Current Clinical Trials of Flavopiridol

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Flavopiridol [2-(2-chlorophenyl 5,7-dihydroxy-8-[cis-(3-hydroxy-1-methyl-4-piperidinyl)-4H-1-benzopyran-4-one, hydrochloride] is a semisynthetic flavone with a novel structure compared with that of polyhydroxylated flavones, such as quercetin and genistein.[1] It is derived from rohitukine, an alkaloid isolated from the stem bark of Dysoxylum binectariferum, a plant indigenous to India.[2] Originally synthesized and supplied by Hoechst India Limited, flavopiridol is provided to the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI) by Aventis Pharmaceuticals, Inc.

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community.

It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician's Data Query (PDQ).*

We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study.

This month’s installment of Clinical Trials Referral Resource is devoted to current clinical trials of the Cancer Trials Support Unit, a National Cancer Institute pilot program.

For patient entry information, see the individual trials.

Flavopiridol [2-(2-chlorophenyl 5,7-dihydroxy-8-[cis-(3-hydroxy-1-methyl-4-piperidinyl)-4H-1-benzopyran-4-one, hydrochloride] is a semisynthetic flavone with a novel structure compared with that of polyhydroxylated flavones, such as quercetin and genistein.[1] It is derived from rohitukine, an alkaloid isolated from the stem bark of Dysoxylum binectariferum, a plant indigenous to India.[2] Originally synthesized and supplied by Hoechst India Limited, flavopiridol is provided to the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI) by Aventis Pharmaceuticals, Inc.

Mechanism of Action

Cell-cycle regulation is dependent on cyclin-dependent kinases (cdks), which require association with cyclin proteins for activation.[3] Flavopiridol was the first compound with the potent ability to disrupt cell-cycle progression by inhibition of regulatory phosphorylations to be considered for clinical development.

Flavopiridol inhibits several cellular kinases and has demonstrated cytostatic and cytotoxic activity in vitro and in vivo in numerous human tumor cell lines and xenograft models (including human breast, prostate, and lung carcinoma) at clinically achievable concentrations.[1,4] Flavopiridol is capable of disrupting progression of cells through the cell cycle at the G1/S and G2/M transitions.[1,5,7] The direct inhibition of cdks 1, 2, and 4 via competitive inhibition of adenosine triphosphate binding by flavopiridol has been demonstrated.[5,7,9] Flavopiridol also inhibits cdk7/cyclin H, thus preventing the phosphorylation and subsequent activation of several cdks[6,8] and down-regulates cyclin D1, the cyclin associated with cdks 4 and 6.[10]

Flavopiridol-induced G1 arrest may be related to inhibition of cdk 2 and 4 activity, as well as diminution of cyclin D levels; G2/M arrest may be due in part to inhibition of cdk1 activity. Cdk4 and
2 kinase activities, as well as cyclins D, E, and A protein levels, are diminished following flavopiridol exposure in a number of in vitro models. In MCF-7 cells, flavopiridol-induced G1/S arrest is associated with the loss of cdk4 and 2 activity and reduced cyclin D levels preceded by hypophosphorylation of Rb protein. The flavopiridol-induced decline in cyclin D1 is an early, specific event, due in part to the transcriptional repression of the cyclin D1 promoter.[11] Similarly, in cdk4-deficient MCF-10A breast epithelial cells, flavopiridol-induced G1 arrest coincided with Rb dephosphorylation and dose-dependent inhibition of cdk6-kinase activity associated with the loss of cyclin D1 expression.[12]

The efficacy of flavopiridol is not based solely on cell cycle arrest, since this agent induces death in noncycling A549 lung cancer cells by a process that depends on RNA and protein synthesis.[4] Parker and co-investigators[13] observed apoptosis in SUDHL-4 leukemia cells without evidence of cell-cycle arrest, suggesting that the antiproliferative effects can be separated from the proapoptotic activity of this agent.

Regulation of gene expression is another potential mechanism of action for flavopiridol. In human monocytes, flavopiridol causes down-regulation of vascular endothelial growth factor (VEGF) messenger (m)RNA and protein expression induced by hypoxia. Flavopiridol does not affect hypoxia-induced transcriptional activation of VEGF but significantly decreases the VEGF mRNA half-life, suggesting that flavopiridol may have antiangiogenic activity.[14] flavopiridol also inhibits the positive transcription elongation factor, which is a protein kinase composed of cdk9 and a cyclin subunit (cyclin T1 or cyclin T2).[15] and controls the elongation phase of transcription by RNA polymerase II.[16] The IC50 of flavopiridol is directly related to the concentration of the positive transcription elongation factor.[17] (It is not known if the antiproliferative effects of flavopiridol are due to inhibition of the positive transcription elongation factor or other cyclin-dependent kinases). A comprehensive review of the mechanisms of action of flavopiridol was recently published.[18]

**Preclinical Activity**

Flavopiridol should exert cytostatic activity because of the pivotal role of the cdks in the cell division cycle. Evidence demonstrating its cytostatic activity includes the finding that it inhibits the growth of a broad spectrum of human tumor cell lines in vitro. In the NCI tumor cell line panel, flavopiridol had significant inhibitory activity against all of the more than 60 human tumor cell lines with no clear selectivity for tumor type. IC50 values ranged from approximately 50 to 200 nM,[1] similar to concentrations required to inhibit cdks. flavopiridol-induced growth inhibition seems to be independent of tumor Rb, cyclin D1, p16, and p53 status.[19,21]

Administration of flavopiridol after or concomitant with antineoplastic agents, including mitomycin C (Mutamycin), paclitaxel, gemcitabine (Gemzar), SN-38 (the active metabolite of CPT-11), imatinib mesylate (Gleevec), and doxorubicin can promote chemotherapy-induced apoptosis.[22-29] Recent reports suggest a marked increase in apoptosis when differentiating agents such as phorbol 12-myristate 13-acetate (PMA), suberoylanilide hydroxamic acid (SAHA), and depsipeptide are combined with flavopiridol.[30-32] Cytotoxic synergy was more pronounced when non-small-cell lung cancer (NSCLC) A549 cells were exposed to flavopiridol after rather than before or concomitant with paclitaxel, cytarabine, topotecan (Hycamtin), doxorubicin, and etoposide.[33]

**Clinical Data**

NCI-sponsored clinical trials of flavopiridol were initiated in 1994. Preclinical data suggested that prolonged exposure was necessary to achieve maximal antitumor effect.[1] Two phase I trials used a 72-hour infusion every-2-weeks schedule. In a trial at the NCI, diarrhea was dose-limiting, and the maximum tolerated dose was 50 mg/m²/24h ³.[34] Aggressive prophylaxis of diarrhea allowed for further dose escalation to a maximum tolerated dose of 78 mg/m²/24h ³, with dose-limiting hypotension seen at higher doses. Anorexia and asthenia were additional major toxicities. Mean steady state plasma flavopiridol concentrations achieved at the maximum tolerated doses were 271 nM (range: 174-2,943 nM) and 344 nM (range: 130-1,557 nM), respectively, with postinfusion peaks suggestive of enterohepatic recirculation.

Diarrhea was also dose limiting in a trial using the same schedule conducted at the University of Wisconsin.[35,36] The maximum tolerated dose was 40 mg/m²/24h ³; nausea, vomiting, and orthostatic hypotension occurred at the maximum tolerated dose. In this trial, a steady state concentration of 415 nM was achieved at the maximum tolerated does. Antitumor activity against renal cell carcinoma, colon carcinoma, non-Hodgkin lymphoma, and gastric carcinoma (a prolonged complete response) was seen in these studies.

Results of four single-agent flavopiridol studies incorporating a continuous infusion 50 mg/m²/24h ³ every 14 days in patients with renal cell, gastric, colon, and non-small-cell lung carcinoma confirmed an adverse event profile dominated by diarrhea, nausea, vomiting, and asthenia.[37-40] In addition,
19 of 89 patients (21%) experienced venous thromboses, including 12 at the central venous catheter site. Two patients experienced transient ischemic attacks, and one, a myocardial infarction. Two complete responses in patients with renal cell cancer were the only objective responses reported in these trials.

Additional schedules of administration are being pursued because of the disappointing degree of antitumor activity achieved with the 72-hour schedule and because of additional preclinical data that suggested higher plasma concentrations of flavopiridol may be necessary to obtain tumoricidal activity.[41] NCI investigators followed their original phase I infusional study with an exploration of daily 1-hour infusions for 1 to 5 days every 21 days. They defined maximum tolerated doses of 37.5, 50, and 62.5 mg/m²/d for 5-, 3-, and 1-day administrations, respectively, and documented median peak plasma concentrations of 1.7, 3.2, and 3.8 µM with these schedules.[42,43] Neutropenia was the primary dose-limiting toxicity, but diarrhea and a proinflammatory syndrome of anorexia, tumor pain, fever, and asthenia were also prominent. Five patients (9%) experienced thrombotic events (three lower-extremity deep-vein thromboses and two catheter-related thromboses).

Investigators at the National Cancer Center East in Japan determined that 80 mg/m² was tolerable on a weekly 24-hour infusion schedule and achieved a mean Cmax of 718 nM.[44]

**Phase II Trials**
The NCI is sponsoring seven phase II single agent trials of flavopiridol utilizing 1-hour infusion schedules in patients with the following cancers: endometrial, head and neck, melanoma, renal cell, soft-tissue sarcoma, chronic lymphocytic leukemia, and mantle cell lymphoma. Published data are available for two trials in which patients with mantle cell lymphoma[45] and previously untreated metastatic malignant melanoma[46] were treated at 50 mg/m²/d 3 days every 21 days. No objective responses were seen in 17 patients with melanoma. Of 25 evaluable patients with mantle cell lymphoma, 3 achieved partial responses lasting 2.8 to 9.1 months, and 18 patients had stable disease for 1.3 to 10.3 months. Of the 27 patients with mantle cell lymphoma, 16 had received prior chemotherapy. Significant toxicities in these trials included grade 3 and 4 neutropenia, fatigue, and diarrhea, and grade 3 nausea, tumor pain, cough, dyspnea, and anorexia.

**Phase I Trials**
The NCI is also the sponsor of a number of clinical trials of flavopiridol in combination with FDA-approved anticancer compounds. Reported results of phase I combination studies are summarized here.

Schwartz and colleagues conducted a two-part dose-finding trial to define the maximum tolerated dose of the combination of paclitaxel on day 1 followed by flavopiridol on day 2 and the maximum tolerated dose of a three-drug sequence of paclitaxel on day 1 followed by flavopiridol and cisplatin on day 2. In the two-drug trial, pulmonary toxicity was dose-limiting, and the recommended phase II dose was 3-hour paclitaxel at 175 mg/m² on day 1 followed by 24-hour flavopiridol, 70 mg/m², on day 2 of a 21-day cycle.[47] Flavopiridol dose escalation to 80 mg/m² with 175 mg/m² of paclitaxel was also tolerated.

Objective responses were achieved in patients with adenocarcinoma of the esophagus (one complete response, one partial response), prostate cancer (one minor response) and adenocarcinoma of the lung (one minor response). When escalating doses of cisplatin were added to fixed doses of the same sequence of paclitaxel and flavopiridol, the maximum tolerated dose was paclitaxel at 175 mg/m² on day 1 followed by cisplatin at 50 mg/m² given just prior to flavopiridol at 80 mg/m² on day 2.[48] Neutropenia, nausea, and cardiac toxicity were dose-limiting. Clinical responses were obtained in patients with esophageal and lung cancer.

Gries and colleagues recently reported the results of a phase I trial of flavopiridol in combination with paclitaxel and carboplatin (Paraplatin).[49] Patients with previously untreated advanced NSCLC were treated with a regimen consisting of a 3-hour infusion of paclitaxel at 175 mg/m² followed by carboplatin at an area under the concentration-time curve of 5 on day 1 and a 24-hour infusion of flavopiridol in escalating doses of 30 to 85 mg/m² on day 2. The maximum tolerated dose of flavopiridol was 70 mg/m², defined by grade 3 anemia, heart arrest, leukopenia, and one patient with a myocardial infarction at the next higher dose. One patient experienced deep-vein thrombosis, another a pulmonary embolus.

A preliminary report on the combination of docetaxel and flavopiridol in breast cancer patients found that neutropenia was dose-limiting when docetaxel, 60 mg/m² on day 1, was followed by a 72-hour infusion of flavopiridol on days 2, 3, and 4, both at the starting flavopiridol dose of 50 mg/m²/24h and a reduced dose of 28 mg/m²/24h.[50] Pharmacokinetic activity of the flavopiridol was in the range seen with single-agent flavopiridol, but no docetaxel pharmacokinetic data were reported. Accrual to cohorts receiving 50 mg/m² of docetaxel on a revised 1-hour infusion schedule of flavopiridol is
ongoing. Additional studies exploring alternative schedules of the combination of docetaxel and flavopiridol are under way.

Bible and colleagues established 60 mg/m² of cisplatin and 100 mg/m² of flavopiridol (24-hour infusion) as the maximum tolerated dose in a phase I study of 25 patients.[51] Principle significant toxicities were gastrointestinal nausea, vomiting, and diarrhea. The trial continues to accrue to a carboplatin-plus-flavopiridol arm.

Shah and colleagues recently reported the preliminary results of a phase I trial of the combination of irinotecan (CPT-11, Camptosar) with flavopiridol, both on a weekly every-4-of-6-weeks schedule [52]. The flavopiridol was administered as a 1-hour infusion, 7 hours after the irinotecan, based on animal model data suggesting timing of administration was relevant to maximize the antitumor effect of the combination. The maximum tolerated dose on this schedule was irinotecan at 100 mg/m² with flavopiridol at 60 mg/m². Dose-limiting neutropenia and diarrhea prevented further dose escalation of flavopiridol. Preliminary pharmacokinetic data suggest a metabolic interaction between irinotecan and flavopiridol. Enrollment continues to cohorts being treated with irinotecan at 125 mg/m²/wk with dose escalation of flavopiridol.

Future Directions
The Cancer Therapy Evaluation Program (CTEP) will continue to support the clinical development of flavopiridol. Presently, the three primary areas for continued clinical development are:
(1) Abbreviated infusional schedules of flavopiridol, both as a single agent and in combination with other agents
(2) Studies designed to ask questions concerning the anticancer effects of flavopiridol in combination with other drugs
(3) Studies designed to ask questions concerning the purported molecular mechanisms of the anticancer effects of flavopiridol in humans. These studies are designed to promote acquisition of relevant human specimens both before and after flavopiridol administration, especially in patients whose tumors have molecular pathophysiology that includes targets with which flavopiridol might directly interact.

Phase II
Title: Phase II Trial of Flavopiridol and Paclitaxel in Patients with Paclitaxel-Refractory Esophageal Cancer
Protocol Number: 1672
Participating Institutions: Memorial Sloan-Kettering Cancer Center, National Cancer Institute Surgery Branch
Protocol Status: Active
Contact: Gary Schwartz, MD, (212) 639-8324
Title: A Phase II Study of Flavopiridol (NSC #649890) in Patients with Fludarabine Refractory B-Cell Chronic Lymphocytic Leukemia
Protocol Number: CALGB-19805
Participating Institution: Cancer and Leukemia Group B
Protocol Status: Active
Contact: John Byrd, MD, (614) 293-9321
Title: A Phase II Evaluation of Flavopiridol (NSC# 648890, IND# 46211) in the Treatment of Recurrent or Persistent Endometrial Carcinoma
Protocol Number: GOG-0129M
Participating Institutions: Gynecologic Oncology Group, University of Chicago
Protocol Status: Active
Contact: Edward Grendys, MD, (813) 972-8478
Title: A Phase II Trial of Daily Bolus Flavopiridol for Five Consecutive Days in Patients with Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)
Protocol Number: T99-0066
Participating Institution: National Cancer Institute Medicine Branch
Protocol Status: Active
Contact: Edward Sausville, MD, (301) 496-8720

Phase I/II
Title: A Phase I/II Trial of Docetaxel Followed by Flavopiridol in Patients with Previously Treated Locally Advanced or Metastatic Breast Cancer
Protocol Number: 952
Participating Institutions: National Cancer Institute Medicine Branch
Protocol Status: Active
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Published on Physicians Practice (http://www.physicianspractice.com)

**Contact:** Sandra Swain, MD, (301) 451-6882
**Title:** A Phase I/II Study of Flavopiridol (NSC 649890, IND 46,211) in Timed Sequential Combination with Cytosine Arabinoside (Ara-C) and Mitoxantrone for Adults with Poor Risk Acute Leukemia and Myelodysplasia
**Protocol Number:** 3170
**Participating Institutions:** Mayo Clinic, University of Maryland Cancer Center, Walter Reed Army Medical Center
**Protocol Status:** Active
**Contact:** Judith Karp, MD, (410) 328-7394

**Phase I**
**Title:** An Open-Labeled, Non-Randomized Phase I Study of Flavopiridol Administered with Irinotecan (CPT-11) in Patients with Advanced Solid Tumors
**Protocol Number:** 2272
**Participating Institution:** Memorial Sloan-Kettering Cancer Center
**Protocol Status:** Active
**Contact:** Gary Schwartz, MD, (212) 639-8324

**Title:** Phase I Study of Flavopiridol in Combination with 5-Fluorouracil, Leucovorin and Irinotecan in Patients with Advanced Malignancies
**Protocol Number:** 2450
**Participating Institution:** Mayo Clinic
**Protocol Status:** Active
**Contact:** Keith Bible, MD, (507) 284-2511

**Title:** An Open-Labeled, Non-Randomized Phase I Study of Flavopiridol Administered with Irinotecan (CPT-11) and Fluorouracil/Leucovorin in Patients with Advanced Solid Tumors
**Protocol Number:** 5757
**Participating Institution:** Memorial Sloan-Kettering Cancer Center
**Protocol Status:** Active
**Contact:** Gary Schwartz, MD, (212) 639-8324

**Title:** Phase I Study of Trastuzumab (Herceptin)/Flavopiridol in HER-2 Positive Metastatic Breast Cancer
**Protocol Number:** 5867
**Participating Institutions:** Dana-Farber Cancer Center
**Protocol Status:** Active
**Contact:** Lyndsay Harris, MD, (617) 632-6766

**Title:** A Phase I Study of Flavopiridol in Patients with Relapsed or Refractory Pediatric Solid Tumors
**Protocol Number:** ADVL0017
**Participating Institutions:** Children’s Oncology Group
**Protocol Status:** Active
**Contact:** James Whitlock, MD, (615) 936-1762

**Title:** Phase I Study of Flavopiridol in Combination with Cisplatin or Carboplatin in Patients with Advanced Malignancies
**Protocol Number:** T97-0032
**Participating Institution:** Mayo Clinic
**Protocol Status:** Active
**Contact:** Keith Bible, MD, (507) 284-2511

**References:**


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