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A phase II evaluation of flavopiridol as second-line chemotherapy of endometrial carcinoma: A Gynecologic Oncology Group study

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Abstract

Objective. A phase II study was conducted to determine the efficacy of single agent flavopiridol therapy in patients with recurrent or persistent endometrial adenocarcinoma refractory to established treatments.

Methods. Eligible patients with measurable disease who failed primary therapy including one cytotoxic regimen were eligible for the trial. They were treated with single agent flavopiridol (50 mg/m^2/day, IV bolus days 1, 2, 3). Treatment was repeated every 21 days with dose adjustments made for toxicity. Patients were treated until progression of disease or adverse side effects precluded further therapy.

Results. A total of 26 patients were enrolled in the study of whom, 23 patients were eligible. There were no objective responses. Five patients had stable disease (22%), 15 (65%) had increasing disease, and response could not be assessed in 3 (13%). The most frequent side effects included anemia, neutropenia, and diarrhea, all of which appeared manageable.

Conclusion. Flavopiridol as a single agent in the above dosing schedule appears to have minimal activity as second-line chemotherapy of endometrial adenocarcinoma.

Keywords: Endometrial cancer; Chemotherapy; Flavopiridol; Flavone

Introduction

Endometrial carcinoma is the most common malignant tumor of the female genital tract. Its incidence appears to be increasing and currently represents 13% of female cancers. Approximately 40,100 cases will be diagnosed in the year 2003, and 6800 women will succumb to this disease [1]. The primary treatment modality is surgical extirpation possibly combined with post-operative adjuvant local and/or regional radiation therapy depending on surgico-pathologic risk factors. The overall 5-year survival is approximately 85%. Localized pelvic disease is obviously managed well with the above-cited modalities; however, patients with extra pelvic disease on primary presentation, or at time of recurrence, have a dismal prognosis.

There are multiple active cytotoxic and hormonal chemotherapy agents for the treatment of recurrent and metastatic endometrial cancer including platinum compounds, taxanes, anthracyclines, and topotecan [2–8]. These agents (often in combination) have lead to statistically significant improvements in response rates and progression-free survival albeit often at the cost of significant toxicity. Still, complete response rates and long-term survival is extremely rare.

Flavopiridol (NSC#46211) (−)-*cis*-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4*R*-(3*S*-hydroxy-1-methyl) piperidinyl)-4*H*-1-benzopyran-4-one hydrochloride) is a synthetic flavone being developed as a novel antineoplastic agent. It is a

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synthetic derivative of the flavonoid rohitukine initially isolated from *Dysoxylum binectaisriferum* plant indigenous to India [9]. It has been shown to have the potential ability to disrupt cell cycle progression by inhibition of regulatory reactions within the cell cycle and both cytotoxic activity (via apoptosis) and cytostatic activity has been demonstrated [9–12].

The controlling proteins for these reactions include: epidermal growth factor receptor tyrosine kinase [13,14], serine/threonine kinase, protein kinase C [15], protein kinase A [13,14], and cyclin-dependent kinases (CDK) [16] which appear to be significantly dependent on serum concentrations of drug. CDK activity appears to be important in multiple phases of the cell cycle including G1, G1/S, G2/M and is competitively inhibited at very low concentrations of flavopiridol [16,17]. These concentrations (100–400 μM) are clinically achievable at doses of 50 mg/m^2/day and appear to correlate with clinical responses in various tumor types [18].

Initial in vitro studies of flavopiridol have demonstrated growth inhibition of several human tumor cell lines in vitro as well as human tumor xenografts (lung, colon, ovary, brain, and breast) in nude mice [15]. Significant inhibitory activity against more than 60 tumor cell lines in the NCI tumor cell line in vitro screening panel was also noted [17,19].

Previous phase I experience has demonstrated a dose-limiting toxicity of secretory diarrhea at doses of 62.5 mg/m^2/day. This diarrhea was controllable with the addition of loperamide or cholestyramine as antidiarrheal prophylaxis and dose escalation to 78 mg/m^2/day was possible. Other minor acute grade I or II toxicities encountered at this dosing level included anorexia, fatigue, hypotension, fever, tumor pain, dermatitis, nausea, vomiting, and hyperbilirubinemia [18,20]. These trials enrolled a total of 114 patients. Antitumor activity including tumor regression and/or stabilization of disease complete response (CR), partial response (PR), or stable disease (SD) >6 months was observed in patients with tumors from multiple origins including renal, prostate, gastrointestinal, and adenocystic carcinoma of the lacrimal gland [20]. It appears that clinical activity is dose dependent and lower than recommended dosing and subsequent serum concentrations appear to produce minimal clinical activity [21,22].

Senderowicz et al. [18] demonstrated a proinflamatory syndrome with alterations in acute-phase reactants particularly at dose of greater than 50 mg/m^2/day. In subsequent phase II studies, investigators have suggested a prothrombotic effect associated with flavopiridol. Schwartz et al. [22] noted 5 patients (33%) developed upper extremity venous thromboses at the central venous catheter directly after completion of the infusion. Stadler et al. [23] reported 3 arterial vascular events (non-fatal myocardial infarction, transient ischemic attack, transient scotomata, and vision loss) and 6 venous thrombotic events (2 associated with vascular access devices) for a total thrombotic event rate of 25%. The relationship of these events to flavopiridol was unclear though appeared to be higher than in the general oncologic population.

Given the interesting properties including activity in solid tumors, good tolerance of this agent along with the potential synergistic activity with other active agents, the GOG decided to proceed with clinical phase II testing of this agent in endometrial carcinoma. To date, no previous studies in this tumor type with this agent have been reported.

Materials and methods

This phase II study was designed to evaluate the clinical activity of flavopiridol in recurrent or persistent endometrial carcinoma. All histologic subtypes were eligible. Patients were required to have measurable disease as well as at least one target lesion to evaluate response as defined by RECIST criteria. Patients were to have had one prior cytotoxic chemotherapy regimen. Prior cytotoxic therapy must have been discontinued at least 3 weeks prior to registration and hormonal therapy (as treatment) must have been discontinued 1 week prior to registration. Patients with prior treatment with cyclin-dependent kinase inhibitors as well as those with prior radiation to more than 25% of marrow-bearing areas were not eligible. Also, patients with prior history of thromboembolic events, thrombophlebitis, recent myocardial infarction, angina, CVA, or transient ischemic attack were similarly not eligible.

Patients were required to have a GOG performance status of 0–2. Adequate hematologic reserve was required including WBC $\geq$3000/μl, ANC $\geq$1500/μl, and platelets normal per institutional standards. Serum creatinine was required to be less than or equal to 1.5 institutional norms as was bilirubin. SGOT and alkaline phosphatase were required to be $\leq$5 times institutional norms. No significant neuropathy greater than CTC grade 1 and normal coagulation profiles were required. All patients gave appropriate informed consent consistent with all federal, state, and local requirements to sign prior to study entry.

A treatment cycle was considered 3 consecutive daily 1-h infusions. Antidiarrheal prophylaxis was given at the investigator's discretion and coumadin prophylaxis (1 mg/day) was recommended given previous phase II toxicity experiences. Patients were to be treated until disease progression, voluntary withdrawal, or the presence of unacceptable toxicity.

Patients were evaluated for toxicity prior to each cycle and no subsequent cycle was to begin until adequate recovery was noted. Coumadin prophylaxis (1 mg/day) was recommended especially for patients with indwelling catheters, but was not required. Antidiarrheal prophylaxis (loperamide, etc.) was given at the investigator's discretion. Prophylactic granulocyte-colony stimulating factor (G-CSF) was not allowed unless recurrent neutropenic complications