

Sunitinib is superior to interferon α with respect to quality of life for patients with renal cell carcinoma

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SUMMARY

Randomized trials have shown that both anti-vascular endothelial growth factor (VEGF) therapy and inhibition of the mammalian target of rapamycin have superior clinical efficacy when compared with interferon α in the first-line treatment of advanced renal cell carcinoma. In 2007, a pivotal phase III trial randomly allocated 750 patients with advanced renal cell carcinoma to receive either the VEGF-receptor tyrosine kinase inhibitor sunitinib or interferon α , and showed that sunitinib led to improved response rates, progression-free and overall survival. In this Practice Point, we discuss the data reported by Cella *et al.*, which showed that the quality of life of patients in this trial was better with sunitinib than interferon α ; these differences were predominantly due to better control of disease-related symptoms by sunitinib. This landmark study is the first to report comparative quality-of-life data for an anti-VEGF therapy and a cytokine therapy.

KEYWORDS interferon α , quality of life, renal cell carcinoma, sunitinib, tyrosine kinase inhibitor

COMMENTARY

Renal cell carcinoma (RCC) accounts for 13,000 deaths per year in the US, and advanced disease is associated with a 5-year survival of less than 10%. The goal of systemic therapy in the management of advanced solid malignancies is largely palliative, with a focus on maximizing duration of life, progression-free interval and the duration of good symptom control. In randomized trials, the anti-vascular endothelial growth factor (VEGF) therapies bevacizumab, sorafenib and sunitinib, and the inhibitors of the mammalian target of rapamycin (mTOR) everolimus and temsirolimus, have been shown to prolong progression-free survival and, in some cases, overall survival, compared with previous therapies.^{1–4} Sunitinib was the first agent to demonstrate superiority compared with interferon α (IFN- α) as first-line therapy for patients with advanced RCC. This randomized, phase III study of 750 patients reported improvements in response rate (31% versus 6%) and progression-free survival (11 months versus 5.5 months) for patients who received sunitinib compared to those who received IFN- α .¹ An update has now reported an overall survival benefit with sunitinib in a censored population that excluded the 60% of patients who received second-line treatment, usually anti-VEGF therapy.²

Cella *et al.* used several validated, patient-reported questionnaires to evaluate quality of life (QoL), which included the general Functional Assessment of Cancer Therapy (FACT-G) questionnaire, the 15-item Kidney Symptom Index (FKSI-15) and Disease Related Symptoms (FKSI-DRS), the EuroQol Group's EQ-5D and a visual analog scale (VAS).⁵ The questionnaires assess symptoms including fatigue, pain, weight loss, cough, fever and hematuria, as well as physical, social, emotional and functional well-being, self-care, usual activities, pain or discomfort and anxiety or depression. The assessments were completed at screening, on days 1 and 28 of each 42-day treatment cycle, and at the end of treatment or study withdrawal. The study reported that patients who received sunitinib had better QoL than those who received IFN- α by all methods evaluated. Sunitinib-treated patients had higher FKSI-15 and FKSI-DRS scores at each cycle than IFN- α -treated patients ($P < 0.0001$), which indicates a better QoL.⁵ Scores associated with either agent actually dropped after cycle 1, but those associated with sunitinib returned to, or rose above, base-line, whereas those with IFN- α remained below base-line throughout the study. FACT-G and EuroQol scores were maintained with sunitinib throughout the study period but dropped significantly with IFN- α (FACT-G,

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$P < 0.0001$; EuroQol EG-5D, $P = 0.0052$; EuroQol VAS, $P < 0.0001$).⁵

Most QoL assessments in RCC have been performed in trials of surgery or in trials comparing immunotherapies. Few studies have addressed QoL in the post-cytokine era of management of advanced RCC. The only other randomized trial to report QoL associated with an anti-VEGF therapy was a placebo-controlled trial in which 80% of the patients were treated in the second-line setting⁶ and, therefore, is not directly comparable. QoL evaluation by FKSI and FACT-G showed no differences in mean overall score between the two groups, although sorafenib-treated patients reported significantly fewer symptoms than placebo-treated patients.⁶ In 2008, two open-label case series assessed QoL by the European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) tool in 51 and 52 patients treated with sunitinib or sorafenib (study 1) or axitinib (study 2), respectively.^{7,8} Both studies described modest deterioration in QoL in the first 4 weeks after initiation of therapy, with a return to base-line by 16 weeks in the first study.^{7,8} The only other reported phase III randomized trials of first-line anti-VEGF therapy are the AVOREN³ and CALGB 90206⁹ trials in which patients received IFN- α with or without bevacizumab. Both trials reported toxicity but neither has reported QoL data. Neither of these randomized, placebo-controlled trials of mTOR inhibitors has reported QoL data; however, in a phase III study of everolimus versus placebo in patients who had progressed following prior anti-VEGF therapy, QoL was similar in both treatment groups.⁴

The study reported by Cella *et al.*, demonstrates the superior QoL associated with sunitinib compared with that of IFN- α in the first-line setting.⁵ The authors are to be commended; this study is the most comprehensive report of QoL in any randomized trial of targeted therapies in advanced RCC to date, with an impressive questionnaire completion rate in excess of 95%.⁵ The authors are clear about the limitations of the study. For example, the outcome might have been confounded by factors such as preference for oral over subcutaneous administration. Adjustments were not made for country of enrollment, sex, age, ethnicity or base-line performance status; however, these factors are unlikely to have influenced the outcome significantly because of the randomized nature of the study. The

authors assessed whether the superior QoL associated with sunitinib related to superior antitumor efficacy and symptom control or to reduced drug-specific toxicity.⁵ Although they were unable to reach a firm conclusion, the longitudinal use of different QoL tools, particularly their own FKSI, suggest that superior antitumor efficacy is probably the most influential factor.

The study by Cella *et al.* provides robust evidence that sunitinib maintains QoL more effectively than IFN- α . Thus, the most important outcome of this study for patients and practicing renal oncologists is the added confidence it brings to the already widely held view that sunitinib is not only more efficacious and better tolerated than IFN- α , but also leads to a better QoL. Further robust QoL analyses are to be encouraged as clinical trials aim to determine the optimal targets and regimens for the plethora of agents becoming available for the treatment of advanced RCC.

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PRACTICE POINT

In addition to its previously established response, progression-free and overall survival benefits, sunitinib maintains quality of life more effectively than interferon α in the first-line systemic treatment of advanced renal cell carcinoma.

Competing interests

The authors have declared associations with the following companies: Bayer, Novartis, Pfizer, Roche and Schering-Plough. See the article online for full details of the relationships.