EDITORIAL

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Intratumoral talimogene laherparepvec therapy in melanoma

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“While T-VEC treatment was shown to be clinically beneficial in this study, with a relatively high overall response rate, especially considering that treatment was only locally injected, these benefits were only observed in patients with limited disease burden...”

Over the past several years, we have witnessed a boom in successful drug development for the treatment of patients with advanced melanoma. A number of novel drugs have demonstrated improved survival in these patients in large, randomized clinical trials. These include ipilimumab (an anti-CTLA4 antibody), vemurafenib and dabrafenib (selective BRAF inhibitors), trametinib (selective MEK inhibitor) and pembrolizumab and nivolumab (anti-PD-1 antibodies) [1–6]. As a result of these advances, we now anticipate a median survival of greater than 2 years in patients with metastatic melanoma when these drugs are given in combination, especially in the case of dabrafenib with trametinib or ipilimumab with nivolumab [7]. In addition to these systemic therapy drugs, a number of local therapies have been shown to be beneficial in a subset of patients with surgically unresectable melanoma. For example, hyperthermic isolated limb perfusion or isolated limb infusion therapy induce significant tumor reduction in a majority of patients with regional in-transit lesions occurring in the extremities [8]. These treatments are capable of delivering high doses of cytotoxic drugs to the affected

area with minimal systemic effects. The current limitation of perfusion/infusion therapies, however, is that they have not been shown to improve overall survival in patients.

Intratumoral injection therapy in melanoma

Another interesting modality of localized therapy that has been investigated in clinical trials for the treatment of advanced melanoma is intratumoral (or intralesional) injection therapy, in other words, the delivery of drugs directly into tumor lesions. Examples of drugs that have been tested with intratumoral injection therapy include bacillus Calmette–Guérin, IL-2, granulocyte–macrophage colony-stimulating factor (GM-CSF), velimogene aliplasmid (Allovecin®) and rose Bengal disodium (PV-10) [9]. Researchers have frequently observed dramatic shrinkage of the injected tumor lesions with these agents, and also variable degrees of tumor reduction in the noninjected, ‘bystander’ lesions. In a Phase II study of intratumoral injection of PV-10 in 80 patients, 62 of whom had stage III melanoma, the observed response rate was 51% among

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injected lesions and 33% among noninjected bystander lesions, showing cautious promise [10]. This overall tumor reduction was accompanied by increased circulating cytotoxic T cells and enhanced release of tumor-specific IFN- γ [11], suggesting immune-stimulatory activity of these drugs remote to the injection location. Recently, a randomized Phase III study comparing intratumoral PV-10 injection therapy with chemotherapy in patients who have failed, or are not candidates for, checkpoint inhibitors has begun. However, not all of the results from these prospective clinical trials of intratumoral injection have been so positive. For example, despite promising results of intratumor injection of velimogene aliplasmid in a Phase II study, a larger, randomized, Phase III study showed that this drug leads to neither higher response rate at 24 weeks nor better overall survival over cytotoxic chemotherapy.

Talimogene laherparepvec intratumoral injection therapy

Talimogene laherparepvec (T-VEC; also called OncoVex^{GM-CSF}) is an oncolytic vaccine produced by deleting the *ICP34.5* gene to improve tumor cell killing, and modifying the *ICP47* gene to enhance viral replication in tumors, and expressing GM-CSF to accentuate the systemic immune-stimulating property of the virus [12]. Therefore, T-VEC has the potential to kill tumor cells both directly via its oncolytic property, and also indirectly via enhanced immune activation in patients.

In a recent randomized Phase III study, intratumoral T-VEC injection therapy was shown to have better clinical activity than subcutaneous GM-CSF injection [13]. The rate of durable response (lasting for 6 months or more) was 16% for T-VEC treatment versus 2% for GM-CSF treatment. The overall response rate was 26% with T-VEC treatment. Among uninjected lesions, 15% of visceral and 34% of nonvisceral metastatic lesions showed a tumor reduction of 50% or more. The time to treatment failure was 8.2 versus 2.9 months, favoring T-VEC treatment. The hazard ratio for death was 0.79 (95% CI: 0.62–1.00); $p = 0.051$ (median OS: 23.3 vs 18.9 months). As anticipated from previous studies, intratumoral T-VEC injection was well tolerated.

While T-VEC treatment was shown to be clinically beneficial in this study, with a relatively high overall response rate, especially considering that treatment was only locally injected, these

benefits were only observed in patients with limited disease burden; the durable response rate and overall survival duration did not differ significantly between the two treatment groups among patients with stage M1b or M1c melanoma [13]. In addition, patients with involvement of more than three visceral organs, patients with any lesion greater than 3 cm, and patients with progressing hepatic metastatic lesions, were excluded from participating in the study, suggesting that the seemingly high response rate of T-VEC intratumoral treatment could be due in part to patient selection bias.

The future of intratumoral T-VEC therapy

On the basis of the Phase III study results, T-VEC is currently under review by the US FDA for the treatment of advanced melanoma. If approved, this will add one more option to the crowding field of systemic therapy for advanced melanoma. Intratumoral T-VEC treatment has many potential clinical advantages. First, like other immunotherapeutic agents, it can render clinical benefit regardless of *BRAF* mutation status. Second, the high likelihood of tumor reduction in injected lesions could translate into palliation of symptoms, such as pain or bleeding, in superficial lesions which are readily accessible for direct injection. Third, intratumoral T-VEC treatment is safe and easy to administer in an outpatient clinic setting, so it will provide an easily adoptable treatment option for community oncologists and surgeons. Finally, treatment duration with intratumoral T-VEC therapy is more clearly defined; treatment with T-VEC injection is to be discontinued when injected/injectable lesions are completely regressed, whereas the optimal duration of treatment, as determined by adequate control of disease, is less clearly defined with checkpoint inhibitors or molecularly targeted drugs.

Despite the advantages; however, T-VEC treatment is only applicable to patients with mostly superficial metastatic lesions which are accessible by direct needle injection. More importantly, the marginal survival benefit with intratumoral T-VEC treatment is a serious limitation in recommending this treatment option to patients, especially when more effective therapy options with clear survival benefit over cytotoxic drugs are currently available. Anti-PD-1 antibodies, for example, are also well tolerated and have significant clinical activity, including clear survival benefit [5,6,14]; most clinicians will likely

prefer these checkpoint inhibitors over intratumoral T-VEC therapy, even in patients with easily injectable superficial lesions. For patients with *BRAF*-mutant advanced melanoma, combinations of BRAF inhibitors and MEK inhibitors have high response rates, ranging from 64 to 67% [15–17]; these targeted drug therapies are also more effective than T-VEC therapy in tumor reduction of visceral organ metastases, meaning that there is a higher likelihood of palliation of symptoms associated with visceral metastatic lesions with these treatments.

The impact of intratumoral T-VEC therapy in treatment of advanced melanoma will be more significant if it synergizes with other immunomodulating treatments. There is scientific rationale for combining intratumoral T-VEC treatment with checkpoint inhibitors, as these drugs activate T cells through different mechanisms: T-VEC through augmenting tumor antigen presentation by dendritic cells, and checkpoint inhibitors through stimulating T effector functions by antagonizing co-inhibitory molecules, such as CTLA4 or PD-1. In a Phase I study of a combination of intratumoral T-VEC treatment with ipilimumab, ten out of 18 patients demonstrated a clinical response, including six patients with a complete response and a median PFS duration was 10.6 months [18]. Currently, two clinical studies are underway investigating intratumoral T-VEC treatment in combination with checkpoint blockade therapies: a randomized Phase II study of ipilimumab with or without intratumoral T-VEC (NCT01740297), and an open-label Phase Ib/II study of the combination of intratumoral T-VEC and an anti-PD1 antibody (pembrolizumab; NCT 02263508).

Conclusion

Intratumoral T-VEC injection therapy has a high response rate among injected lesions and has been shown to regress bystander lesions. However, overall survival benefit is marginal, especially comparing with the survival benefit of checkpoint inhibitors or BRAF/MEK inhibitors, and the clinical benefit appears to be limited to patients with skin, soft tissue and/or nodal metastases, and low tumor load. If approved for commercial use, T-VEC intratumoral therapy may be ideal for the subset of patients with injectable lesions and low overall tumor load who do not wish for long-term treatment with anti-PD-1 antibodies or molecularly targeted drugs. In addition, if the cost of T-VEC injections is determined to be much lower than conventional checkpoint inhibitors or BRAF/MEK inhibitors, which can cost over US\$100,000 per year, intratumoral T-VEC therapy may provide a treatment option with some demonstrated clinical benefit for those patients with limited financial resources. While, as a single agent, it will not likely change the landscape of melanoma therapy in any significant manner, it may show promise in combination with checkpoint inhibitor therapies.

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