Sunitinib versus interferon-α in metastatic RCC

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Motzer and colleagues presented updated results from a multicentre, phase III trial of sunitinib versus interferon-α as first-line treatment for patients with metastatic renal-cell carcinoma. The observed improvement in overall survival for patients treated with sunitinib further establishes this agent as the reference standard for first-line treatment of good-risk and intermediate-risk patients with metastatic renal cancer.

The care of patients with metastatic renal-cell carcinoma (mRCC) has advanced substantially in the past few years, with the approval of targeted therapies including sunitinib, bevacizumab, sorafenib, temsirolimus and everolimus. Approximately three-quarters of renal cancers are clear-cell carcinomas, and most tumours of this histologic subtype have inactivating mutations of the von Hippel–Lindau gene. This inactivation ultimately causes increased secretion of vascular endothelial growth factor (VEGF).[1]

A recent publication of updated results from a randomised phase III trial by Motzer and colleagues has demonstrated that sunitinib improves overall survival compared with interferon-α as first-line therapy in patients with mRCC. Sunitinib is an orally administered, multitargeted tyrosine kinase inhibitor (TKI) that affects multiple receptors, including the VEGF receptor. In two phase II studies of patients with cytokine-resistant mRCC, treatment with sunitinib resulted in overall response rates of 33% and 40%, with a large percentage of patients achieving stable disease or better.[2] Median progression-free survival (PFS) was around 8.8–8.9 months.[2,3] The results of these studies led to accelerated approval of sunitinib by the US regulatory agency, the FDA, in January 2006 for the treatment of advanced kidney cancer.

The phase III trial of sunitinib was an international trial performed in 101 centres, in which patients with treatment-naive mRCC of clear-cell histology were randomly allocated to either six-week cycles of sunitinib (50 mg once daily for four weeks

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followed by two weeks off therapy) or interferon-α (9 million units subcutaneously three times per week).[3] Randomisation was stratified by patients' baseline levels of lactate dehydrogenase, performance status and history of nephrectomy. Patients with a poor performance status, brain metastases or significant cardiovascular disease were excluded. The primary endpoint was PFS as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included objective response rate, overall survival, quality of life and drug safety. A preplanned interim analysis demonstrated a significant six-month improvement in median PFS for patients who were treated with sunitinib.

Given the improvement in PFS, the study protocol was amended to allow crossover from interferon-α to sunitinib upon disease progression. After an extended follow-up, Motzer and colleagues have now reported updated results, including overall survival.[4] The objective response rates were 47% and 12% for sunitinib and interferon-α, respectively ($P<0.001$). The median overall survival was 26.4 months for sunitinib and 21.8 months for interferon-α ($P=0.051$). The difference in overall survival reached statistical significance ($P=0.0096$) in a multivariate analysis that controlled for performance status, haemoglobin levels, time from diagnosis to treatment, corrected calcium levels, alkaline phosphatase levels, lactate dehydrogenase levels and the number of metastatic sites.

The borderline significance of the *P*-value for the unadjusted overall survival data may have been a consequence of the crossover and administration of post-study treatments. Each of these effects may have obscured the overall survival benefit of sunitinib. The authors attempted to control for these effects by performing exploratory analyses. After excluding the 25 patients who crossed over to the sunitinib arm, median overall survival was 26.4 months (range 23.0–32.9 months) in the sunitinib arm versus 20.0 months (range 17.8–26.9 months) in the interferon-α arm ($P=0.036$). In contrast to the small number of patients who were allowed to cross over, most patients received post-study treatment. Following discontinuation of interferon-α, nearly 60% of patients received alternate therapies, including other VEGF inhibitors, cytokines, mTOR inhibitors or chemotherapy, and more than half of these patients received sunitinib.[4] Once the patients who received post-study treatment had been excluded from the analysis, the difference between the groups in median overall survival became much more prominent – 28.1 months versus 14.1 months ($P=0.003$).

OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL ACCORDING TO RISK STATUS

Risk groups	Sunitinib	Interferon-α
	Overall survival (months)	
All risk groups	26.4 (23–32.9)[1]	21.8 (17.9–26.9)
Good risk (*n*=143)	NR[2]	NR[2]
Intermediate risk (*n*=209)	20.7 (18.2–25.6)[3]	15.4 (13.6–18.2)
Poor risk (*n*=23)	5.3 (4.2–10)[4]	4.0 (2.7–7.2)
	Progression-free survival (months)	
All risk groups	11 (11–13)[5]	5 (4–6)
Good risk (*n*=143)	14.5[6]	7.9
Intermediate risk (*n*=209)	10.6[6]	3.8
Poor risk (*n*=23)	3.7[6]	1.2

[1]$P<0.051$. [2]Median overall survival not reached in either group; [3]Hazard ratio 0.787, 95% CI 0.617-1.004; [4]Hazard ratio 0.660, 95% CI 0.360–1.207; [5]$P<0.001$. [6]Hazard ratio and confidence intervals not available.
Abbreviation: NR, not reached

In support of the validity of these exploratory analyses, when a Wilcoxon analysis was performed instead of logrank calculation, the *P*-value was 0.0128. As the Wilcoxon test preferentially weights early events, this statistical test may be more appropriate than logrank calculations, given the observed effects of crossover and post-study treatment.[4] Thus, the adjusted data from the exploratory analyses form a compelling argument for a true overall survival benefit. This argument is particularly relevant when one considers the extended median overall survival of patients in the interferon-α group – almost 22 months,

compared with the historical survival of 13 months before the advent of targeted therapies.[4]

Similar statistical issues were noted in TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial), which was a phase III trial of sorafenib versus placebo in patients with mRCC who had been treated with prior cytokine therapy.[5] Although a difference in PFS of 2.7 months that favoured sorafenib was demonstrated, overall survival did not differ between the groups (P=0.146). When patients in the placebo arm who crossed over to the sorafenib arm were excluded from the analysis, the difference in overall survival became significant.[5] The median overall survival of patients in the placebo group was more than 15 months, which is longer than the historical survival of patients treated with immunotherapy. This improvement in overall survival of patients in the placebo group might have been related to the effects of crossover and post-study treatment. Similarly, in another phase III trial, patients with mRCC whose disease had progressed on VEGF-targeted therapy were randomly allocated to receive everolimus or placebo.[6] PFS improved by 2.1 months in the everolimus arm, but no difference was observed in overall survival. Since the protocol permitted crossover to everolimus upon disease progression, the lack of an overall survival benefit was not surprising. Allowing patients to cross over to an effective therapy is arguably the only ethical option and, therefore, selection of PFS as the primary study endpoint may be necessary in the context of crossover designs precipitated by increasingly available and effective targeted therapies.

Two phase III studies – Avastin for Renal Cell Cancer (AVOREN)[7] and Cancer and Leukemia Group B (CALGB) 90206[8] indicated significant improvements in PFS for bevacizumab plus interferon-α compared with interferon-α alone. This effect applied to patients in the good-risk group (12.9 months vs 7.6 months in AVOREN, 11.1 months vs 5.7 months in CALGB 90206) and intermediate-risk group (10.2 months vs 4.5 months in AVOREN and 8.4 months vs 5.3 months in CALGB 90206).

The magnitude of the PFS benefit seemed to be smaller than that of sunitinib. However, definitive conclusions about the magnitude of this benefit cannot be drawn until a direct comparison of these two agents is made in a randomised trial. The efficacy of single-agent bevacizumab in the first-line setting merits evaluation, and the relative toxicity profiles of different regimens might influence the selection of first-line treatment.

For poor-risk patients, temsirolimus remains the standard first-line treatment, because of a proven benefit in PFS and overall survival in a randomised, phase III trial.[9] The efficacy of sunitinib in this population of patients remains to be demonstrated. Many patients with poor-risk disease were excluded from the phase III trial of sunitinib, which limited the study's ability to detect a difference in overall survival. Some data suggest sunitinib may be effective in this setting. In an international expanded-access programme, in which 4564 patients with mRCC were treated with sunitinib, 13% (n=582) of participants were considered to have poor performance status.[10] Among evaluable patients in this subpopulation (n=319), the median overall survival was 6.7 months, which compared favourably to historic overall survival in patients with a poor performance status. Poor-risk patients comprised 9% of this group and had a median overall survival of 5.3 months.[10]

Sunitinib seems to improve overall survival compared with interferon-α, a finding that adds to previously published data of superior PFS. Although the statistical significance of the improvement seems to be marginal at first glance, the effect of sunitinib on overall survival is almost certainly underestimated. Sunitinib remains the standard first-line treatment for good-risk and intermediate-risk patients with mRCC, although the availability of multiple other targeted agents highlights the need for continued clinical research.

Areas for ongoing and future investigations include combination regimens, sequencing of targeted therapies, intermittent dosing strategies and incorporation of individualised biomarker and pharmacodynamic profiles to predict response and resistance to therapy.

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

First-line sunitinib improves progression-free survival in good-risk and intermediate-risk patients with mRCC, and confers an overall survival benefit compared with interferon-α

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