Combination Therapy of Immunocytokines with Ipilimumab: A Cure for Melanoma?

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Although biological therapy has shown promising clinical responses in many cancers including metastatic melanoma, only a subset of patients has shown marked regression of lesions. In most patients, systemic administration of biological therapies with cytokines is associated with severe toxicities. Schwager et al., in this issue of Journal of Investigative Dermatology, have examined the role of immunocytokines L19-IL2 and L19-TNF to minimize toxicities, and in combination with Ipilimumab they report complete regression of tumors using syngeneic mouse models. The results, if confirmed in clinical trials, will have major implications for the treatment of human cancers, including melanomas.


Metastatic melanoma is an aggressive form of skin cancer with limited treatment options. Melanoma patients are resistant to conventional chemotherapy (dacarbazine and temozolomide), and they also develop resistance to a recently approved targeted therapy drug Vemurafenib. Vemurafenib has shown marked reduction of tumor burden with near doubling of the overall survival of melanoma patients to ~16 months (Flaherty and Fisher, 2011). Clinical trials are underway to improve overall survival of melanoma patients, further using combination therapy of Vemurafenib and Ipilimumab. Ipilimumab (also known as Yervoy) is a human monoclonal antibody directed against cytotoxic T-lymphocyte antigen 4 (CTLA4), an immune checkpoint molecule on the surface of activated T cells. Treatment of patients with Ipilimumab alone prolongs survival of ~20% of patients, leading to renewed interest in immunological therapies of melanoma (Mellman et al., 2011). In the past, biological therapies in melanoma patients with cytokines such as IL2 or IFN-α showed transient responses but little benefit in overall survival. In a small subset of melanoma patients, however, high-dose IL2, which enhances both T-cell– and natural killer (NK) cell–mediated antitumor activities, can induce significant responses. Locally administered high-dose tumor necrosis factor-α (TNF-α) in combination with melphalan is very effective in reducing tumor burden (Grunhagen et al., 2004). However, in most patients, cytokine therapies are invariably accompanied by severe toxicities (Mellman et al., 2011).

To overcome the toxicities of systemic administration of cytokines, several studies have used targeted delivery of cytokines, either alone or in combination with chemotherapy, with encouraging results (Dehal et al., 2002; Fan et al., 2010; Moschetta et al., 2012). TNF (scFv) of an antibody fused with a cytokine (immunocytokine) has also been used successfully to reduce toxicities effectively and to improve the survival of cancer patients (Johannsen et al., 2010; Eigentler et al., 2011). An antibody (L19) directed against the unique ED-B domain of fibronectin, a matrix protein expressed in tumor blood vessels, has been used in the clinics for radioimaging and radioimmunotherapy (Tijink et al., 2006; Rossin et al., 2007; Tijink et al., 2009). The scFv of the L19 antibody was fused with the cytokines IL2 or TNF-α for targeted delivery to the tumor. These immunocytokines, when tested in several phase I/II clinical trials, showed beneficial effects and minimal toxicity for a wide range of tumor types, including metastatic melanoma (Eigentler et al., 2011). In several animal tumor models, immunocytokine L19-IL2 showed potent antitumor activity by activating several types of immune cells, including macrophages, NK cells, and CD4+ and CD8+ T cells (Halin et al., 2002; Wagner et al., 2008; Schliemann et al., 2009). In a small cohort of patients with unresectable melanoma lesions in the limbs, local administration of L19-TNF plus melphalan with mild hyperthermia induced objective responses (Papadia et al., 2012). Collectively, immunocytokines showed potent antitumor activities and less toxicity compared with systemic administration of cytokines.

In this issue of Journal of Investigative Dermatology, Schwager et al. (2012) have used immunocytokines to specifically deliver IL2 or TNF-α to tumor sites. In the mouse F9 teratocarcinoma model, anti-CTLA4 antibodies alone had no effect on tumor growth, as these cells lack major histocompatibility complex-class I molecules, and hence lack T-cell–mediated tumor inhibition. However, L19–IL2 fusion protein treatment led to significant tumor growth delay due to IL2 activation of NK cells, but not complete regression owing to the lack of T-cell activity. Combining L19–IL2 with anti-CTLA4 antibody also resulted in significant tumor growth delay compared with either treatment alone. Complete tumor regression was seen in a small number of mice. Similar results were seen with the combination therapy of L19–IL2 and anti-CTLA4 in

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the CT-26 colon carcinoma model. Antitumor immunity in this model was due mainly to T cells, but not due to NK cells. Interestingly, when mice with complete tumor regression were rechallenged with CT-26 tumor cells, no tumor growth was observed, indicating a protective T-cell memory response against CT-26 cells. Tumors were infiltrated by T cells, NK cells, B cells, and macrophages. Surprisingly, combination therapy of L19–IL2 with anti-PD-1 antibody, a more potent immune check-point reagent similar to anti-CTLA4 antibody, resulted in delayed tumor growth but not complete tumor regression. Finally, combining immunocytokine L19–IL2 and L19–TNF locally in the F9 teratocarcinoma resulted in strong synergistic antitumor activities leading to complete regression.

Combination therapies using immunocytokines and Ipilimumab are on the horizon for clinical trials.

On the basis of the above observations and the promising therapeutic activity of L19–IL2 in early clinical trials, Schwager et al. (2012) have suggested two therapeutic options for the treatment of metastatic melanoma. The first is to combine L19–IL2 with Ipilimumab, and the second is to combine L19–IL2 with L19–TNF to eradicate superficial lesions of late-stage melanoma.

Although there is a potential benefit of combining L19–IL2 with anti-CTLA4 or L19–IL2 with L19–TNF, further studies need to be conducted in patients to confirm these findings. Only a subgroup of melanoma patients treated with Ipilimumab show prolonged survival. In this group, patients with increased number of tumor-infiltrating lymphocytes after treatment with Ipilimumab benefited the most. Similar beneficial responses of increased lymphocyte infiltration after combined treatment with L19–IL2 and Ipilimumab were also observed in Schwager’s mouse tumor models. However, it is unclear whether the increased lymphocyte infiltration caused direct regression of tumors. An in-depth analysis of the mechanism of tumor regression after treatment of Ipilimumab and L19–IL2 would provide a foundation for future trials. In Schwager’s study, Schwager et al. (2012) the administration of immunocytokine L19–IL2 did not increase the number of regulatory T cells (Tregs). This may be because of low baseline levels of Tregs in the mouse models. In some cancer patients, higher baseline levels of Tregs may lead to further enhancement and functional activation of regulatory cells due to the presence of L19–IL2 in the tumor microenvironment, resulting in dampening of the overall immune response. The presence of Ipilimumab should not reverse the overwhelming functional activation due to IL2. This may lead to inhibition of antitumor responses. Such events need to be taken into consideration before combination therapies using immunocytokines and Ipilimumab are adapted to clinical trials.

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES