ORIGINAL ARTICLE

Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma

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ABSTRACT

BACKGROUND

Interferon alfa is widely used for metastatic renal-cell carcinoma but has limited efficacy and tolerability. Temsirolimus, a specific inhibitor of the mammalian target of rapamycin kinase, may benefit patients with this disease.

METHODS

In this multicenter, phase 3 trial, we randomly assigned 626 patients with previously untreated, poor-prognosis metastatic renal-cell carcinoma to receive 25 mg of intravenous temsirolimus weekly, 3 million U of interferon alfa (with an increase to 18 million U) subcutaneously three times weekly, or combination therapy with 15 mg of temsirolimus weekly plus 6 million U of interferon alfa three times weekly. The primary end point was overall survival in comparisons of the temsirolimus group and the combination-therapy group with the interferon group.

RESULTS

Patients who received temsirolimus alone had longer overall survival (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.58 to 0.92; P=0.008) and progression-free survival (P<0.001) than did patients who received interferon alone. Overall survival in the combination-therapy group did not differ significantly from that in the interferon group (hazard ratio, 0.96; 95% CI, 0.76 to 1.20; P=0.70). Median overall survival times in the interferon group, the temsirolimus group, and the combination-therapy group were 7.3, 10.9, and 8.4 months, respectively. Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimus group, whereas asthenia was more common in the interferon group. There were fewer patients with serious adverse events in the temsirolimus group than in the interferon group (P=0.02).

CONCLUSIONS

As compared with interferon alfa, temsirolimus improved overall survival among patients with metastatic renal-cell carcinoma and a poor prognosis. The addition of temsirolimus to interferon did not improve survival. (ClinicalTrials.gov number, NCT00065468.)

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Renal-cell carcinoma accounts for 2.6% of all cancers in the United States, and nearly 39,000 new cases of this disease and 13,000 associated deaths were expected in 2006.[1] Surgical resection is the mainstay of treatment for tumors that are confined to the kidney. Distant metastases develop in about one third of patients, and most of these cases cannot be cured. Interleukin-2 and interferon alfa, alone or in combination, are the main treatments for metastatic renal-cell carcinoma. Treatment with these agents results in a median survival of 12.0 to 17.5 months.[2-6] These cytokines, however, have limited efficacy and substantial toxicity, and they rarely benefit patients with an extensive tumor burden and adverse prognostic factors. Such patients have a median survival of only 4 to 8 months.[7-9]

Temsirolimus (CCI-779) is an inhibitor of mammalian target of rapamycin (mTOR) kinase, a component of intracellular signaling pathways involved in the growth and proliferation of cells[10,11] and the response of such cells to hypoxic stress.[12] Temsirolimus binds to an abundant intracellular protein, FKBP-12, and in this way forms a complex that inhibits mTOR signaling.[13,14] The disruption of mTOR signaling suppresses the production of proteins that regulate progression through the cell cycle[15,16] and angiogenesis.[17,18] The inhibition of angiogenesis by temsirolimus is clinically relevant because unregulated angiogenesis is prominent in renal-cell carcinoma.[19]

Control of advanced renal-cell carcinoma was observed over a broad dose range in phase 1 trials of temsirolimus.[20,21] A phase 2 study of temsirolimus in cytokine-refractory metastatic renal-cell carcinoma showed evidence of improved survival,[22] and a study of temsirolimus plus interferon alfa identified tolerable doses and clinical indications of antitumor activity.[23] Encouraged by these results, we conducted a phase 3 trial in which we compared temsirolimus alone or temsirolimus plus interferon alfa with interferon alfa alone in metastatic renal-cell carcinoma.

METHODS

PATIENTS

Eligibility criteria included histologically confirmed advanced renal-cell carcinoma (stage IV or recurrent disease) and a Karnofsky performance score of 60 or more (on a scale of 0 to 100, with higher scores indicating better performance), with no previous systemic therapy. Additional eligibility criteria were a tumor that was measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST),[24] and adequate bone marrow, renal, and hepatic functions, which were defined as a neutrophil count of at least 1500 cells per cubic millimeter, a platelet count of at least 100,000 cells per cubic millimeter, and a hemoglobin count of at least 8 g per deciliter; a serum creatinine level of no more than 1.5 times the upper limit of the normal range; an aspartate aminotranferase level of no more than 3 times the upper limit of the normal range (≤5 times if liver metastases were present); and a total bilirubin level of no more than 1.5 times the upper limit of the normal range. A fasting level of total cholesterol of no more than 350 mg per deciliter (9.1 mmol per liter) and a triglyceride level of no more than 400 mg per deciliter (4.5 mmol per liter) were required. Patients with a history of brain metastases were eligible if their condition was neurologically stable and they did not require corticosteroids after surgical resection or radiotherapy.

At least three of the following six predictors of short survival were required: a serum lactate dehydrogenase level of more than 1.5 times the upper limit of the normal range, a hemoglobin level below the lower limit of the normal range; a corrected serum calcium level of more than 10 mg per deciliter (2.5 mmol per liter), a time from initial diagnosis of renal-cell carcinoma to randomization of less than 1 year, a Karnofsky performance score of 60 or 70, or metastases in multiple organs.

Wyeth Research designed the trial and developed the study protocol in collaboration with the principal academic investigators. Data were collected and analyzed by Wyeth Research and the academic investigators. Radiologic assessments were performed by the study investigators and Bio-Imaging Technologies. The academic investigators were responsible for the decision to publish the data. All the authors had access to the primary data and vouch for the integrity and completeness of the data reported in this article. Dr. Hudes drafted the manuscript and revised it on the basis of suggestions from the coauthors. The sponsor played no role in writing or revising the manuscript.

The institutional review board at each participating center approved the study protocol, and the study was conducted in accordance with international standards of good clinical practice. All patients provided written informed consent.

TREATMENT

Patients were stratified according to the geographic location of the center (United States; Western Europe, Australia, and Canada; or Asia-Pacific, Eastern Europe, Africa, and South America) and whether they had undergone nephrectomy. Patients were randomly assigned in equal proportions, with the use of permuted blocks of three, to one of three treatment groups.

The interferon group received interferon alfa-2a (Roferon-A, Roche) at a starting dose of 3 million U given subcutaneously three times per week for the first week. The dose was raised to 9 million U three times per week for the second week and to 18 million U three times per week for week 3, if this dose was tolerated. Patients who were unable to tolerate 9 million U or 18 million U received the highest tolerable dose, which could be 3 million U, 4.5 million U, or 6 million U.

The temsirolimus group received 25 mg of temsirolimus (Wyeth Research) in a weekly 30-minute intravenous infusion. Premedication with 25 to 50 mg of intravenous diphenhydramine or a similar H_1 blocker was given approximately 30 minutes before each weekly temsirolimus infusion as prophylaxis against an allergic reaction. The combination-therapy group received 15 mg of temsirolimus in a 30-minute infusion weekly plus interferon at a starting dose of 3 million U three times per week for week 1 and 6 million U subcutaneously three times per week thereafter.

Treatment was continued as long as there was no disease progression, symptomatic deterioration, or intolerable adverse events. It was withheld for grade 3 or 4 adverse events (defined according to the National Cancer Institute Common Toxicity Criteria, version 3.0) and restarted at a reduced dose after recovery to grade 2 or lower. For the combination-therapy group, one or both agents were withheld, depending on the adverse event. For grade 2 adverse events that were poorly tolerated, dose reduction without treatment interruption was permitted at the discretion of the treating physician. Dose reduction was not required for adverse events that could be managed with supportive therapy.

EVALUATION

At baseline, a complete blood count was performed, along with assessments of levels of serum cholesterol and triglycerides and renal and hepatic function. Adverse events, serum chemical analyses, and blood counts were monitored weekly or biweekly. Required imaging studies before treatment included computed tomographic (CT) scans of the chest, abdomen, and pelvis; a radionuclide bone scan; and a magnetic resonance imaging or CT scan of the brain. Scanning was repeated at 8-week intervals to evaluate tumor size. Response to treatment was assessed with the use of RECIST.

STATISTICAL ANALYSIS

The primary end point was overall survival, calculated on an intention-to-treat basis. We targeted a 40% improvement in median overall survival, from 4.9 months for interferon alone to 6.9 months for either of the temsirolimus-containing regimens. The planned sample size of 200 patients per group was based on a power of 80% to detect a 40% improvement for each comparison with the use of a two-sided stratified log-rank test at an overall 2.5% level of significance, with two planned interim analyses after approximately 164 and 430 deaths had occurred, and a final analysis, if necessary, after a total of 504 deaths had occurred.

Secondary efficacy end points were progression-free survival as determined by the site investigators' assessment and a blinded assessment of imaging studies (performed by Bio-Imaging Technologies), the objective response rate, and the clinical benefit rate, defined as the proportion of patients with stable disease for at least 24 weeks or an objective response. All patients who received any treatment were included in the analysis of safety. The characteristics of the patients in each group were compared with the use of the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. The proportion of patients with adverse events in each group was analyzed with the use of Fisher's exact test.

We explored the potential effect of the baseline characteristics of patients on progression-free and overall survival. The prespecified factors included age, sex, geographic region, nephrectomy status, tumor histologic type, time from metastasis to randomization, Karnofsky performance score, and levels of hemoglobin, serum lactate dehydrogenase, and corrected serum calcium. These analyses were performed by testing for a nonzero interaction between the treatment group and the baseline variable in a stratified Cox proportional-hazards model that included the treatment group, baseline factors, and their interaction as explanatory variables. We conducted separate analyses for the comparison of the temsirolimus group with the

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Interferon (N=207)	Temsirolimus (N=209)	Interferon plus Temsirolimus (N=210)	Total (N=626)
Age				
Median — yr	60	58	59	59
Range — yr	23–86	32–81	32–82	23–86
<65 yr — no. (%)	142 (69)	145 (69)	153 (73)	440 (70)
≥65 yr — no. (%)	65 (31)	64 (31)	57 (27)	186 (30)
Sex — no. (%)				
Male	148 (71)	139 (66)	145 (69)	432 (69)
Female	59 (28)	70 (33)	65 (31)	194 (31)
Karnofsky performance score — no. (%)				
>70	34 (16)	41 (20)	33 (16)	108 (17)
≤70	171 (83)	168 (80)	177 (84)	516 (82)
Previous nephrectomy — no. (%)	139 (67)	139 (66)	141 (67)	419 (67)
Tumor histologic type — no. (%)				
Clear-cell	170 (82)	169 (81)	163 (78)	502 (80)
Other	37 (18)	40 (19)	47 (22)	124 (20)
Protocol-defined poor prognostic features — no. (%)				
Lactate dehydrogenase level >1.5 times upper limit of normal	48 (23)	36 (17)	33 (16)	117 (19)
Hemoglobin level <lower limit of normal	168 (81)	172 (82)	178 (85)	518 (83)
Corrected serum calcium level >10 mg/dl (2.5 mmol/liter)	72 (35)	54 (26)	58 (28)	184 (29)
Time from initial diagnosis to randomization <1 yr	164 (79)	174 (83)	179 (85)	517 (83)
Karnofsky performance score ≤70†	171 (83)	168 (80)	177 (84)	516 (82)
≥2 sites of organ metastasis	165 (80)	166 (79)	168 (80)	499 (80)
No. of poor prognostic features — no. (%)				
≥3 of 6	196 (95)	195 (93)	198 (94)	589 (94)
<3 of 6	11 (5)	14 (7)	12 (6)	37 (6)
MSKCC risk classification — no. (%)‡				
Poor risk (≥3 of 5 factors)	157 (76)	145 (69)	160 (76)	462 (74)
Intermediate risk (1 or 2 of 5 factors)	50 (24)	64 (31)	50 (24)	164 (26)

* Percentages may not total 100 because of rounding.
† A Karnofsky performance score of 70 (scores range from 0 to 100, with higher scores indicating better performance) signifies that the patient is unable to work but is able to perform activities of daily living.
‡ The Memorial Sloan-Kettering Cancer Center (MSKCC) model includes the first five poor-prognostic features listed in the table.

interferon group and for the comparison of the combination-therapy group with the interferon group.

Statistical analysis was performed by the study's sponsor, Wyeth Research. An independent data and safety monitoring committee reviewed the study at 6-month intervals and at the predefined event milestones for the interim analyses. We report here on the results of the second interim analysis, conducted after 446 patients had died. On the basis of these data, the committee determined that the O'Brien–Fleming condition[25] for

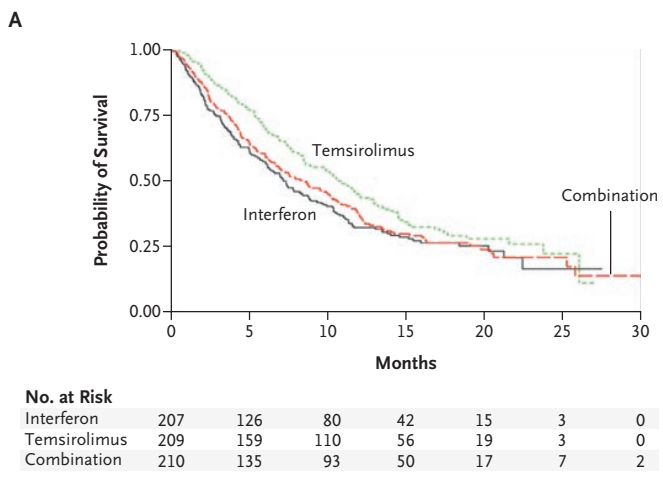
early acceptance of the alternative hypothesis was reached, and the data were released to the sponsor. The significance level for stopping the study at the second interim analysis was P<0.0135. All reported P values are two-sided and have not been adjusted for multiple testing.

RESULTS

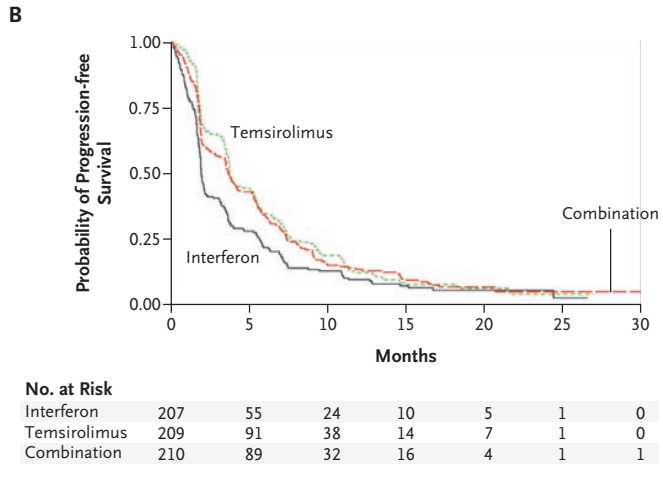
From July 2003 to April 2005, a total of 626 patients were enrolled in the study. We randomly assigned 207 of these patients to receive interferon, 209 to receive temsirolimus, and 210 to receive a combination of interferon and temsirolimus. A total of 45 patients were ineligible (15 in the interferon group, 17 in the temsirolimus group, and 13 in the combination-therapy group), and 10 patients did not receive any treatment (7 in the interferon group, 1 in the temsirolimus group, and 2 in the combination-therapy group).

CHARACTERISTICS OF THE PATIENTS

Table 1 shows that the three treatment groups were well balanced on the basis of age, sex, and performance-status score. Approximately 80% of patients in each group had a Karnofsky performance score of 60 or 70. Clear-cell carcinoma was the histology of the tumor in approximately 80% of patients. Two thirds of the patients had undergone nephrectomy, and approximately 80% had received a diagnosis of metastatic disease within 12 months before enrollment. Three or more poor prognostic factors were present in 94% of the patients. A total of 19 patients were lost to follow-up (10 in the interferon group, 4 in the temsirolimus group, and 5 in the combination-therapy group).



No. at Risk							
Interferon	207	126	80	42	15	3	0
Temsirolimus	209	159	110	56	19	3	0
Combination	210	135	93	50	17	7	2



No. at Risk							
Interferon	207	55	24	10	5	1	0
Temsirolimus	209	91	38	14	7	1	0
Combination	210	89	32	16	4	1	1

Figure 1. Kaplan–Meier Estimates of Overall Survival (Panel A) and Progression-free Survival (Panel B).

EFFICACY

As compared with interferon alone, treatment with temsirolimus alone was associated with a hazard ratio for death of 0.73 (95% confidence interval [CI], 0.58 to 0.92; P=0.008). As compared with interferon, the combination of interferon plus temsirolimus resulted in a hazard ratio for death of 0.96 (95% CI, 0.76 to 1.20; P=0.70). Figure 1A shows the overall survival times in the three groups. 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 (Table 2). As determined by the site investigators, the median progression-free survival times in the interferon, temsirolimus, and combination-therapy groups were 1.9, 3.8, and 3.7 months, respectively (Fig. 1B). According to the independent radiologic assessments, the median progression-free survival times for the interferon, temsirolimus, and combination-therapy groups were 3.1, 5.5, and 4.7 months, respectively. The shorter estimate of progression-free survival by the site investigators reflected the inclusion of patients with symptomatic deterioration that had begun before scheduled radiologic measurements of the tumor.

The objective response rates of 4.8%, 8.6%, and 8.1% among patients receiving interferon, temsirolimus, and combination therapy, respectively, did

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