

The Times They Are A-Changin' (Bob Dylan, 1964)

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In this issue of *Cancer*, the French Immunotherapy Intergroup¹ reports results of the PERCY Quattro trial, which compares medroxyprogesterone acetate (MPA), subcutaneous interferon- α (INF- α), subcutaneous interleukin-2 (IL-2), or a combination of the 2 cytokines for front-line treatment of patients with intermediate prognosis metastatic renal cell carcinoma (RCC). Between January 2000 and July 2004, 492 patients were accrued to this trial. The primary endpoint of the trial was overall survival. Secondary endpoints included disease-free survival, response rate, toxicity, and quality of life. No significant survival differences were seen between the INF- α and non-INF- α treated patients (15.4 vs 15.1 months; hazard ratio [HR], 1.00; 95% CI, 0.81–1.24; log rank, 0.99) or between the IL-2 and non-IL-2 treated patients (15.7 vs 14.9 months; HR, 1.07; 95% CI, 0.87–1.33; log rank, 0.52). However, grade 3–4 toxicities were significantly more frequent in patients treated with cytokine.

The authors should be commended. Overall this was a well designed, large (n = 492), multi-institutional (44 centers) trial by a highly experienced group of investigators. Few criticisms can be made of the overall conduct and report of the trial. However, the question of how results of this trial become current treatment options for metastatic RCC must be asked. Our ability to pose this question is refreshing, as it is a sign the times are finally changing.

Metastatic RCC has long been recognized to be resistant to chemotherapy and radiation therapy. Observation of spontaneous remissions in prospective trials with observation or placebo arms and after nephrectomy led to recognition of the importance of immune regulation in RCC and, subsequently, to an era of cytokine therapy including IL-2 and IFN as single agents and as combination therapy.²

Initial phase 2 trials of high-dose IL-2 showed promising response rates with reports of complete responses. A landmark trial published by Fyfe and colleagues^{3,4} reporting on 255 patients treated with high-dose IL-2 from 7 phase 2 trials with response rates of 14%, including 12 complete responses and 24 partial responses, many of which were durable (median response of more than 80 months for complete responders), led to approval of high-dose bolus IL-2 by the United States Food and Drug Administration (FDA). This approval was based on small numbers of complete but

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durable responses observed in clinical trials.^{3,4} Toxicities encountered during high-dose IL-2 treatment, with benefit to only a small proportion of patients, led to investigation of lower doses and alternative routes of administration.⁵⁻⁸ Initial phase 2 trials showed comparative response rates with less toxicity. However, in randomized clinical trials, fewer, less durable responses were seen while most patients still experienced significant toxicity.^{8,9} Addition of IFN to low-dose IL-2 also did not result in the durable complete responses that had been observed with high-dose IL-2.¹⁰ Overall, with cytokine therapy, clinical benefit was modest with response rates of 12% to 15%, progression-free survival of 4.7 months, and overall survival of 12 months.²

At the time the current trial was initiated, no systemic therapy was considered standard care for treatment of metastatic RCC given lack of proven increase in overall survival in any large randomized therapeutic trial. Since initiation of the currently discussed trial, there has been an increase in understanding molecular pathways associated with the malignant phenotype of metastatic RCC leading to a change in treatment to that of targeted therapy. The hallmark of sporadic clear cell carcinoma is the inactivation of the von Hippel-Lindau (VHL) tumor-suppressor gene resulting in over-expression of hypoxia-inducible factor (HIF). Downstream effects of HIF over-expression include expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).¹¹

Proof of the principle of targeting the VHL/HIF/VEGF pathway was first demonstrated in a randomized, double-blind, phase 2 trial that compared bevacizumab (Avastin; Genentech, South San Francisco, Calif) at doses of 3 and 10 mg per kilogram with placebo.¹² The primary endpoints of the trial were time to progression and response rates. A modest response rate of 10% was observed, but at the time of second interim analysis, a statistically significant increase in progression-free survival was observed in the high-dose bevacizumab arm (4.8 months vs 2.5 months; $P < .001$). There were no significant differences in overall survival between groups. However, this trial confirmed that inhibiting VEGF could change the natural history of the disease and, therefore, prompted further investigation of other agents known to inhibit the VEGF pathway.

Sorafenib

Sorafenib (Nexavar; Bayer, West Haven, Conn) is an orally bioavailable multitargeted serine/threonine/tyrosine kinase inhibitor (TKI) of VEGF receptors (VEGFR) VEGFR-1, VEGFR-2, and VEGFR-3; PDGF

receptor; fms-like tyrosine kinase 3 (Flt-3); c-KIT; and the RAF/MEK/ERK signaling pathway. In a randomized phase 2 discontinuation trial of sorafenib versus placebo in patients with disease refractory to cytokine, progression-free survival (primary endpoint) was significantly longer in the sorafenib arm at 12 weeks (24 weeks vs 6 weeks; $P = .0087$).¹³ The results of this trial led to a phase 3 randomized, placebo controlled, blinded trial of sorafenib versus placebo in the same patient population.¹⁴ A planned interim analysis demonstrated a significant increase in progression-free survival for patients who received sorafenib (24 weeks vs 12 weeks; $P < .000001$) with a trend toward increased survival favoring sorafenib (not reached vs 14.7 months; HR, 0.72; $P = .018$). At this time, the trial was unblinded, and crossover was permitted. On the basis of these results, sorafenib was approved by the FDA in December of 2005 for treatment of metastatic RCC. At 6 months after crossover, the trend toward improved overall survival persisted (19.3 months vs 15.9 months; HR, 0.77; $P = .015$). However, the final survival analysis (recently reported at the 2007 American Society of Clinical Oncology Annual Meeting with 48% of patients originally treated on the placebo arms crossing over) did not show a significant improvement in overall survival (17.8 months vs 15.2 months; HR, 0.88; $P = .148$) with a confounding effect of crossover likely.¹⁵

Sunitinib

Sunitinib (Sutent; Pfizer, New York, NY) is an oral, multitargeted TKI of VEGFR-1, VEGFR-2, and VEGFR-3; PDGF- α receptor and PDGF- β receptor; stem cell-receptor factor (KIT); and Flt3 known to inhibit angiogenesis. Sunitinib also exerts direct antitumor activity on cells that express target RTKs associated with tumor-cell proliferation, such as KIT, PDGFR, and RET. Sunitinib was granted FDA approval for the treatment of metastatic RCC on the basis of objective response rates of 34% to 40%^{16,17} observed in 2 sequential phase 2 studies (compared with historical response rates of $< 5\%$ to second-line cytokine therapy) in patients with cytokine-refractory disease. The activity of sunitinib was confirmed in a phase 3 trial in which sunitinib was compared with INF- α for frontline treatment of metastatic RCC.¹⁸ The median progression-free survival was significantly longer in the sunitinib arm (11 months vs 5 months; $P < .001$). Sunitinib was also associated with a higher objective response rate (31% vs.6%; $P < .001$). Interim overall survival analysis was not significant, but results remain immature, and final overall survival analysis is awaited. This trial has

established sunitinib as a new reference standard for frontline treatment of metastatic RCC in patients not eligible for high-dose IL-2 treatment.

Temsirolimus

Temsirolimus (Torisel; Wyeth, Madison, NJ) is an inhibitor of the mammalian target of rapamycin (mTOR) kinase, a component of intracellular signaling pathways involved in the growth and proliferation of cells and response to hypoxic stress.¹⁹ Disruption of mTOR signaling suppresses production of proteins that regulate progression through the cell cycle and angiogenesis.¹⁹ Efficacy of temsirolimus in treatment of metastatic RCC was recently demonstrated in a phase 3 trial that compared temsirolimus, INF- α , and combination temsirolimus with INF- α in previously untreated, poor-prognosis patients.¹⁹ The primary endpoint was overall survival with secondary endpoints of progression-free survival, response rate, and clinical benefit defined as the proportion of patients without progression for at least 24 weeks. At the time of the second interim analysis, conducted after 446 patients had died, a survival benefit was demonstrated for patients in the temsirolimus alone arm (HR, 0.73; $P = .008$). Median overall survival for treatment with interferon, temsirolimus, and combination therapy was 7.3, 10.9, and 8.4 months, respectively. There was also a progression-free survival benefit for patients treated with temsirolimus alone (5.5 months; $P < .001$) compared with 3.1 months with interferon and 4.7 months with combination therapy. Objective response rates of 4.8%, 8.6%, and 8.1% among patients who received interferon, temsirolimus, and combination therapy, respectively, did not differ significantly. However, the proportion of patients without progression for at least 24 weeks was greater with temsirolimus treatment (32.1%) and combination therapy (28.1%) than with interferon (15.5%). Results of this trial led to recent FDA approval of temsirolimus for treatment of metastatic RCC.

Cytokine Therapy: An Historical Standard

With the approval of 3 new agents by the FDA for treatment of metastatic RCC over the last 1.5 years (sorafenib, sunitinib, and temsirolimus), can cytokine therapy now be relegated to medical history? As further supported by results of this recent trial and others, there is no clinical benefit associated with single-agent INF- α treatment or low-dose IL-2 regimens. We argue that the only remaining role for cytokine therapy alone is with high-dose IL-2 in a highly select group of patients who have the potential to achieve a durable complete response. Signifi-

cant toxicity for this small, but important, potential benefit necessitates careful selection of patients. Ongoing efforts to further define the subset of patients with clear cell carcinoma who will benefit from high-dose IL-2 are important.^{20,21}

Current Dilemma

With change come more questions. With FDA approval of sorafenib, sunitinib, and temsirolimus for treatment of metastatic RCC, it has become clear that interferon is no longer a valid reference standard. However, in what order to use the above agents and whether to use them in combination or sequentially remain undefined. We also do not know if the doses and schedules currently being used are optimal. As newer targeted agents are developed, it is currently unclear how best they should be tested. Should they be third-line therapy or beyond? Considering the number of agents and potential combinations, are large, randomized phase 3 trials the best use of resources, or are randomized smaller phase 2 trials adequate? What endpoints should we choose? Is progression-free survival a valid endpoint, or is the more traditional endpoint of overall survival more important? If so, will we be able to show survival benefits with crossover designs and availability of sequential therapy, or will results be confounded? Temsirolimus has shown a survival benefit but in a poor-prognosis group of patients who otherwise had short life-expectancies and who were likely ineligible for treatment with other targeted agents. We also do not know what duration of therapy is needed for patients who do benefit from treatment with these agents. Is continuous drug exposure required, or will patients be able to have drug-free periods?

In conclusion, over the last several years, tremendous advances have been made in the treatment of metastatic RCC. However, many new questions have resulted. It is a sign that, at last, the times are a-changin'.

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