Temsirilimus, interferon alfa or both in advanced renal-cell carcinoma: One plus one does not always equal two

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Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356:2271-81.

SUMMARY

This Phase 3 multicenter randomized trial compared interferon alone, temsirolimus alone or the combination of both for the treatment of newly diagnosed metastatic renal-cell carcinoma. From July 2003 to April 2005, a total of 626 patients were randomly assigned to one of the three study groups. Two hundred and seven were assigned to receive three million units of interferon alfa (with an increase to 18 million units subsequently) thrice weekly, 209 to receive 25mg of intravenous temsirolimus weekly and 210 to receive a combination of interferon and temsirolimus with 15mg of temsirolimus weekly plus six million units of interferon alfa thrice weekly. Those with histologically confirmed advanced renal-cell carcinoma (Stage IV or recurrent disease) and a Karnofsky performance score of 60 or more, with no previous systemic therapy and at least three of the six predictors of short survival were included. Patients were stratified according to the geographic location of the center and whether they had undergone nephrectomy. Treatment was continued as long as there was no disease progression, symptomatic deterioration or intolerable adverse events. Required imaging studies were done before treatment and were repeated at eight-week intervals to evaluate tumor size. The primary end point was overall survival, calculated on an intention-to-treat basis. This report was the second interim analysis conducted after 446 patients had died. Median survival was 7.3 months in the interferon group, 10.9 months in the temsirolimus group and 8.4 months in the combination therapy group and the median progression-free survival times in the interferon, temsirolimus and combination therapy groups were 1.9, 3.8 and 3.7 months, respectively. The objective response rates were 4.8%, 8.6% and 8.1% among patients receiving interferon, temsirolimus and combination therapy, not differing significantly. The effect of temsirolimus on overall survival was greater among patients under 65 years of age than among older patients and among patients with a serum lactate dehydrogenase level of more than 1.5 times the upper limit of the normal range than among those with lower levels.

COMMENTS

Management of advanced renal-cell carcinoma (RCC) has made considerable progress in recent years and new emerging strategies are being developed. As distant metastases develop in about one-third of patients with RCC and most of these cases cannot be cured surgically, other options play an important role. Sunitinib, sorafenib and bevacluzimab have been proven to have efficacy in this scenario. Both temsirolimus (CCI-779) and sirolimus (rapamycin), its primary metabolite, are potent and specific inhibitors of the mammalian target of rapamycin (mTOR) kinase, involved in intracellular signaling pathways of cell proliferation. Interleukin-2 and interferon alfa, alone or in combination, have been the main treatments for metastatic renal-cell carcinoma. In select groups treatment with these agents results in a median survival of 12.0 to 17.5 months. They rarely benefit patients with an extensive tumor burden and adverse prognostic factors. It
was hoped that a combination of these agents may increase the degree of their antitumor effects.\(^5\) In this Phase 3 trial, the principal finding was that, in patients with advanced renal-cell carcinoma and a poor prognosis, treatment with temsirolimus was associated with a moderate prolongation of overall survival than with interferon alone or the combination. The median overall survival in the group given temsirolimus alone was 10.9 months, as compared with 7.3 and 8.4 months in the groups given interferon alfa or combination therapy, respectively.

The combination of temsirolimus plus interferon did not improve overall survival. This could be due to greater adverse effects resulting in more delays and reductions in treatment and lower mean dose intensity of temsirolimus (10.9mg vs. 23.1mg per week). Patients with extensive and rapidly progressive disease may be less able to tolerate treatment and may have tumors that are inherently more resistant to therapy. Accordingly, the moderate efficacy of temsirolimus in advanced disease suggests that the drug might benefit patients with less extensive metastatic renal-cell carcinoma. The results of this trial point to mTOR as a target for cancer treatment and the possibility of using temsirolimus as first-line treatment for metastatic renal-cell carcinoma.

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Can Reflex UroVysion fluorescence in situ hybridization predict tumor recurrence during follow-up?

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Yoder BJ, Skacel M, Hedgepeth R, Babineau D, Ulchaker JC, Liou LS, et al. Reflex urovysion testing of bladder cancer surveillance patients with equivocal or negative urine cytology: A prospective study with focus on the natural history of anticipatory positive findings. Am J Clin Pathol 2007;127:295-301.

SUMMARY
The primary aim of this study was to demonstrate the usefulness of multitarget fluorescence in situ hybridization (FISH UroVysion) testing in the early detection of recurrent urothelial carcinoma (UC). The study population comprised patients with bladder tumor on follow-up, who had negative or atypical urine cytology with no evidence of recurrence by cystoscopy. Some of these patients had positive UroVysion FISH in the urine cell sample. The paper looks at the course of these "anticipatory positive" cases with special reference to the recurrence and the time to tumor recurrence. Fifty-six (26.5%) of the 211 patients with negative cystoscopy and negative or atypical cytology had positive FISH results. This group formed the anticipatory positive subset of patients. Recurrent urothelial carcinoma developed in 35 (62.5%) of these 56 patients. Of these recurrent tumors 22 were high-grade UC and 12 low-grade UC. In about 65% of this anticipatory positive group, recurrent bladder UC developed within 29 months. The recurrence rate was 48% in six months and 54% within 10 months of the positive FISH result. In contrast recurrent UC developed in only eight (5.2%) of the 155 cystoscopically negative, cytologically negative or atypical and FISH negative cases.

COMMENTS
Urothelial carcinoma has a high rate of recurrence and progression, necessitating frequent patient surveillance by follow-up cystoscopy and urine cytology.\(^1\) The invasive nature of cystoscopy and the relative low sensitivity of cytology are the limitations of this approach. This has led to many adjunctive assays to stratify individuals into high- and low-risk categories.\(^2\) UroVysion is a multitarget FISH assay to detect chromosomal alterations by three DNA probes directed...