Dendritic Cells for the Treatment of Metastatic Renal Cell Carcinoma: At a Low Ebb?

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1. Dendritic cell vaccination and adoptive cellular therapy in the management of metastatic renal cell carcinoma: a smart concept for an old story

It is well-known that renal cell carcinoma (RCC) represents a good model for immunotherapy. Spontaneous regressions of metastases after nephrectomy have been observed, and robust data exist proving that interleukin 2 (IL-2) or interferon (IFN)-based therapy do have a certain degree of efficacy in this setting. However, complete responses and long-term survivals are rare, and a lot of research has been undertaken to try to develop more-effective or more-specific approaches on the basis of tumor antigen targeting. Historically, lymphokine-activated killer cells and tumor-infiltrating lymphocytes were the two main populations that have been investigated for use in adoptive immunotherapy for metastatic RCC [1]. Although initial phase 2 results were encouraging, with response rates reaching 35%, all phase 3 trials failed to show any superiority for the adjunction of adoptive immunotherapy to conventional IL-2 therapy, compared with IL-2 therapy alone [2,3]. Therefore, new strategies were developed for identifying antigen targets at the tumor cell surface, and new therapeutic approaches were investigated. However, it must be acknowledged that, to date, a limited number of potentially interesting antigens have been identified in RCC, compared with other immunogenic tumors such as melanoma [4]. At the same time, a lot of interest has been given to dendritic cells (DCs), which are the most potent antigen-presenting cells (APCs) of the immune system [5]. Logically, DC-based therapeutic strategies have been developed in metastatic RCC. In this issue of European Urology, Berntsen et al. [6] provide a comprehensive view of all the clinical experience that has been accumulated in recent years with DCs in metastatic RCC. All exploitable results are reported along with details on methodologic aspects. This article provides a good overview on the conceptual strength as well as a realistic picture of the clinical weakness of this approach. Fourteen series including 197 patients were analyzed. It is obvious that a great variety of vaccine strategies were used; the strategies included different sources of DCs at different maturation grades, with various antigens, routes of administration and number of vaccines used. Overall, a 37% "clinical response" rate was noted along with minimal toxicity.

2. DC-based therapy in metastatic RCC: Rationale for and critical analysis of clinical results

The rationale for DC-based therapy is to target through effective cellular mediators either identified or supposed existing tumor antigens and, therefore, to stimulate a specific antitumor immune response. Because DCs are the most potent APCs with the capacity to interact with T cells, B cells,
natural killer (NK) cells and NKT cells, DCs are supposed to be the ideal immune intermediates between tumor cells and a potentially effective immune system. Once an antigen has been loaded, and appropriate maturation and migration has occurred, DCs are able to interact with immune T cells. In this interaction, major histocompatibility complex molecules together with costimulatory molecules play an important role. Berntsen et al. have presented well in their article that antigen concentration, affinity to the T-cell receptor, duration of the T cell-DC contact together with the integrity of the immune machine and the absence of immune escape mechanisms are important theoretically for the success of the treatment.

Berntsen et al. also have reported well in their review article the limitations of the available data regarding clinical experience with DC therapy in metastatic RCC. The 14 phase 1 and 2 studies and no phase 3 trial identified in the article include 197 patients who were treated by 11 distinct groups with a great variety of protocols. In the majority of the cases, these studies included a limited number of patients. This review has to be compared with the more than 53 randomized studies including more than 6000 patients that were reported in a recent meta-analysis on the role of cytokine-based therapy in metastatic RCC [7]. In addition, the most recent studies with anti-angiogenic drugs were the largest phase 3 studies performed to date in RCC with more than 900 patients participating in the study [8]. Finally an impressive number of large randomized studies are planned for establishing the efficacy of anti-angiogenic drugs in RCC [9]. In comparison, it is obvious that data from a limited number of patients included in small trials with uncertain methodology make it hard for this approach to compete with cytokine-based therapy or anti-angiogenic therapy. In addition, because of the nonstandardized protocols, it is impossible to compare and accumulate the results, raising the question of the reproducibility of this approach. Although an overall clinical response rate of 37% has been noted in these studies including mainly disease stabilisation and rare objective responses, it is absolutely impossible to draw any conclusion from such a compilation because of the different sources of DCs that were used, with different kinds of potential antigens (tumor lysate, cell fusion, peptides, transfection with RNA or DNA) and various routes of administration. Finally, no validated tool has been designed for use in immune monitoring or as a surrogate marker for response. However, the previous point is not a definitive limitation, because no accurate predictive marker has been identified either for cytokine therapy or anti-angiogenic therapy.

3. Is the adjuvant approach a future perspective for DC therapy?

From a theoretical point of view, there is a good rationale for targeting specific tumor antigens with effective immune cells; however, there also are many limitations for such an approach in the metastatic setting. Because of the importance of tumor burden, the immune system is likely to be overtaken and become anergic. On the other hand, a minimal tumor volume is required to stimulate tumor angiogenesis; therefore, the rationale for using anti-angiogenic drugs in the adjuvant setting is less clear than in the metastatic setting, even though large randomized studies will be conducted soon [9]. Therefore, it can be postulated that after complete primary tumor removal, a cancer vaccine could be more effective in eliminating microscopic residual tumors than in fighting a huge tumor burden. In this respect, the example of bacille Calmette-Guérin immunotherapy in preventing recurrence and progression in aggressive superficial bladder tumors is informative. Although mechanisms of prophylaxis are not understood perfectly, it is likely that long-term T-cell memory is necessary to prevent progression, and it is clear that such a treatment is effective only in case of minimal residual disease. Therefore, we probably should position cellular adoptive therapy in the adjuvant setting rather than in high-volume tumor cases. From this perspective, the recent publication of Jocham et al. [10] provides an interesting contribution. It is the only randomized study that has proven a positive effect in the adjuvant setting. Using an autologous renal tumour cell vaccine strategy, the authors showed in selected high-risk patients a significant improvement in progression-free survival. Although this strategy has not been registered yet by regulatory authorities as a recognized adjuvant treatment, it encourages the concept of tumor vaccination in the adjuvant setting. Therefore, because of the low-toxicity profile of DC therapy, the low tumor burden that characterises the adjuvant setting and the possibility of recruiting locally effective killer cells, it still makes sense to conduct well-designed clinical trials in this setting. However, if anti-angiogenic drugs also are effective in the adjuvant setting, it definitely will be difficult to develop a DC strategy, because it is still currently characterized by a lot of methodologic uncertainty. It is obvious that more preclinical data are required to determine the optimal protocol and the required immune monitoring. Nevertheless, research for optimizing treatment protocols and proposing standardized
approaches should continue, because DC adjuvant strategy is an attractive alternative approach.

4. Towards a realistic strategy for developing DC therapy in RCC

Although DC-based therapy represents a rationale and low-toxic approach, many further steps are required before it will become an accepted, proven effective and standardized treatment in metastatic RCC. More preclinical studies and a more-demanding methodology are required for further clinical trials. The question on how this approach should be positioned in comparison with current anti-angiogenic therapy, which is gaining popularity because of oral administration, efficacy and low-toxicity profile, is crucial for the future of DC therapy. From a theoretical point of view, the ideal positioning of DC therapy would be in the adjuvant setting. However, because of the uncertainty of the optimal protocol, it is likely again that such an approach will be strongly challenged by anti-angiogenic drugs in the adjuvant setting as well. However, the concept of DC-based therapy in RCC is valid, and both preclinical research and well-designed clinical trials are required.

References


