Commentary

Interleukin-2 as anticancer immunotherapy in the age of checkpoint inhibition

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Comment on: Rekers NH, Zegers CM, Yaromina A, *et al.* Combination of radiotherapy with the immunocytokine L19-IL2: Additive effect in a NK cell dependent tumour model. Radiother Oncol 2015;116:438-42.

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Rekers and coworkers recently published their study on anti-tumor effects of recombinant interleukin-2 (IL2) and the immunoconjugate L19-IL2 with and without combined radiotherapy. Immunocompetent mice were injected with F9 teratocarcinoma cells. As soon as an average tumor volume of 200 mm³ resulted, different therapy schedules were administered including IL2, L19-IL2 and radiotherapy. Tumor growth was monitored until the tumor volume reached 4 times the volume at the start of therapy (1). This study raises the question on the role of immunotherapy with IL2 and IL2-related immunocytokines, after immunotherapy with checkpoint inhibitors has been widely established.

IL2 is a long-known immunocytokine, which acts as a growth factor for T-cells and for NK-cells (2). First described in 1976, multiple clinical studies in cancer patients have been conducted since 1984. Treatment with high dose IL2 in melanoma and renal cell cancer led objective tumor responses in ~15% of patients with ~6% of complete tumor responses being long-lasting. Additionally, patients with stable disease under this treatment benefited with prolongation of survival (3). In the 1990s, IL2 (Aldesleukin®) was approved in the United States for renal cell cancer and melanoma and in the European Union for renal cell cancer only. Approval was based on the observation that a small percentage of patients obviously achieved cures of their cancer. No significant prolongation of overall survival in comparative trials has ever been shown (4).

Interestingly, the exact mechanism of tumor cell killing by IL2 remains still unclear after 40 years of research. The role of the innate and of the adaptive immune system in IL2-treatment remains to be determined. In mouse models, obviously $CD8^+$ T cells and NK cells both contribute to the antitumor effect (5). In the 1980s, Rosenberg and coworkers coined the terminus "lymphokine activated killer cells" (LAK-cells), implicating that the tumor effect of IL2 is mainly mediated via the innate immune system. But this has never been convincingly proven, and there are data that IL2 may also act via the adaptive immune system and specific cytotoxic T-cells as stimulated with vaccines (6). Now, in the publication of Rekers and coworkers, the effect of IL2-treatment via the innate immune system was studied in a tumor mouse model lacking MHC-I expression on tumor cells, and, therefore, not responsive to a specific cytotoxic T-cell action. Immunotherapy via the innate immune system may gain higher importance in future, particularly for patients not responding to tumor specific cytotoxic T-cells.

Ipilimumab, an inhibiting CTLA-4 antibody, was the first immunotherapy shown to significantly prolong overall survival in metastatic melanoma (7). Its mechanism is to block inhibiting receptors on T-cells, which inactivate these cells. Ipilimumab achieved ~15% of objective anti-tumor responses, whereas inhibiting PD-1 antibodies achieve 30–40% objective anti-tumor responses in metastatic melanoma (8). Both types of antibodies are likewise effective in lung cancer and other solid tumors. They act via release of the already present adaptive immune response to the tumor and they show that probably 50% and more of the patients (valid for melanoma) may already have a specific cytotoxic T-cell response to the tumor. This may also explain why vaccination trials failed: The specific T-cell response was already present, but inactivated by inhibitory T-cell receptors. However, not all patients respond to this release of specific cytotoxic T-cells by checkpoint inhibitors, and probably half of all patients do not develop stable disease or tumor remission. For these patients, the option of an innate anti-tumor response by natural killer

cells may remain a promising option. This topic has not yet been addressed in clinical trials, to the best of our knowledge.

What are the new aspects of the publication of Rekers and coworkers? First, the bispecific antibody L19-IL2 is seemingly more active than classical IL2. The L19-chain binds to the extra-domain B of fibronectin (9). This ED-B is strongly expressed in the tumor stroma of solid tumors and has been described as a marker of angiogenesis. The second chain of this antibody consists of recombinant IL2, which is enriched in the tumor environment by the immunoconjugate L19-IL2. Inhibition of tumor growth was double as effective with L19-IL2 compared to classical IL2 without the combination of radiotherapy. IL2 was administered at a dose 6.7 µg and L19-IL2 at a dose of 20 µg. However, it remains unclear, whether these dosages are equivalent in their activity. Secondly, the interaction with radiotherapy was examined in these animal experiments. The combination of systemic L19-IL2 with radiotherapy before the immunotherapy led to an increased anti-tumor efficacy. However, radiotherapy during the immunotherapy schedule did not enhance the anti-tumor effect. The anti-tumor effect was mediated seemingly by NK-cells, which were found significantly increased within the tumors. There were no increased levels of $CD8^+$ T-cells inside the tumors after the IL2 based immunotherapies.

Checkpoint inhibition is presently on the rise as immunotherapy in many solid tumors. Therefore, it becomes more and more difficult to find a place for other immunotherapeutic approaches. The role of IL2 and L19-IL2 should preferentially be examined in patients not responding to checkpoint blockade, this means not developing a specific cytotoxic T-cell response to the tumors. In these patients, IL2 driven immunotherapy may become active via tumor response to the innate immune system.

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