Targeted Therapy for Cytokine-Refractory Metastatic Renal Cell Carcinoma, and Treatment in the Community

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This report of a case of cytokine-refractory metastatic, clear-cell renal cell carcinoma (RCC) presents some current issues related to use of targeted therapy in the community. Due to the different mechanisms of cytostatic vs cytotoxic agents, traditional response assessments may not always apply in deciding when to either continue or stop treatment. While community physicians may increasingly focus more on duration of response, symptom relief, and how well patients tolerate treatment, there is a clear need for validated surrogate markers of biologic activity and response, as well as randomized trials that directly compare some of the targeted therapies being applied in advanced RCC.

This article presents the case of a 59-year-old male with metastatic renal cell carcinoma (RCC) initially treated with interleukin-2 (IL-2, Aldesleukin, Proleukin) plus pegylated interferon-alfa (PEG IFNα), who then developed disease progression requiring further therapy. Since identification in 1993 of the Von Hippel-Lindau (VHL) gene, which is involved in the majority of genetic alterations in clear cell RCC, several agents targeting key molecular pathways active in RCC tumorigenesis (eg, vascular endothelial growth factor receptor [VEGF], epidermal growth factor receptor [EGFR], platelet-derived growth factor B [PDGF-B] receptor, and others) have been developed and are being evaluated in clinical trials, including the recently approved targeted agent sorafenib (Nexavar; formerly known as BAY 43-9006) (Table 1).[1,2]
These biologic agents are generally more tolerable than cytotoxic or immunotherapeutic therapies, and offer an alternate approach to improve outcome in patients with advanced RCC. At the same time, new issues surrounding evaluation of targeted therapies have been raised, including optimal trial design, the utility of traditional response criteria, and identification of molecular markers of drug activity and clinical response. While answers to these issues may help establish standard therapies and treatment guidelines through large randomized trials, physicians in daily practice also need practical evaluation tools that, when combined with other considerations regarding the patient's
status, will aid in making treatment decisions in the clinic that are appropriate for each patient.

Case Report: Metastatic Renal Cell Carcinoma

A 59-year-old man underwent routine physical examination by his medical doctor in March 2002. He had no significant complaints, but physical examination revealed a mass in the left upper quadrant of the abdomen. Abdominal computed tomography (CT) scan showed a 10-cm renal mass on the right side and a normal left kidney. He also had enlarged mediastinal and hilar lymph nodes on chest CT scan and a negative bone scan. Results of laboratory assessments were within normal limits, including hemoglobin of 14.9 g/dL, creatinine of 1.0 mg/dL, calcium of 9.5 mg/dL, white blood cell (WBC) count of 8,950/µL, and lactate dehydrogenase (LDH) level of 150 IU/L. Results of transbronchial biopsy revealed a malignancy.

In April 2002 he was referred to a urologist because of the large renal mass, and subsequently underwent a right nephrectomy. The excised tumor was an RCC of clear cell histology, Furhman grade 3, and was 10.5 cm in size (T4). Recovery from surgery was uneventful.

The patient was referred to the Cleveland Clinic Foundation (CCF) Taussig Cancer Center in May 2002 for an opinion regarding additional therapy. He was asymptomatic with excellent Eastern Cooperative Oncology Group (ECOG) performance status (PS = 0). CT scans showed enlarged mediastinal and hilar lymph nodes, a 4-cm mass in the infrarhil region, and a 3-cm retroperitoneal lymph node. Brain CT and bone scans showed no metastases. Biochemical parameters remained relatively within normal ranges: hemoglobin, 13.9 g/dL; LDH, 188 IU/L; creatinine, 1.6 mg/dL; WBC count 8,670/µL; platelet count 267,000/µL; Ca+2, 10.9 mg/dL.

In June 2002, the patient was enrolled in a phase I trial of IL-2 15 mIU/m2 administered subcutaneously (SC) on days 1, 3, and 5 (weekly × 6), plus PEG IFNα 3.0 µg/kg on day 1 (weekly × 6). He received nine treatment courses through August 2003. Toxicity was moderate. His disease was stable with no changes in the sizes of affected lymph nodes and no new disease sites. (The best response observed was stable disease [SD]). At that point, the treatment regimen was discontinued.

The patient was seen every 3 months for laboratory assessments and CT scans. He remained asymptomatic, but follow-up CT scans in February 2004 showed evidence of progressive disease. The infrarhil mass had increased to 4.5 cm, there was a 3.1-cm mediastinal lymph node, and the retroperitoneal lymph node measured 5.7 cm. Laboratory values remained relatively normal: hemoglobin, 14.9 g/dL; hematocrit, 46.7%; WBC count 4,890/µL; platelet count, 408,000/µL; LDH, 190 IU/L; Ca+2, 10.9 mg/dL; creatinine, 1.0 mg/dL; total bilirubin, 0.4 mg/dL.

Treatment options were discussed with the patient, including supportive care and clinical trials including the ongoing Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGETs). The patient was entered into TARGETs, and therapy was initiated in March 2004. He had some toxicity, grade 1 diarrhea and grade 1 hand/foot syndrome, which suggested he was receiving active drug. The patient had a partial response (PR) of approximately 12 months' duration and then developed progressive disease. With unblinding, it was determined that the patient had received sorafenib 400 mg bid. Therapeutic options discussed with the patient at this point included a period of observation, a phase I trial of IMOxine plus IFNα with or without MG98, or continuing sorafenib treatment. The TARGETs protocol allowed for continuing therapy in the presence of progressive disease, if the patient seemed to benefit clinically from treatment.

The patient elected to continue sorafenib. At the time of this writing, treatment has continued for another 10 months. He continues with SD, with no new disease sites, and adverse effects have been acceptable. On December 20, 2005, the US Food and Drug Administration (FDA) approved sorafenib for the treatment of adults with advanced RCC, the most common type of kidney cancer.

Discussion

This case is a typical presentation of a patient with RCC and synchronous disease. He was asymptomatic, and scans revealed enlarged lymph nodes and a negative bone scan. Several groups have proposed models to predict survival based on risk factors.[3,4] The Memorial Sloan-Kettering Cancer Center criteria identified five prognostic factors associated with shorter survival in stage IV RCC patients, including poor performance status (Karnofsky < 80%), high serum LDH level (> 1.5 times the upper limit of normal), low hemoglobin (< lower limit of normal), high "corrected" serum calcium (> 10 mg/dL), and no previous nephrectomy. Multivariate analysis of these factors in 670 patients was used to develop a model to stratify patients into low-, intermediate-, or high-risk categories.[3] With none of the five risk factors, this case falls into the low-risk group, wherein the model predicts a median survival of 20 months, and 1-, 2-, and 3-year overall survivals (OS) of 71%, 45%, and 31%, respectively. The median survival (MS) duration decreases to 10 months in the intermediate-risk group (1-2 risk factors), and to 4 months in the poor-risk group (3-5 risk factors).[3] When this patient received first-line treatment in 2002, our group was involved in trials of cytokines,
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and he was entered on a phase I trial of SC IL-2 and PEG IFNα. High-dose IL-2 is a standard treatment for patients with advanced RCC and the only FDA-approved cytokine in this setting, but it is associated with significant toxicities. In a recent study in 400 metastatic RCC patients, Yang et al reported response rates (RRs) of 21% in patients receiving high-dose intravenous (IV) IL-2 (720,000 U/kg and 13% in those receiving low-dose IV IL-2 (72,000 U/kg) (P = .048), with no significant survival differences in the two arms.[5] A third arm of this trial was SC IL-2, which resulted in a 10% RR-similar to that in the low-dose IV IL-2 group but lower than in the high-dose group (P = .033). Response durations varied widely (2 to 130+ months) and tended to be longer with high-dose IL-2, particularly in patients achieving complete response. Toxicity was also markedly increased in the high-dose vs the low-dose group. IFNα is associated with an approximately 15% RR in patients with metastatic RCC, and the side-effect profile allows its use combined with other agents. Previous trials administering SC IL-2 (either high- or low-dose) and IFNα at varying doses have yielded mixed results.[6-9]

The patient in our case ultimately accrued onto the TARGETs trial investigating sorafenib, a novel bio logic targeting multiple kinases that are involved in pathways reported to be active in renal cell tumor growth and angiogenesis, including Raf kinase and VEGF receptor tyrosine kinases; sorafenib had demonstrated activity in previous phase I and phase II trials.[10,11] While the patient was on study, progression-free survival (PFS) data from TARGETs became available, with 769 patients enrolled and 342 PFS events reported.[12] PFS significantly improved from 12 weeks with placebo to 24 weeks with sorafenib treatment, a highly statistically significant difference (P < .00001). The 12-week PFS rates were 50% and 79% for the two treatment groups, respectively. Moreover, a benefit of sorafenib was seen among all patient subgroups regardless of age, previous treatments, or disease duration. Seventy-eight percent of sorafenib patients had SD, and 2% had PRs by initial independent review (55% and 0%, respectively, in the placebo group), underscoring the apparent importance of disease control (SD + PR) in achieving clinical benefit in advanced RCC. (These data also indicate that randomized PFS may be a better predictor of OS and clinical benefit or disease control than objective tumor response.) Furthermore, 74% of sorafenib patients (20% of placebo patients) had some degree of tumor regression.[12] In a subsequent interim analysis, there was an estimated 39% significant improvement in OS (the primary study endpoint) for patients receiving sorafenib vs placebo (hazard ratio [HR].72; P = .018), with a corresponding RR of 10% by investigator assessment.[13] Tolerability of sorafenib was good: grades 3 and 4 drug-related effects included rash (1% of patients), diarrhea (1%), hand-foot skin reaction (5%), fatigue (2%), and hypertension (1%).[12,13]

After receiving sorafenib on study, the patient in our case achieved a PR that lasted for 12 months, with SD maintained for a further 6 months and continuing at the time of this report (Figure 1).

In this lesion, development of a cystic or necrotic center was noted. This has been seen after therapy with other TKIs, and it is most common in soft tissue and similar lesions, but can be seen in almost any site. The etiology is presumed to be an effect similar to that seen in patients with gastrointestinal stromal tumors (GIST) treated with imatinib (Gleevec).[14] The possibility of obscuring a response because of this type of development, and over producing with an expanding cystic lesion exists. The importance of a surrogate PFS demonstrating clinical benefit is again illustrated. Tumor necrosis may be an important indicator of anticancer activity and may mask RR.
Interestingly, when the patient initiated treatment, we assumed he was receiving sorafenib because of the mild toxicities exhibited (eg, grade 1 diarrhea and hand-foot skin reaction). Notably, however, when the study was unblinded, we found that our assumptions regarding the probable treatment arm to which patients were assigned were often incorrect. For example, several placebo-treated patients in the trial had diarrhea or hand-foot skin reaction.

A primary question raised by this case in terms of treatment in the community relates to duration of treatment and subsequent-line therapies. The TARGETs protocol specified that patients with disease progression could continue therapy based on potential for clinical benefit. This may mirror what will happen in the community, given the good tolerability of sorafenib and other novel molecular therapies. Experience in the community with combinations of conventional chemotherapy with the VEGF inhibitor bevacizumab (Avastin) indicates that targeted therapy is often continued when disease progresses, whereas the cytotoxic agent might be changed or another targeted agent added. Thus, the ability to combine targeted therapies with cytotoxic chemotherapy or cytostatic agents, which will depend on side effects, will become key as clinicians move forward in using these agents.

Another consideration regarding use of targeted agents in the community relates to evaluating response in individual patients. Defining disease progression based on an increase in tumor size at a specified time point may have different implications in the community, compared with assessments that have to meet response criteria in clinical trials (eg, Response Evaluation Criteria in Solid Tumors [RECIST]). Physicians in the community may focus more on relief of symptoms and on toxicities (or lack thereof) to decide when to make a change in treatment. In patients with indolent disease, continuation of therapy in the presence of progressive disease may be reasonable, if a patient's symptoms are controlled. In the case presented herein, the patient on sorafenib was continued following disease progression, and then did well with long-duration SD. Subjective experience from TARGETs revealed that some patients "seemed to feel better," even though tumor size may have increased. Changes in tumor size may occur over a prolonged period, and on the other hand, stability of disease may also provide significant patient benefit even in the absence of an objective response, as illustrated in the pivotal, phase III, placebo-controlled trial of bevacizumab in 813 patients with metastatic colorectal cancer receiving up-front irinotecan (Camptosar)/fluorouracil/leucovorin (IFL) ± bevacizumab. Even in patients who failed to achieve an objective response ("nonresponders" based on RECIST criteria), PFS and MS increased significantly ($P < .001$ and $< .05$, respectively).[15,16] These and other findings support the current focus on re-evaluation of response criteria in patients treated with targeted therapies. Perhaps, the rate of tumor growth or the occurrence of any tumor shrinkage, regardless of the amount, may be important clinical response clues in patients treated with targeted therapies.

Surrogate markers of biologic effect and response are also needed, and will aid in application of these treatments in the clinic. No reliable pharmacodynamic markers are currently available for targeted agents in RCC. One area of interest in this regard is to measure tumor blood flow as a surrogate for VEGF inhibitor-induced antiangiogenic effects. For example, in the TARGETs trial, color Doppler ultrasound was used to track changes in tumor blood flow.[17] Preliminary data in a 30-patient subset showed that reductions in tumor blood flow were evident as early as 3 weeks after treatment initiation, and correlated with improved PFS.

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**References:**


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