A phase I study of pentosan polysulfate sodium in patients with advanced malignancies


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Summary

Background: Pentosan polysulfate (xylanopolyhydrogensulfate) is a semi-synthetic sulfated heparinoid polysaccharide which has been used as an anticoagulant for nearly thirty years in Europe. It antagonizes the binding of bFGF to cell surface receptors and has thus been evaluated for antitumor activity in several animal models and human tumor cell lines. In two angiogenic models pentosan has been shown to inhibit bFGF stimulation of angiogenesis. Previous clinical studies have determined the coagulation effects of pentosan to be the dose-limiting toxicity.

Patients and methods: We conducted a phase I study designed to define the duration-limiting toxicity associated with progressive prolongation of a continuous intravenous infusion (three, five, and eight weeks). This study was not designed to escalate the dose of pentosan beyond that required to maintain the activated partial thromboplastin time (aPTT) between 1.8 and 2.2 times the baseline value.

Results: Thirteen patients with advanced stage metastatic cancer were enrolled (median age 50 years, range 34 to 61 years). Four patients were treated in cohort #1 (three weeks of infusion therapy), five patients were treated in cohort #2 (five weeks of therapy), and four patients in cohort #3 (eight weeks of therapy). All patients experienced a progressive prolongation of their aPTT and PT. Furthermore, all patients experienced at least grade I thrombocytopenia. Other complications were, in general, mild. One patient developed grade III liver abnormalities while receiving the eight-week infusion and another patient developed grade IV thrombocytopenia while receiving the same regimen. One patient with colon cancer had stable disease for 24 weeks, while the remaining 12 patients had no objective evidence of response.

Conclusion: Pentosan was well tolerated when doses were adjusted for aPTT prolongations and a five-week cycle appeared to be the maximum tolerated duration of infusion (initially 4 mg/kg/day). One patient had stable disease, but there was no objective tumor response noted in the remaining 12 patients.

Key words: aPTT, cancer, growth factors, heparan sulfate, heparinoid, pentosan, phase I

Introduction

Pentosan polysulfate (xylanopolyhydrogensulfate, Figure 1) is a semi-synthetic sulfated heparinoid polysaccharide that has been used in Europe as an anticoagulant for nearly 30 years [1-3]. It is obtained from extract of beechwood shavings and consists of a mixture of polymers with molecular weight ranging from 1,800 to 9,000 daltons (mean 4,700 daltons) [3]. Pentosan has been shown to antagonize the binding of basic fibroblast growth factor (bFGF) to its cell surface receptor [4, 5]. Furthermore, it has been shown to inhibit extracellular growth factor (EGF) associated tyrosine kinase in lysed tumor cells. Pentosan's antitumor activity has been evaluated in several animal models, and activity has been noted in vitro against several human tumor cell lines including A204 (human rhabdomyosarcoma), SW-13 (human adrenal cortical carcinoma), and Ovar Cal (human ovarian carcinoma) cell lines, as well as non-small-cell lung cancer, prostate adenocarcinoma cell lines, and breast carcinoma cell lines [6-9]. The IC50's for those cell lines evaluated were between 6 and 39 μg/ml [10]. In addition, pentosan has been shown to inhibit bFGF stimulation of angiogenesis in both bovine aortic endothelial cells and human umbilical vein endothelial cells. Thus, the primary proposed antitumor mechanism of action for pentosan is thought to be through inhibition of bFGF-induced angiogenesis [11].

With regards to its anticoagulant properties, the interaction between pentosan and the coagulation and fibrinolytic systems is complex. Unlike heparin, pentosan does not bind to antithrombin II (AT-II) although its most pronounced effect, like that of heparin, is to prolong the activated partial thromboplastin time (aPTT) [12-14]. Prolongation of the aPTT has been shown to arise primarily from pentosan's ability to potentiate thrombin inactivation by heparin cofactor II
[15]. Normally, the small amounts of thrombin generated by activation of the clotting cascade plays a major role in converting zymogen factors VIII and V to their active forms, both of which are critical to the formation of the prothrombinase complex [16, 17]. Thus, pentosan, via its interaction with heparin cofactor II, circumvents this positive feedback loop [18]. Pentosan is essentially devoid of any anti-Xa activity in vitro; however, plasma obtained from patients receiving pentosan contains substantial anti-Xa activity, which is largely (70%-80%) attributed to enhancement by pentosan of hepatic triglyceride lipase release [19, 20]. Additionally, when given as an injection subcutaneously, intramuscularly, or intravenously, or when administered orally, pentosan has been shown to shorten the euglobulin lysis time. The effect may be mediated by the release of tissue plasminogen activator and is also associated with activation of factor XII and kallikrein [21].

In previous clinical trials, the main dose-limiting trait of pentosan was its effect on coagulation [11, 22-24]. Therefore, this phase I study was not designed to escalate the dose of pentosan beyond that required to maintain the aPTT between 1.8 and 2.2 times the baseline value. Instead, the primary objective of this study was to define the duration-limiting toxicity associated with progressive prolongation of a continuous intravenous infusion (three, five, and eight weeks). Given that maximal in vitro anti-tumor activity required prolonged drug exposure, we felt that it was most rational to evaluate the effect of pentosan when administered by progressively longer intravenous infusions. An initial fixed dose was administered (4 mg/kg/day) with subsequent adjustments to maintain the aPTT between 1.8 and 2.2 times the patients’ baseline value. Subsequent cohorts of patients received increasingly prolonged infusions from an initial three-week continuous infusion to a maximum of eight weeks.

Patients and methods

Patient eligibility criteria

Patients were eligible for this study if they had an advanced metastatic malignancies (histologically confirmed by the Laboratory of Pathology of the National Cancer Institute, National Institutes of Health) that was refractory to conventional therapy, a performance status greater than 80% on the Karnofsky scale, a life expectancy greater than three months, normal hepatic transaminases and bilirubin, hemoglobin greater than 10 g/dl, a creatinine clearance greater than 60 ml/min, normal WBC (>4.0 x 10^9/L) and platelet counts (>150 x 10^9/L), as well as aPTT, prothrombin time (PT), thrombin clotting time (TCT), and fibrinogen within the normal range. Patients were ineligible if they had a history of bleeding diathesis, coagulation disorder or were requiring anticoagulation therapy (aspirin, warfarin, or heparin). All patients were required to have progressive disease after any previous therapeutic intervention for their primary malignant disease which must have been completed at least one month prior to enrolling in the present study. No other form of antitumor therapy was allowed during the study period, including radiation therapy. The protocol was approved by the National Cancer Institute’s Institutional Review Board and all patients gave written informed consent prior to participating in the study.

Drug source and formulation

Pentosan polysulfate (NSC 626201; CAS 116001-96-8) is a semi-synthetic oligomer of xylopyranose obtained by sulfation of pentosans extracted from beechwood shavings. The carbohydrate polymer consists of β-(1→4)-α-D-xylose chains with α-(1→2) lateral fixation of 4-O-methylxylopyranuronic acids (Figure 1). The mean number of sulfate substitutions per saccharide subunit is 1.9 (theoretical maximum = 2). Pentosan polysulfate has a mean molecular weight of 4,700 daltons with 80% of polymers constituting the mixture having a molecular weight between 1,800 and 9,000 daltons.

The finished drug product was supplied by the Cancer Therapy Evaluation Program, Division of Cancer Treatment Diagnosis and Centers, National Cancer Institute, in clear glass ampules containing one milliliter of a clear, colorless to pale yellow aqueous solution of pentosan polysulfate sodium 100 mg (Bene-Chemie GmbH, Munchen, Germany), buffered with sodium levulinate 13.8 mg and sodium hydroxide (to a pH between 5.5 and 6.5), and Water for Injection, USP, qs. 1 ml.

Drug preparation and administration

All patients were initially admitted to the Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, MD, for inpatient treatment. Participating patients were assigned to receive a 24- or 48-hour supply of pentosan polysulfate sodium diluted to a total volume of 90 ml with 0.9% Sodium Chloride Injection, USP, in a 100-ml capacity Medication Cassette® Reservoir (product no. 602100A; Pharmacia Deltec, Inc., St. Paul, MN [PDI]). Pentosan was administered by continuous intravenous (i.v.) infusion with a portable CADD-1® pump (model no. 5100 HFX; PDI). Since pentosan has an anticoagulant effect qualitatively similar to heparin and other glycosaminoglycans, the aPTT was monitored as a measure of anticoagulant effect. The initial infusion rate in each patient was 4 mg/kg (actual body weight) per day; however, the pentosan dose rate was modified to maintain the aPTT between 1.8 and 2.2 times baseline value. The aPTT was determined daily and the infusion rates adjusted until the aPTT remained within the target range for three consecutive days. Subsequently the aPTT was monitored every 48 hours for two additional measurements and then at least once weekly until pentosan administration was complete. Pentosan was withheld for six hours for an aPTT greater than 2.2 times baseline and subsequently restarted at a dose rate decreased by 20% from that previously administered. Conversely, aPTT values less than 1.8 times patients’ baseline value were an indication to continue pentosan at a 20% incrementally increased dose rate.

\[ \text{Figure 1. Chemical structure of pentosan polysulfate.} \]
Treatment

Before starting therapy, all patients underwent a complete history and physical examination, plus had measurement of appropriate tumor markers (i.e., PSA, CEA, CA-125), complete blood cell counts (including platelet count and differential), a coagulation panel (PT, aPTT, TCT, and fibrinogen), thyroid assessment, routine serum chemistries, and liver function test. In addition, each patient was evaluated by bone scan, chest X-ray, magnetic resonance images (MRI) and/or computed tomography (CT) scan prior to starting therapy (as appropriate for their type of cancer). Chest X-ray, MRI, CT and/or radionuclide bone scans were routinely repeated serially two weeks after the completion of each cycle of therapy (except in cohort #1 in which follow-up was after every two cycles), provided the original study was positive.

Because this was a dose-escalation study, rather than increasing patients' daily dosage or the rate at which pentosan was administered, treatment duration was escalated in consecutive patient cohorts. Four, five, and four patients received pentosan for three, five, and eight weeks, respectively. In addition, all treatment cycles included a four-week period following active treatment during which pentosan was not administered. Subsequent treatment cycles were given at the same dose rate and duration as the first cycle. If there was no evidence of disease progression at the end of each treatment cycle or severe adverse effects, the patient was eligible to receive another cycle of therapy. Intrapatient dosage escalation was not permitted.

Patients were not entered on the next highest cohort until at least three patients had completed one pentosan infusion treatment cycle (including four weeks of follow-up) at the previous duration without any grade III or greater toxicities. If toxicities greater than or equal to grade III developed in two of six patients at any cohort, then no further dose escalations were made and that dose was considered the dose-limiting treatment infusion duration.

Clinical response assessment

Patients were examined daily for toxicity while receiving pentosan and were evaluated at least weekly for disease status while receiving the drug. Follow-up examinations were performed two and four weeks after completing each treatment cycle. Therapeutic activity was assessed by standard response criteria including standard tumor marker assessments for their respective disease. A complete response was defined as the disappearance of all evidence of the malignancy for at least two measurement periods separated by at least four weeks. A partial response was a decrease of 50% or greater in the product of the largest perpendicular bidimensional diameters (diameter product) of signal lesions or all measurable lesions without the appearance of any new lesions for at least four weeks. Stable disease was defined as a decrease of less than 50% to an increase of less than 25% in the diameter product of any measurable lesions without the appearance of new lesions for at least eight weeks. Progressive disease was an increase of more than 25% in the diameter product of any measurable lesion or the appearance of new lesions. Adverse reactions were graded by the National Cancer Institute Common Toxicity Criteria [25].

Results

Patient demographics

Thirteen patients were enrolled in this study. Six of those patients had adenocarcinoma of the colon, two had rectal adenocarcinoma, two patients had breast carcinoma, and three additional patients had renal cell, bronchioalveolar, or poorly differentiated adenocarcinoma of unknown primary, respectively. The median age was 50 years (range 34 to 61 years). Eight patients were male and five were female. Twelve of the 13 patients had received previous therapy with combination chemotherapy and three had received prior biological response modifiers. Four patients had received radiation therapy (three of those patients received radiation to the pelvis and one to the mediastinum). Four patients were treated in cohort #1 (three weeks of infusional therapy) and received eight total cycles of therapy. Five patients were treated in cohort #2 (five weeks of therapy) and received a total of eight cycles. Cohort #3 (eight weeks of therapy) included four patients, each of whom received only one treatment cycle (one patient completed the first cycle, the remaining three patients only received 9, 25, and 38 days of therapy).

Clinical assessment of toxicity and activity

The toxicities associated with pentosan are listed in Table 1. As anticipated, all patients experienced a progressive prolongation of their aPTT and PT resulting in a reduction in dose to avoid excessive anticoagulation (see Figure 2A, 2B, and 2C). Furthermore, all patients experienced an immediate (within 24 hours of the initiation of treatment) decline in the platelet count which reached a plateau within 7 to 10 days (at least grade I thrombocytopenia). The platelets returned to baseline following the discontinuation of therapy. Other complications were, in general, mild. Five patients developed liver abnormalities (elevation of SGPT/SGOT); four grade II, and one grade III. Greater than grade I thrombocytopenia was noted in five patients (four grade II and one grade IV). In addition, four episodes of central line complications were observed (two epi-

Table 1. CTEP grade II or greater toxicities associated with pentosan.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>3 wk</th>
<th>5 wk</th>
<th>8 wk</th>
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<tr>
<td>Hepatic</td>
<td></td>
<td></td>
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<tr>
<td>T. Bili</td>
<td></td>
<td></td>
<td>III</td>
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<tr>
<td>SGPT/SGOT</td>
<td>II</td>
<td>II, II, II, III</td>
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<tr>
<td>Alk Phos</td>
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<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>II, II</td>
<td>II, IV</td>
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<td>n/a</td>
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<tr>
<td>aPTT</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>III, III, III*</td>
<td></td>
</tr>
<tr>
<td>Catheter complications</td>
<td></td>
<td>II, II*</td>
<td></td>
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<tr>
<td>Infection</td>
<td></td>
<td>II</td>
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<td>Pneumothorax</td>
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<td>Atrial fibrillation</td>
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<td>Gastrointestinal bleeding</td>
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The roman number indicated the grade of toxicity and the number of symbols indicate the frequency of the event.

* Same patient.

n/a - not applicable; all patients had prolongation of their aPTT/PT, but doses were adjusted to maintain the value within 1.8 to 2.2 of the baseline.
Figure 2. Average dose and aPTT for patients treated with pentosan. Data represents mean dose (mg/day) administered (○) and aPTT (sec., •) for patients treated for three weeks (A), five weeks (B) and eight weeks (C). Bars represent standard deviation of mean dose and aPTT. Error bars presented for dose are only plotted for every third data point for clarity.

Discussion

In this study we found that pentosan was generally well tolerated by patients as a continuous i.v. infusion when given for three or five weeks. The eight-week regimen
resulted in two dose-limiting complications (n = 4). As noted in prior clinical trials all patients experienced prolongation of the aPTT and at least grade I thrombocytopenia [11, 26]. The dose-limiting toxicities reported in those trials were changes in liver enzymes and thrombocytopenia [11, 26–28]. The exact mechanism of the thrombocytopenia is unclear. A process mediated by antibodies similar to that seen with heparin has been identified in patients receiving pentosan [29] and our patients that developed grade IV thrombocytopenia did show a pentosan-induced aggregation response. Although one patient did have stable disease for approximately six months, no other antitumor activity was observed in this study. However, it should be noted that we did not look for biological activity (i.e., changes in bFGF, microvessel count).

Pluda et al. [11] administered pentosan to sixteen patients with HIV associated Kaposi’s sarcoma for three to six weeks by continuous i.v. infusion (2–4 mg/kg/day as a continuous (i.v.) infusion followed by the same dose administered SQ three times per week). After receiving pentosan for six weeks, concomitant zidovudine was initiated. None of their patients were noted to have any objective clinical responses with the exception of stable disease (3–27 weeks) seen in three patients. The maximally tolerated dose was 3 mg/kg/day and their dose-limiting toxicities were anticoagulation and thrombocytopenia, both of which were reversible following discontinuation of therapy [11]. Similar to our data reported above, they noted that the aPTT continued to rise in some patients while receiving a fixed dose of pentosan by continuous i.v. infusion. In fact, all patients required at least one dose reduction and most required three to four decreases in dose as a result of increasing aPTT values.

The pharmacokinetics of pentosan has been reported to be similar to that of standard heparin. The clearance of pentosan is dose dependent [30, 31]. When given to normal volunteers as an intravenous short-infusion of 1, 10, and 100 mg, the terminal elimination half-life was 7, 21, and 55 minutes, respectively. The bioavailability of pentosan is poor and only 4%–8% is excreted unchanged in the urine. Pentosan is desulfated in the liver and primarily excreted renally into the urine [32]. Our in vitro experience shows a linear relationship between aPTT (25 seconds to 60 seconds) and pentosan concentration (0 to 12 μg/ml). As noted in Figures 2A, 2B, and 2C we maintained aPTTs of approximately 50 to 60 seconds, this appears to translate to plasma concentrations of 8.5 to 11 μg/ml. The IC50’s, as reported above for several cell lines, range between 6 and 39 μg/ml. Thus, it appears we were able to achieve plasma concentrations within the desired range for antitumor activity (albeit in the mid to lower portion of the range). Also noted from Figures 2A, 2B, and 2C a reduction in dose was necessary throughout the duration of each exposure to maintain the targeted aPTT (especially obvious in cohort #3). In fact, such a modification in dose leads us to speculate whether saturation of elimination is occurring. The terminal half-life had been estimated to be 55 hours; thus, the time to steady-state should be 11.4 days. However, looking at Figure 2C suggests that steady-state was not reached by eight weeks. This leads us to question whether the half-life of effect is different than the plasma half-life or if the terminal half-life was simply inaccurately estimated (i.e., a deep compartment that was not characterized). Nonetheless, it is obvious that continued dose reductions were necessary throughout the treatment course to maintain the aPTT in the desired range.

In summary, pentosan is well tolerated when doses are adjusted for aPTT prolongations and a five week cycle appears to be the maximum tolerated duration of infusion (initially 4 mg/kg/day). Although, with the exception of one patient that had stable disease, no objective tumor response or evidence of antitumor activity was seen in the other patients. Further evaluation of pentosan administered in cycles of five weeks of continuous i.v. infusion may be warranted, however, the side effect profile from continuous infusion may preclude further development as an anticancer agent.

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References


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