RENAL CELL CARCINOMA IN FOCUS

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Improving the Therapeutic Index of IL-2

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H&O What is the current state of therapy in metastatic renal cell carcinoma?

DM Over the past 5 years, there is probably no area in oncology that has seen more improvements and new therapies than kidney cancer. The US Food and Drug Administration (FDA) has approved 6 new drugs that target angiogenesis through either vascular endothelial growth factor (VEGF) receptor inhibition or the mammalian target of rapamycin (mTOR) pathway. Most of these agents improve survival, in some cases considerably more than previous agents. These new drugs can be offered in the outpatient setting and have become widely adopted.

Although these treatments have improved outcomes for patients, many of them have limitations. They can have chronic side effects that can be debilitating for some patients. They do not produce—except in rare cases—complete remissions, so patients must continue therapy to experience benefits. We need to develop treatments that achieve complete remission of the cancer and allow the patient to discontinue therapy.

H&O What was the goal of the SELECT trial?

DM The goal of the High-Dose Aldesleukin (IL-2) "Select" Trial for Patients With Metastatic Renal Cell Carcinoma (SELECT) was to improve the therapeutic index of interleukin-2 (IL-2). IL-2 has been approved for almost 30 years in the United States. Its application is very narrow, however, because it is associated with significant toxicity and limited benefit. Our primary goal was to identify which patients are more likely to benefit from IL-2, so that patients who are less likely to benefit can be spared the adverse reactions associated with this therapy.

A secondary goal was to assess whether patients who are suitable for treatment with IL-2 do in fact receive it. Despite its drawbacks, IL-2 is the only approach available to kidney cancer patients that can offer them a chance at a durable remission or a cure of their cancer.

H&O What retrospective analyses prompted this study?

DM Clinical and correlate trials have suggested we can do a better job of selecting patients for treatment with immunotherapy; several trials have focused on the use of IL-2 therapy in kidney cancer patients. Studies from the University of California, Los Angeles (UCLA) have suggested that patients with high expression of the protein carbonic anhydrase IX on their tumors were more likely to respond to IL-2. Work from our group at the Dana-Farber/Harvard Cancer Center has suggested that patients with certain histologies of clear cell renal cell carcinoma were more likely to respond to IL-2.

In the SELECT study, we were attempting to prospectively confirm previous data suggesting that there might be tumor markers that could be used to predict which patients were likely to benefit from treatment. We looked into other endpoints as well, both clinical, such as the patient's clinical characteristics when treatment began, and more general, such as whether the patient had clear cell cancer versus non–clear cell cancer.

H&O What were the inclusion criteria of the SELECT trial?

DM The inclusion criteria were rather broad. Patients had kidney cancer of any histologic type. They had to have a good performance status and good organ function. They had to pass a stress test and a pulmonary function test prior to treatment, which is typical for high-dose IL-2 patients. They could not have received prior therapy.

H&O What was the trial design?

DM It was an open-label, phase II design in which we treated 120 patients at 14 centers over about 2 and a half years. Patients were required to allow us to access their tumors for pathology analysis and to provide us with a small sample of blood before treatment. Treatment was the FDA-approved, standard of care regimen for high-dose IL-2, which is 600,000 international units of treatment every 8 hours for up to 14 doses per week. A 2-week treatment was a course of therapy.

After patients received this standard treatment, we then tried to correlate their response outcomes with their tumor characteristics. Tumor samples were examined by pathology review. Computed tomography scans were reviewed by independent radiologists.

H&O What were the primary and secondary objectives?

DM The primary objective was to prospectively determine if the response rate to high-dose IL-2 was significantly higher in patients with good pathologic predictive features than in an unselected population. When IL-2 was approved in 1992, the major response rate was 14%, with half of those responses durable. We hoped to be able to show that we can now double that response rate with patient selection.

For secondary objectives, we examined whether prognostic models, such as the Memorial Sloan-Kettering Prognostic Score and the UCLA Survival After Nephrectomy and Immunotherapy (SANI) score, could further define the best population to receive IL-2. We looked at predictive factors, such as VEGF levels and B7H1 staining on tumor. We also hoped to identify a group of patients with poor-risk features who were likely to not respond to IL-2 treatment.

H&O What were the results of the trial?

DM The main clinical result of the trial was that the response rate was the highest we have seen with high-dose IL-2 in patients with metastatic kidney cancer. The response rate was 28%, of which 6% were complete responses and 22% were partial responses. Approximately 40 of the 120 patients treated in the trial had some tumor shrinkage. The response rate of 28% was significantly higher than the historical rate of 14%. In many ways, the entire group of patients did better than we expected and better than historical rates. We hope to have final results in the next few months.

The main goal of the trial, however, was to identify a subgroup of patients who had an even better chance of responding than the entire cohort. We determined that tumor histology and carbonic anhydrase IX staining, alone or together, did not predict for better outcome. We had high response rates across all of the pathologic categories. We were unable to confirm the prior work of our group and the UCLA group showing that carbonic anhydrase IX staining and tumor histology could identify patients likely to benefit from treatment. In fact, some of our best patients came from the poorest pathology risk categories. It was quite surprising.

The results of the study were mixed. In general, we are doing better—not because IL-2 is a better drug than it was 20 years ago, but because patients are being screened before receiving therapy. It is also likely that the availability of alternative treatments has narrowed the group of patients who are receiving IL-2. Another factor that might explain the improved response rate is that a majority of the patients had undergone a debulking nephrectomy prior to entering the study. In past studies, almost one-third of patients were treated with their original kidneys in place, and in this study, 99% of patients had undergone surgery. Those factors likely explain the improved results.

Because the response rate was so high in the trial and because we collected samples from so many patients, we hope to be able to design a model that can further enrich for patients who are more likely to benefit from treatment. For example, there were no responders among patients who had non–clear cell tumors. There were also no responders among patients with a high-risk UCLA SANI score. In general, it seems likely that the future treatment of those patients will not include high-dose IL-2, but we have not completed our modeling yet. We hope to perform all the appropriate assays, and then create a model that will identify a population of patients who should receive the drug and, perhaps, a population of patients who probably should not receive the drug.

H&O What does this study suggest for management of renal cell carcinoma patients?

DM The study shows that IL-2, even in this era in which we have many alternative treatments, is an active drug that can produce durable benefits. The response rate was 28%, but even more important is that 14% of these patients continue to respond to treatment. Many of these durable responses have lasted longer than 2 years. IL-2 is still relevant for patients who are fit, who meet the eligibility criteria, and who are motivated to pursue a durable benefit.

That being said, we are always trying to do better. In this study, we were unable to further enrich for a response. The study results did not allow us to provide community oncologists with a test they can use in their

practice to study a patient's tumor to determine whether the patient should be referred for IL-2 or not. The work goes on, however. We have some reason to believe that if we cannot confirm which patients should receive IL-2, then we can do the opposite, which is to show that there are certain patients who should not receive it, and thus narrow therapy to those patients who are most likely to benefit.

I think this work will also help in the near future, when immunotherapy for kidney cancer is likely to become more targeted and less toxic than high-dose IL-2 because a variety of drugs are emerging from clinical trials. There are several agents that seem to produce durable responses with far less toxicity than is seen with IL-2. As those drugs get closer to becoming available in the clinic, it is hoped that some of this work will guide their development and provide a firm population of patients for clinical trials. These agents, I hope, will have a much broader application because they will be able to be given as an outpatient treatment and not in an intensive setting.

Suggested Readings

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