could be seen in ~50% of patients, including durable, likely curative, complete responses in ~25% of patients. Only two patients (of 46) with complete responses have recurred, and 5- and 10-year overall survival approached ~30%(6,7). The current study by Atay et al combining BRAF inhibition with TIL appears to be comparable with these results. Similarly, our published efforts combining vemurafenib with adoptive transfer of TIL reported a 64% objective response rate (7 of 11 patients) with two complete responses(8). Even in a pre-checkpoint blockade era, a randomized trial would have been necessary to identify superiority of the combination compared to TIL alone. However, the majority of patients in each of these trials were naïve to checkpoint therapy hindering interpretation in today's landscape (Table 1)(1,6–11).

Checkpoint-refractory tumors and the lymphocytes that they harbor may be qualitatively or quantitatively different. In much the same way that BRAF inhibition may exert a selection pressure to create treatment-resistant clones, the application of checkpoint inhibitors results in immunoedited tumors comprised of clones without known antigen recognition or lacking important antigen processing molecules. In a small sample of patients undergoing serial biopsy while receiving pembrolizumab, the tumors of non-responding patients had lower CD8+ T cell density at all time points(12). It is also possible that intratumoral T cell diversity is also affected by anti-PD-1 treatment(13).

Exploration of adoptive transfer as a salvage therapy after checkpoint blockade has demonstrated that objective responses are possible and provide meaningful clinical outcomes for patients with limited options. While the overall response rate is likely to be

lower than historical efforts, the ability to mediate regression suggests a component of adoptive cell transfer acts by mechanisms separate from checkpoint inhibition. The potential value of Atay's findings may lie in the concept of increasing responsiveness to T cell-mediated cytolysis via upregulation of M6PR regardless of the treatment mechanism employed.

Our initial efforts in broadening the applicability of TIL for cancer therapy were based in transitioning the concept from melanoma, where conventionally grown TIL could work, to more common cancers, where it did not. Careful retrospective analysis of responding patients identified TIL clonotypes that recognized nonsynonymous mutations in random intracellular proteins(14,15). Identifying and reinfusing TILs of the latter category has been a successful strategy when applied to selected epithelial cancers, including a complete regression of metastatic breast cancer(16,17). The intratumoral milieu of checkpoint-refractory melanoma may be similar to that of epithelial cancers; selecting TIL on the basis of neoantigen reactivity may improve response rates over current efforts. Further refinement of this neoantigen-selection concept may involve the introduction of mutation-specific T cell receptors into a patient's peripheral blood to provide a more enriched, perhaps less differentiated, infusion product.

The development of an autologous cell product, however, requires an investment of time, which may be limited for this patient population. The current treatment options for patients diagnosed with metastatic melanoma should be mapped carefully with strategic timing to harness the benefit of approved therapeutics and optimize access to experimental clinical trials. The high response rates of BRAF/MEK inhibitors make them an attractive bridge therapy for patients navigating entry and registration into early phase clinical trials.

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Table 1.

Selected Trials of Adoptive Cell Therapy for Metastatic Melanoma

Study	Year	Strategy	Total # patients treated (enrolled)	# patients with checkpoint refractory disease*	Objective Response Rate # (%)	Complete Response Rate # (%)
Rosenberg et al[6]	2011	TIL ± total body irradiation	93	8	52 (56)	20 (22)
Pilon-Thomas et al[9]	2012	TIL	13 (19)	Not reported	5 (38)	2 (15)
Radvanyi et al[10]	2012	TIL	31	0	13 (42)	2 (6)
Besser et al[11]	2013	TIL	57 (80)	5	23 (40)	5 (9)
Goff et al[7]	2016	TIL ± total body irradiation	99 (101)	40	55† (56)	26† (26)
Deniger et al[8]	2017	Vemurafenib + TIL	11	2	7 (64)	2 (18)
Atay et al[1]	2019	Vemurafenib + TIL	16 (17)	3	10 (63)	1 (6)

*includes disease refractory to anti-CTLA-4, anti-PD-1, or both

†one additional objective response has been identified and two patients developed complete responses since publication