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Could Interferon Still Play a Role in Metastatic Renal Cell Carcinoma? A Randomized Study of Two Schedules of Sorafenib Plus Interferon-Alpha 2a (RAPSODY)

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Abstract

Background: Sorafenib has proven efficacy in metastatic renal cell carcinoma (mRCC). Interferon (IFN) has antiangiogenic activity that is thought to be both dose- and administration-schedule dependent.
Objective: To compare two different schedules of IFN combined with sorafenib.
Design, setting, and participants: Single-stage, prospective, noncomparative, randomized, open-label, multicenter, phase 2 study on previously untreated patients with mRCC and Eastern Cooperative Oncology Group performance status 0–2.
Intervention: Sorafenib 400 mg twice daily plus subcutaneous IFN, 9 million units (MU) three times a week (Arm A) or 3 MU five times a week (Arm B).
Outcome measurements and statistical analysis: Primary end points were progression-free survival (PFS) for each arm and safety. Data were evaluated according to an intent-to-treat analysis.
Results and limitations: A total of 101 patients were evaluated. Median PFS was 7.9 mo in Arm A and 8.6 mo in Arm B ($p = 0.049$) and the median duration of response was 8.5 and 19.2 mo, respectively ($p = 0.0013$). Nine partial responses were observed in Arm A, and three complete and 14 partial responses were observed in Arm B (17.6% vs 34.0%; $p = 0.058$); 24 and 21 patients (47% and 42%), respectively, achieved stable disease. The most common grade 3–4 toxicities were fatigue plus asthenia (28% vs 16%; $p = 0.32$) and hand-foot skin reactions (20% vs 18%).
Conclusions: Sorafenib plus frequent low-dose IFN showed good efficacy and tolerability. Further investigations should be warranted to identify a possible positioning of this intriguing regimen (6% complete response rate) in the treatment scenario of mRCC.

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1. Introduction

The mainstay of medical treatment of metastatic renal cell carcinoma (mRCC) for >20 yr has been immunotherapy, often resulting in inadequate and/or contradictory response rates and severe toxicities [1,2]. Advances in the understanding of RCC molecular biology led to the development of new anticancer agents targeted directly against cell-specific pathways at a molecular level, including gene expression, growth regulation, cell-cycle control, apoptosis, and angiogenesis. These agents proved to be effective in terms of progression-free survival (PFS) and had acceptable toxicity profiles in the clinical setting [3,4].

Drug combination strategies were then developed to improve the inhibition of a single pathway (vertical blockade) or to hamper different pathways (horizontal blockade), in view of increased efficacy and reduced toxicity [5]. In this regard, the combination of interferon (IFN) with the targeted agent sorafenib, a Raf-kinase and vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor whose activity as a single agent has been widely documented in mRCC [3,6], appeared worthy of further investigation.

IFN-alpha is a pleiotropic molecule endowed with antiangiogenic activity: Early in vitro studies showed that IFN downregulates basic fibroblast growth factor expression in human cancer cells [7], and experimental studies in mice demonstrated that this antiangiogenic effect is optimal at frequent low doses, whereas it declines at higher doses [8]. The existence of schedule-dependent antiangiogenic activity of IFN, with possible increased activity when IFN is used at low frequent doses as compared with standard doses, was subsequently confirmed in humans by Judah Folkman, a pioneer in angiogenic studies [9]. With regard to advanced RCC, the combination of sorafenib plus IFN has previously been explored in experimental and phase 1 and 2 clinical studies using standard doses of IFN, demonstrating that this combination is effective and adequately tolerated [10–13]. The aim of the current study was to evaluate the efficacy and safety of two regimens consisting of sorafenib combined with either standard doses or frequent low doses of IFN.

2. Patients and methods

This was in a single-stage, prospective, noncomparative, randomized, open-label, multicenter, phase 2, pick-the-winner trial [14]. The primary end points were PFS and safety. The main secondary end points were overall response rate, duration of response, and overall survival (OS). The study planned to enroll 100 patients over 18 mo in 11 centers located throughout Italy.

Eligible patients were aged ≥18 yr, had histologically or cytologically confirmed metastatic clear cell RCC with a clear cell component of ≥50%, measurable disease (at least one unidimensional lesion detected by computed tomography [CT] scan or magnetic resonance imaging [MRI]) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria [15], life expectancy ≥3 mo, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, baseline absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin values ≥10 g/dl, serum creatinine ≤2.0 times the upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and alanine aminotransferase or aspartate aminotransferase ≤2.5 times ULN (≤5.0 times ULN in the presence of liver metastases). All patients had undergone previous nephrectomy and none had been previously treated with any type of systemic therapy for metastatic disease.

Exclusion criteria were the following: history of brain metastases; concomitant important illnesses or medical conditions, such as serious respiratory or cardiovascular diseases, unstable diabetes mellitus, serious bacterial or fungal infections, and potentially life-threatening autoimmune disorders; pregnancy or breastfeeding (both women and men of reproductive potential must have agreed to use adequate barriers for birth control); and other prior malignancies, with the exception of adequately treated basal or squamous cell skin cancer or in situ cervical cancer. Following protocol approval by the ethical committees of each institution, each patient signed the written informed consent at the time of enrollment. Patient enrollment began in January 2006 and no clinical trial registration was needed. However, this study was registered in the Italian Health's Institute Study Registry with the number 0861.

Patients were randomly allocated to receive two 200 mg sorafenib tablets twice daily continuously combined with subcutaneous IFN at doses of either 9.0 million units (MU) three times a week (Arm A) or 3.0 MU five times a week (Arm B). The randomization list was generated according to random permuted blocks stratified by center, using a validated SAS program (SAS Institute Inc, Cary, NC, USA). Other stratification criteria were not applied. To increase patients' compliance, IFN administration could be initiated at lower doses (eg, 3.0 MU three times a week for Arm A, 1.5 MU five times a week for Arm B) provided that full doses would be achieved within the first 2 wk of treatment. Treatment was continued until tumor progression, symptomatic deterioration, or the onset of unacceptable toxicity requiring drug discontinuation and patient's withdrawal from the study. Each 4-wk (28-d) treatment period was considered one cycle.

Toxicity was assessed using the US National Cancer Institute Common Toxicity Criteria v.3.0. If grade 3–4 toxicity occurred that was probably correlated to sorafenib, treatment was discontinued temporarily, then continued at a reduced sorafenib dose of 600 mg once daily. If further dose reductions were required, doses of 400 mg or 200 mg once a day were applied. In the event of no recovery to grades 0–1 after a 2-wk discontinuation period, treatment with sorafenib was discontinued. If grade 3–4 toxicity probably correlated to IFN, the drug was initially reduced to 6.0 MU three times a week in Arm A and to 1.5 MU five times a week in Arm B. If required, 3.0 MU three times weekly in Arm A and 1.5 MU three times weekly in Arm B were applied. If no recovery to grades 0–1 was observed after 2 wk at reduced doses, IFN was discontinued. Patients who discontinued one drug during the study because of specific toxicities could, at the investigator's discretion, continue treatment with the other drug or withdraw from the study.

RECIST criteria 1.0 were used to assess response [15]. Tumor measurements were carried out by CT scan or MRI within the last 10 d of the third cycle and then every 12 wk. All evidence of complete and partial responses and of stable disease had to be confirmed 4 wk apart.

All clinical and instrumental variables and toxicity data were analyzed by usual descriptive statistics: mean, standard deviation, minimum and maximum values for continuous variables, and absolute and relative frequencies for categorical variables. All comparisons between groups were performed in an explorative fashion.

Both PFS and OS were calculated using the Kaplan-Meier method in the Statistical Package for the Social Sciences (SPSS) v.15.0 (IBM Corp., Armonk, NY, USA) [16]. PFS was defined from the date of the first dose of sorafenib to death from any cause or disease progression. Duration of response was defined from the date of response to disease progression in responding patients. OS was defined from the date of the first dose of sorafenib to death from any cause. The number of patients to be accrued was calculated by hypothesizing a median PFS treatment period of 6 mo for Arm A with a hazard ratio of 1.5 between the worst and best arm.