Correspondence

IL2 based immunotherapies: towards a personalized and curative antitumor response

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In his commentary, Claus Garbe described our study on the combination of radiotherapy (RT) and the immunocytokine L19-IL2 in the F9 fibrosarcoma model (1) and discussed our work in a checkpoint inhibitor related context. The author is positioning interleukin-2 (IL2) based immunotherapies in the so-called 'age of the checkpoint inhibition' and concluded that the role of IL2 and/or L19-IL2 should preferentially be examined in patients not responding to checkpoint blockade, since these patients are not able to develop specific cytotoxic T cell responses. Therefore, IL2 based immunotherapeutic approaches might circumvent this problem by activating the innate immune response against the tumor (2).

The comparison of IL2 based therapies and checkpoint inhibitors made in this commentary is based on the fact that checkpoint inhibitors act on the modulation of an already present adaptive immune response (cytotoxic T cells) and IL2 based therapies are only able to trigger the innate immune system (NK cells). Indeed, we have shown that L19-IL2 (an immunocytokine binding to EDB present in the tumor vasculature and known for its locally operating immune modulating effects) is able to cause a significant growth delay associated with an intratumoral increase of NK cells in a MHCI negative tumor model (1). These effects were significantly higher as compared with equimolar levels of IL2 and are explained by the larger proportion of IL2 reaching the EDB positive tumor by using L19 as a tumor specific vehicle. Therefore, we agree with the statement that the ability of L19-IL2 to activate members of the innate immune system, in our study NK cells, indeed creates an interesting alternative for checkpoint inhibitors in case the cytotoxic T cell 'baseline' is insufficient.

Furthermore, we have shown that the delivery of a single RT dose prior to the L19-IL2 treatment schedule further enhanced the antitumor response of this treatment, while a schedule administrating RT during L19-IL2 treatment was less effective. Since NK cells can become activated by L19-IL2 to target MHCI negative tumor cells directly and do not necessarily need activation via cross-presentation of antigen presenting cells, this may explain why we have found an additive and not a synergistic effect of the combination treatment in this model (1). However, in addition to this tumor model we found long-lasting synergistic and additive effects of RT administrated prior to L19-IL2 in other tumor models. These models were all MHCI positive, therefore the RT + L19-IL2 combined treatment approach was highly dependent on the action of cytotoxic T cells instead of NK cells (3). In clinical setting, tumors tend to have a heterogeneous expression of MHCI (4) and therefore a mixture of cytotoxic T cells and NK cells may become activated when patients are treated with a combination of radiation and L19-IL2 based immunotherapy.

For decades, the focus of RT related research was on its direct and local effects, depending on DNA damage and the intrinsic repair capacity of irradiated cells (5). However, RT additionally can cause immunogenic cell death of cancer cells, promoting the uptake and cross-presentation of released tumor (neo)antigens by dendritic cells (DC) to T cells in the draining lymph node and converting the irradiated tumor into an *in situ* personalized tumor vaccine (6). The concept that

personalized vaccination is based on the recognition of (neo)antigens generated by tumor specific T cells (7), placed the use of RT in a totally different context (8). However, the commentary (2) addresses the issue that not all patients respond to treatment with checkpoint inhibitors via the release of specific cytotoxic T cells, a problem also observed in our MHCI positive tumor models when treated with L19-IL2 as single treatment. Based on recent publications (9,10) and our observations we believe this may be caused by the insufficient cross-presentation of specific (neo)antigens to cytotoxic T cells and a decreased expression of (neo)antigens on MHCI by the tumor. In our opinion, RT can be the solution for both of these problems, and therefore RT can be used to further optimize and personalize an immunotherapeutic approach, including L19-IL2 and checkpoint inhibitor treatments. Furthermore, L19-IL2 may be favorable in case the RT triggered immunogenic cell death is not optimally capable of increasing the tumors immunogenicity, i.e., increasing the MHCI expressing tumor specific (neo)antigens, providing the immune system an extra cytotoxic tool, the NK cells.

Radiotherapy (RT) is one of the major treatment options for cancer and approximately 52% of all cancer patients receive RT during their treatment. The possibilities of RT to initiate an antitumor response by creating an *in-situ* tumor vaccine and its potential to change a tumors (neo)antigen landscape, has the potential to greatly enhance the personalization and effectiveness of immune modulating agents. Indeed, the mechanisms of checkpoint inhibitors relay on the re-activation of already present but exhausted tumor (neo)antigen specific T cells, L19-IL2 function relies more on the activation and proliferation stage of these tumor specific T cells. In other words, checkpoint inhibitors are able to get rid of the brake, and L19-IL2 is able to push the gas. In our opinion, the first line treatment must consist of RT to create a personalized in situ vaccine and increase a tumors immunogenicity, followed by L19-IL2 to stimulate the proliferation of tumor (neo)antigen specific T cells at the tumor site. When these specific T cells become exhausted, expressing CTLA-4 and/or PD1 immune downregulating molecules, we see a clear role for checkpoint inhibitors. In case RT was insufficient to initiate a proper antitumor immune response against the tumor, indeed, L19-IL2 is even able to stimulate NK induced cytotoxicity. However, we believe that a long-lasting (memory effects) and off target (abscopal effects) antitumor immune effect can be reached when the right RT dose/schedule will be combined with the right immunotherapeutic approach in order to stimulate an immune response of adaptive origin.

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Footnote

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