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ORIGINAL ARTICLE

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# A phase II study of flavopiridol in patients with advanced renal cell carcinoma: results of Southwest Oncology Group Trial 0109

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**Abstract** *Purpose*: Flavopiridol is a cyclin-dependent kinase inhibitor that prevents cell cycle progression and tumor growth. In initial phase I studies, encouraging responses were seen in advanced renal cell cancer (RCC). In a phase II study of flavopiridol given as a 72-h continuous infusion every 2 weeks in RCC, a response rate of 6% was seen but with considerable grade 3 or 4 asthenia, diarrhea, and thrombosis. Subsequently, an alternative 1-h bolus schedule was reported to have enhanced tolerability in a phase I trial. We therefore conducted a phase II study of this bolus regimen. *Methods*: A total of 38 patients with advanced RCC were entered into this multi-institutional phase II study. Flavopiridol (50 mg/m$^2$ per day) was administered by bolus intravenous injection daily for three consecutive days, repeated every 3 weeks. *Results*: Out of 34 eligible patients, one complete response and three partial responses were observed, for an overall response rate of 12% (95% CI 3–27%). Of the 34 patients, 14 (41%) had stable disease (SD). The probability of not failing treatment by 6 months was 21% (95% CI 9–35%). Median overall survival time was 9 months (95% CI 8–18 months). The most common grade 3 or 4 toxicities were diarrhea (35%) and tumor pain (12%) along with anemia, dyspnea, and fatigue (9% each). *Conclusions*: Flavopiridol at this dose and schedule is feasible with an acceptable toxicity profile. Flavopiridol has some modest biologic activity against advanced RCC, as evidenced by its single-agent objective response and SD rates.

**Keywords** Flavopiridol · Cyclin-dependent kinase inhibitor · Renal cell neoplasm

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## Introduction

Renal cell carcinoma (RCC) is diagnosed in approximately 30,000 Americans annually, resulting in 11,600 deaths. Many patients present with advanced or unresectable disease, and up to 30% of patients treated by nephrectomy for localized disease will relapse [16]. The 5-year survival rate for metastatic RCC is estimated to be 0–10% [6]. Hormonal, chemotherapeutic, and radiation therapy approaches have failed to significantly improve outcomes, particularly for patients with metastatic disease. Immunotherapy with agents such as

interferon and interleukin-2, administered at variable doses either alone or in combination, have generated only modest results. In a recent randomized clinical trial, response rates were 6.5%, 7.5%, and 18.6% for patients receiving interleukin-2, interferon alfa-2a, and interleukin-2 plus interferon alfa-2a, respectively. Event-free survival rates at 1 year were 15%, 12%, and 20%, respectively [17].

The Southwest Oncology Group explored the concept of a palliative nephrectomy in patients with metastatic RCC in a phase III trial randomizing patients to treatment with radical nephrectomy followed by therapy with interferon alfa-2b or interferon alfa-2b therapy alone [7]. The median survival time for patients assigned to surgery followed by interferon was 11.1 months, versus 8.1 months in the patients assigned to interferon alone ($P = 0.05$).

The administration of high-dose bolus interleukin-2 has also produced modest durable responses in a small percentage of patients (19% overall response rate). Significant toxicities occur with these regimens, thus limiting the population of patients eligible for such treatments. New agents with unique mechanisms of action are therefore needed for this patient population.

Flavopiridol is a semisynthetic flavonoid isolated from the rohitukine plant. It is a potent inhibitor of cyclin-dependent kinase (CDK) and acts by competing for the ATP-binding site [3, 5, 11, 13, 27]. It also has many other biologic effects, including inhibition of the epidermal growth factor receptor (EGFR), inhibition of protein kinase A (PKA), depletion of vascular endothelial growth factor and cyclin D1, and induction of cell cycle arrest and apoptosis [4, 14, 23]. When flavopiridol was tested in the National Cancer Institute's anticancer drug screen with 60 cancer cell lines, it was found to have an $IC_{50}$ of 66 n *M*, a level 1000 times lower than the concentration required for PKA or EGFR inhibition, but similar to the concentration required for CDK inhibition, demonstrating that CDK inhibition is probably flavopiridol's main mechanism of antineoplastic activity [20]. In preclinical models, the CDK-inhibiting properties of flavopiridol resulted in cell cycle arrest at $G_1$ and $G_2$. This has been reported to be independent of p53 activity, but has been associated with downregulation of Bcl-2 [2, 12, 18].

Phase I trials of 72-h infusional flavopiridol have demonstrated antitumor activity in patients with non-Hodgkin's lymphoma, and prostate, colon, gastric, and renal cancers [21]. In light of this, Stadler et al. [24] subsequently performed a phase II trial of infusional flavopiridol (50 mg/m$^2$ per day for 72 h every 2 weeks) in 35 minimally pretreated patients with advanced RCC. Two objective responses were observed for an overall response rate of 6%. Asthenia was seen in 83% of patients (dose limiting in 9%) while secretory diarrhea was observed in 77% (grade 3 or 4 in 20%). In addition, nine patients (26%) experienced grade 3 or 4 vascular thrombotic events. The investigators concluded that this dose and schedule of flavopiridol is ineffective for advanced RCC and that toxicities are considerable.

To address concerns regarding toxicities associated with infusional flavopiridol, an alternative dose-schedule of flavopiridol administered as a daily 1-h infusion every 3 weeks was explored in a phase I trial sponsored by the NCI in patients with advanced solid tumors [25]. The investigators concluded that flavopiridol as a daily 1-h infusion could be safely administered and can achieve concentrations in the micromolar range, sufficient to inhibit CDKs in preclinical models. The recommended phase II dose for the daily x3 bolus schedule was 50 mg/m$^2$ per day with dose-limiting toxicities of neutropenia, hepatotoxicity and diarrhea. Other side effects observed included nausea, vomiting, hypotension, and a proinflammatory syndrome characterized by anorexia, fatigue, fever, and tumor pain. We subsequently performed a phase II trial evaluating this alternate dosing schedule in patients with advanced RCC.

## Patient and methods

### Patients

This was a multi-institutional study conducted through the Southwest Oncology Group. All patients had to have histologically or cytologically confirmed stage M1 (except known brain metastases) RCC. Patients with M0 RCC with an unresectable primary tumor were also eligible. Patients had to have measurable disease by RECIST (response evaluation criteria in solid tumors) criteria, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. Radiography, scans or physical examinations used for tumor measurement had to have been completed within 28 days prior to registration.

One prior immunotherapy with interferon (IFN) and/or interleukin-2 was allowed; however, patients were not allowed to have had any prior cytotoxic chemotherapy. Prior radiation therapy was allowed. Patients with metastatic disease who had a resectable primary tumor and were deemed a surgical candidate were allowed to have undergone resection but were required to have adequately recovered from surgery.

Patients were required to have adequate functional status (Zubrod score of 0–2) and adequate end-organ function defined as an AGC of $>1500/\mu l$, a platelet count of $>100{,}000/\mu l$, serum bilirubin not more than 1.5 times the upper limit of normal, SGOT not more than 2 times the upper limit of normal and a serum creatinine of less than 2 times the upper limit of normal, all obtained within 28 days prior to registration. Due to the unknown effects of flavopiridol on the fetus or nursing infant, patients were not allowed to be pregnant or nursing and women/men of reproductive potential had

to have agreed to use an effective contraceptive method prior to participation.

Patients with any uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements were deemed ineligible. Patients with a known coagulation disorder or other predisposing factors for thrombosis such as a history of deep venous thrombosis or immobilization were also not eligible. No other prior malignancy was allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated stage I or II cancer from which the patient was currently in complete remission, or any other cancer from which the patient had been disease-free for 5 years.

All patients had to have been informed of the investigational nature of this study and were required to sign and give written informed consent in accordance with institutional and federal guidelines. All participating institutions were required to have protocol approval from their respective ethics committees or institutional review boards.

### Treatment plan and dose modifications

Flavopiridol was administered intravenously by bolus infusion over 1 h at 50 mg/m$^2$ on days 1–3 every 21 days in an outpatient setting. Patients continued treatment until disease progression. Primary diarrheal prophylaxis was not given; however, at the first sign of diarrhea, patients were instructed to take 4 mg of loperamide followed by 2 mg every 4 h. If diarrhea did not resolve within 24 h, the loperamide dose was increased to 2 mg every 2 h. Prophylactic antiemetic therapy, given 30 min prior to infusion, was required with either intravenous ondansetron 8 mg or an equivalent agent and dexamethasone 10 mg given either intravenously or orally.

Toxicities were graded using the National Cancer Institute Common Toxicity Criteria version 2.0. Doses were reduced to 37.5 mg/m$^2$ (dose level 1) or 25 mg/m$^2$ (dose level 2) for grade 3 or 4 toxicities. No re-escalations of doses were allowed once reduced. If treatment was delayed longer than 3 weeks for any reason, the patient was removed from protocol treatment.

### Study endpoints and patient follow-up

The primary endpoint was tumor response. Response was assessed using standard RECIST criteria [26]. Patients were assessed for response after every third treatment (or every 9 weeks). Additional assessments at least 4 weeks apart were used for confirmation of response. Secondary endpoints were time to treatment failure, overall survival, and toxicity (National Cancer Institute Common Toxicity Criteria version 2.0). Time-to-treatment failure was defined from the date of registration to date of first observation of progressive disease, death due to any cause, symptomatic deterioration, or early discontinuation of treatment.

Patients were removed from protocol therapy for disease progression, intercurrent illness that prevented further administration of protocol treatment, or unacceptable toxicity. The patients could withdraw from the study at any time for any reason or because of changes in their condition that rendered the patient unacceptable for further treatment in the judgment of the investigator. Patients were to be followed for a maximum of 3 years after registration.

### Study design

The primary objective of this study was to evaluate the response rate (confirmed and unconfirmed) in patients with metastatic or locally unresectable RCC. Secondary endpoints included time-to-treatment failure and overall survival. A response probability of 30% or greater was of interest, while further testing would not be pursued if the response probability was 10% or lower. A two-stage accrual design was initially planned. However, due to brisk patient enrollment, the full accrual goal was reached early and only one stage was needed. In a one-stage design with 34 eligible patients, 7 or more responses would be considered evidence warranting further study of the regimen, provided other factors such as toxicity and survival also appeared favorable. This design had a significance level of 5% and power of 92%.

## Results

### Demographic data

A total of 38 patients were entered on the trial between 1 May 2001 and 15 November 2001. Of the 38 patients, 3

**Table 1** Baseline patient characteristics for 34 evaluable patients

| | | |
|---|---|---|
| Age (years) | | |
| Median | 60.3 | |
| Range | 38.6–76.9 | |
| Sex | | |
| Male | 22 | 65% |
| Female | 12 | 35% |
| Race | | |
| White | 34 | 100% |
| Performance status | | |
| 0 | 10 | 29% |
| 1 | 23 | 68% |
| 2 | 1 | 3% |
| Prior therapy | | |
| Immunotherapy | 13 | 38% |
| Radiation | 10 | 29% |
| Nephrectomy | 24 | 71% |
| Time since nephrectomy (days) | | |
| Median | 332 | |
| Range | 31–10,235 | |

were ineligible due to the following reasons: no measurable disease at baseline, no M1 disease or unresectable primary at baseline, and baseline disease assessment not done within 28 days prior to registration. One additional patient received no protocol treatment and therefore was not analyzable.

Table 1 lists the baseline characteristics of the 34 eligible and analyzable patients. The median age was 60.3 years (range 38.6–76.9 years). Of these 34 patients, 68% had a performance status (PS) of 1% and 29% a PS of 0, 21% had prior radiation, 35% prior immunotherapy, and 71% had a prior nephrectomy. Ten patients (29%) had both prior immunotherapy and prior nephrectomy.

**Table 3** Disease response by prior therapy for 34 evaluable patients. Of the ten patients with both prior nephrectomy and immunotherapy, seven had stable or better disease (two responders)

| | Stable disease or better | | Total |
|---|---|---|---|
| | Yes | No | |
| Prior nephrectomy | | | |
| Yes | 14 (58%)[a] | 10 | 24 |
| No | 4 (40%) | 6 | 10 |
| Total | 18 | 16 | 34 |
| Prior immunotherapy | | | |
| Yes | 7 (54%)[b] | 6 | 13 |
| No | 11 (52%) | 10 | 21 |
| Total | 18 | 16 | 34 |

[a]Three were responders
[b]Two were responders

## Treatment

A total of 29 patients were removed from treatment for progressive disease, one was removed for unacceptable toxicity, and one patient elected to discontinue therapy after three cycles when follow-up scans showed only stable disease. Additionally, one patient with stable disease was removed from study after six cycles of therapy by his treating physician who felt the patient had had no appreciable benefit, and one patient with stable disease was removed at the discretion of the treating physician after having received 26 cycles of therapy. One patient completed 37 cycles of treatment and was still receiving treatment at the time of this writing. The median number of cycles received was 4 (range 1–37+). At least two cycles of therapy were completed by 22 patients.

## Response and survival

Response was evaluated in 34 patients (Table 2). The response rate was 4 of 34 or 12% (95% CI 3–27%). Responses included one confirmed complete response (CR), two confirmed partial responses (PR), and one unconfirmed partial response (UPR). One patient with a PR was still receiving treatment at the time of this writing (>825 days). Time on treatment for the remaining responders was 423 days (CR), 314 days (PR), and 145 days (UPR). The patient with the UPR was removed from study at his request because of fatigue, although by clinical history the treating physician felt his fatigue was grade 1. That patient had disease progression with the development of brain metastases 93 days after discontinuing flavopiridol. Of the 34 patients, 14 (41%) had stable disease as the best response (95% CI 25–59%), and 18 (53%) had stable disease or better (95% CI 35–70%).

With regard to the characteristics of the treatment responders, the patient with a CR had a prior nephrectomy, radiation to a bone lesion, and had failed a combination of IL-2/IFN. At the time of enrollment, he had a PS of 0 with bone disease and mediastinal lymph nodes up to 4.5 cm. One patient with a PR had a prior nephrectomy but no prior immunotherapy. At the time of enrollment, he had a PS of 2 with periaortic and retroperitoneal lymph nodes measuring up to 4 cm. The second patient with a PR was newly diagnosed and with no prior nephrectomy or immunotherapy. He had a Zubrod PS of 1 and had predominantly nodal and skin metastases. The patient with a UPR had a prior nephrectomy with metastatic disease in the pericaval and paraortic lymph nodes. He had previously failed a combination of IFN/IL-2. Although underpowered, there was no evidence that having either a treatment response or SD was associated with either prior nephrectomy or prior immunotherapy (all *P* values

**Table 2** Response assessment

| | | |
|---|---|---|
| Complete response | 1 | 3% |
| Partial response | 2 | 6% |
| Unconfirmed complete response | 0 | 0% |
| Unconfirmed partial response | 1 | 3% |
| Stable/no response | 14 | 41% |
| Increasing disease | 16 | 47% |
| Total | 34 | 100% |

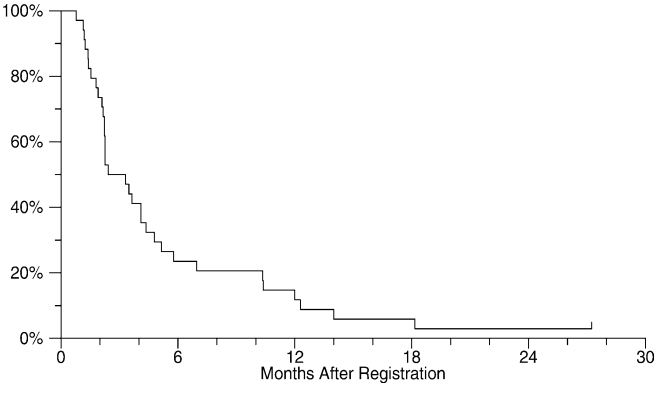


**Fig. 1** Time to treatment failure

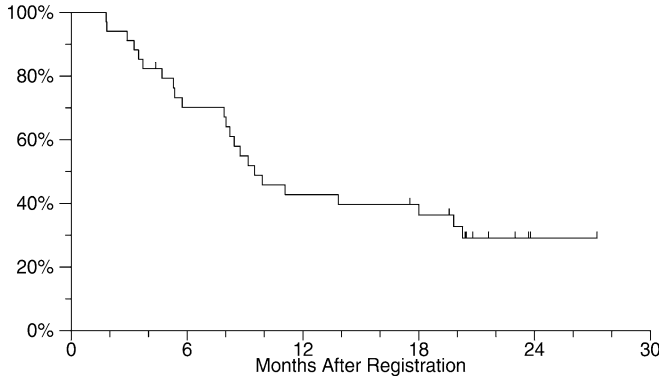


**Fig. 2** Overall survival

$>0.3$ from Fisher's exact tests). Table 3 shows disease outcome by prior therapy.

The estimated probability of not failing treatment by 6 months was 21% (95% CI 9–35%), and median time to treatment failure was 3 months (95% CI 2–4 months). Median overall survival time was 9 months (95% CI 8–18 months). Figure 1 shows the Kaplan–Meier curve for time to treatment failure and Fig. 2 shows that for overall survival.

### Toxicity

All 34 eligible and analyzable patients were assessed for toxicities (Table 4). There were four grade 4 toxicities: dyspnea (one), hyperglycemia (one), and neutropenia/granulocytopenia (two). The patient with grade 4 dyspnea had significant chronic obstructive pulmonary disease and presented with a respiratory infection. One patient experienced grade 4 hyperglycemia after three cycles of flavopiridol. There was a known history of diabetes mellitus and pretreatment dexamethasone was limited to 10 mg intravenously. This patient was taken off study because of disease progression and did not receive further treatment. One patient was hospitalized with febrile neutropenia after his first cycle of therapy. Treatment was continued at dose level 1(37.5 mg/m$^2$) and two additional cycles were given until the patient was removed from study for disease progression. One other patient had grade 4 neutropenia after the second flavopiridol cycle but continued on study without dose reduction, receiving one addition cycle prior to being removed for disease progression. There were no treatment-related deaths and only one patient was removed from treatment due to toxicity. Diarrhea, which occurred in 35% of patients, was the most common grade 3 or 4 toxicity. Tumor pain was seen in 12%, while anemia, dyspnea, and fatigue were each seen in 9% of patients. There were two thrombotic events: one pulmonary embolism and one deep venous thrombosis. Asthenia/fatigue was the most common grade 1 or 2 toxicity. Only minimal myelosuppression was seen.

**Table 4** Number of episodes of the most common toxicities for 34 evaluable patients. There was no grade 5 toxicities or other grade 4 toxicities

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Anemia | 10 | 6 | 3 | 0 |
| Anorexia | 16 | 3 | 1 | 0 |
| Creatinine increase | 6 | 4 | 0 | 0 |
| Diarrhea without colostomy | 12 | 7 | 12 | 0 |
| Dyspnea | 0 | 3 | 3 | 1 |
| Fatigue/malaise | 15 | 13 | 4 | 0 |
| Hyperglycemia | 4 | 4 | 1 | 1 |
| Hypotension | 1 | 0 | 2 | 0 |
| Nausea | 17 | 5 | 1 | 0 |
| Neutropenia | 2 | 2 | 0 | 2 |
| Thrombosis | 0 | 0 | 2 | 0 |
| Tumor pain | 1 | 5 | 4 | 0 |
| Vomiting | 4 | 6 | 1 | 0 |
| Maximum grade of any toxicity | 5 | 8 | 17 | 4 |

## Discussion

In this report, we describe a phase II evaluation of the CDK inhibitor flavopiridol in patients with advanced RCC given as a 1-h bolus daily for 3 days, cycled every 21 days. Initial experiments in xenograft models in which flavopiridol was administered over a protracted period demonstrated that flavopiridol is cytostatic. Encouraging responses in RCC were seen in phase I trials employing a prolonged (72-h) infusion schedule cycled every 2 weeks. Subsequently, flavopiridol was evaluated in a phase II trial in RCC patients employing this prolonged infusion schedule [24]. That trial demonstrated a modest response rate of 6% but found substantial flavopiridol-related toxicities that included asthenia, thrombosis, and diarrhea. Subsequent studies in some models of human leukemia/lymphoma xenografts demonstrated that flavopiridol administered as a bolus renders animals tumor-free, whereas flavopiridol administered as an infusion only delays tumor growth [22]. In addition, phase I studies have demonstrated improved tolerability of the bolus regimen [25].

In the current phase II study, thrombotic events were observed in only two patients (6%), partly due to the exclusion of patients with a prior thrombotic history. Nevertheless, the thrombogenic potential of this agent remains a concern for future studies. The incidence of diarrhea is still a major issue, particularly because we observed grade 3 severity in 35% of patients. Our study did not mandate diarrhea prophylaxis and a more aggressive antidiarrheal approach may help limit this toxicity in future studies. Furthermore, preclinical data on flavopiridol metabolism indicates that flavopiridol undergoes hepatic glucuronidation. One pharmacokinetic study found that the incidence of diarrhea with flavopiridol is related to the degree of systemic glucuronidation with patients who are poor glucuronidators having a higher likelihood of developing diarrhea with

findings suggesting a potential genetic etiology [8]. However, an additional study evaluating the different promoter polymorphisms did not find a correlation with the incidence and severity of the diarrhea in patients treated with flavopiridol [28]. Stratification of patients for future prospective studies with this agent to evaluate glucuronidation status must be considered in order to deliver the appropriate flavopiridol dose and supportive care measures to the patient cohorts at highest risk for diarrhea. The incidence of low-grade fatigue was notable, but patients with stable or responding tumors were able to tolerate multiple cycles of therapy with only one patient discontinuing treatment because of toxicity.

We observed a response rate of 12% with an additional 41% of patients having stable disease. In this patient population, a number of patients can have an indolent tumor growth pattern; therefore, the clinical significance of stable disease cannot be fully evaluated in this phase II study. The overall median survival, however, was not significantly different from that seen in other phase II trials in advanced RCC. Although our response rate was modest, given the durability of the responses, this may potentially be clinically relevant in this otherwise refractory malignancy. This response rate compares favorably to that with the continuous infusion schedule [24], although the actual number of responders is small in both studies. Further study is required to determine whether this difference is clinically significant and whether it could be a result of increased cytotoxicity with the bolus schedule compared to the continuous infusion schedule, as was seen in the animal model systems [22].

A number of preclinical studies have shown potential sequence-dependant synergy of flavopiridol with a variety of antineoplastic agents including cytarabine, paclitaxel, docetaxel, doxorubicin, and 5-fluorouracil [1, 9, 10, 15, 19]. With the exception of S phase-active agents 5-FU and cytarabine, this synergy was seen when flavopiridol was given following the other chemotherapeutic agent and appeared to be related to the arrest of cells in $G_1$ and $G_2$ phases in the cell cycle [1]. In the case of 5-FU and cytarabine, the synergy was most pronounced when flavopiridol was given initially and correlated with an increase in the percentage of cells in the S phase 48–72 h following flavopiridol exposure. Although several trials are in progress, currently there are only limited clinical data on combination therapy [19].

In conclusion, flavopiridol at this dose and schedule is feasible and has an acceptable toxicity profile. Flavopiridol also appears to have some modest biologic activity against advanced RCC, as evidenced by its single-agent objective response and stable disease rates. Ongoing preclinical and clinical investigations of flavopiridol are warranted to evaluate the utility of flavopiridol in combination with other biologic, chemotherapeutic or immunotherapeutic agents and to define the cohort of patients mostly likely to respond and benefit from therapy based on molecular or genotypic markers.

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