CONCISE REPORT

Treatment of Refractory Splenomegaly in Myeloproliferative Disease by Splenic Artery Infusion

By G. P. Canellos, S. B. Sutliffe, V. T. DeVita, and T. A. Lister

Five patients in the blastic phase of chronic granulocytic leukemia with massive splenomegaly were treated by intraarterial splenic artery infusion of cytosine arabinoside. All patients had massive splenomegaly associated with pain and/or hyper-splenism and were refractory to previous therapy. All 5 patients demonstrated responses to treatment, with reduction in spleen size as well as symptomatic relief. Systemic toxicity was minimal in 4 of the 5 patients.

Massive splenomegaly can complicate the course of myeloproliferative disorders. This is especially true in the accelerated phase of chronic granulocytic leukemia (CGL), when massive splenomegaly refractory to irradiation and chemotherapy can result in painful splenic infarcts and hypersplenism. The latter is especially disturbing, since the production of mature blood elements is compromised either by transformation of the disease to a more blastic leukemia or as a result of suppression by chemotherapeutic agents. The severity of this complication has served as a justification for splenectomy during the chronic phase of the disease because of the high morbidity associated with attempted splenectomy in the accelerated or blastic phase. Systemic chemotherapy or radiation therapy directed to the enlarged spleen in the blastic phase of CGL rarely results in significant regression, but it is often complicated by marked myelosuppression.

Direct infusion of the splenic arterial circulation of an enlarged spleen with a cytotoxic agent would expose leukemic cells to maximal concentrations of drug. However, the reduction of massive splenomegaly without compromise of bone marrow would require an agent that could be safely infused through the splenic circulation and metabolized by normal tissues, including the liver, to a nonmyelotoxic product. Cytosine arabinoside was chosen as a chemotherapeutic agent to be perfused through the splenic artery for three reasons: (1) its demonstrated effectiveness against myeloblastic leukemia, (2) its cell cycle specificity, and (3) the fact that it can be converted to uracil arabinoside by cytidine deaminase, which is present in most tissues, including the blood and liver. Direct intraarterial infusion might be expected to inhibit the leukemic cells in the spleen, with deamination of the drug as it passes through the spleen and liver via the splenic portal circulation.
MATERIALS AND METHODS

Five patients in the blastic phase of Philadelphia-chromosome-positive CGL with marked splenomegaly refractory to systemic cytotoxic chemotherapy were selected for splenic artery infusion. The interval between the end of previous systemic chemotherapy and the beginning of intraarterial infusion varied from 5 to 10 days. Refractoriness to systemic therapy was determined as (1) stable or increasing splenomegaly or (2) persistence of blast cells in the bone marrow and peripheral blood despite at least two courses of systemic treatment.

Under fluoroscopic guidance a No. 5 French catheter was placed in the splenic artery via the femoral artery. Cytosine arabinoside in a dosage range from 40 to 200 mg dissolved in 500 ml of normal saline was infused over a 24-hr period from 5 to 11 days. Two patients received the medication as continuous infusion at dosages of 50 and 100 mg/sq m for 24 hr over 5–11 days, respectively. Three patients received a dosage of 40 mg administered over 6 hr during each 24-hr period for 5 days. Four of the 5 patients received a second course 10–30 days after the previous course. Complete blood counts were obtained daily during infusion. Assessment of the response of spleen size was based on clinical criteria. Spleen size was measured daily during infusion. Renal and hepatic function studies were performed every 4–5 days during the study period.

RESULTS

The clinical characteristics of the patient population are shown in Table 1. The patients ranged in age from 17 to 44 yr. The median period from onset of blastic transformation to the beginning of infusion was 2 mo. All patients had received vincristine and prednisone prior to intraarterial splenic infusion. In addition, 4 patients had received systemic cytosine arabinoside, 6-thioguanine, and BCNU (2 patients). Splenomegaly was either persistent or increasing despite chemotherapy prior to selection for intraarterial infusion. Two patients had painful splenomegaly, and both experienced relief of their symptoms. Two patients with massive splenomegaly to the right iliac fossa experienced dramatic regression of spleen size to 11 and 8 cm below the left costal margin. Three of 5 patients had white cell counts of less than 10,000/cu mm at the inception of infusion. The results of the completed courses of treatment are shown in Table 2. Two of the 5 patients had white cell counts over 100,000/cu mm, and in both instances following two courses of intrasplenic infusion the blood counts came down to a normal range. All 5 patients had thrombocytopenia, with platelet counts ranging from 10,000 to 50,000/cu mm. The platelet count in patient R.S. rose from 41,000 to 113,000/cu mm following infusion. The duration of regression of spleen size was short, averaging approximately 4–6 wk following cessation of treatment. No patient had splenectomy
Table 2. Changes in Spleen Size Following Intraarterial Infusion With Cytosine Arabinoside

<table>
<thead>
<tr>
<th>Dosage of Cytosine Arabinoside*</th>
<th>Spleen Size (cm below left costal margin)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preinfusion</td>
<td>Postinfusion†</td>
</tr>
<tr>
<td>1. R.S. 50 mg/sq m/24 hr X 5 days, continuous infusion</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>2. J.B. 100 mg/sq m/24 hr X 7 days, continuous infusion</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>3. I.N. 40 mg/6 hr X 5 days</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>4. T.P. 40 mg/6 hr X 5 days</td>
<td>Entire abdomen</td>
<td>11</td>
</tr>
<tr>
<td>5. T.W. 40 mg/6 hr X 5 days</td>
<td>Entire abdomen</td>
<td>8</td>
</tr>
</tbody>
</table>

*All but patient J.B. received second courses within 10-30 days.†Maximal decrease.

following regression. Transient myelosuppression to 1000/cu mm was noted in 1 patient.

DISCUSSION

The splenic enlargement that characterizes the accelerated-phase of myeloproliferative disorders such as CGL, myeloid metaplasia, and polycythemia vera can be a source of great discomfort, as well as a contributing cause to the anemia and thrombocytopenia. Splenectomy has been advocated for this complication, but with limited success, since the operation for massive splenomegaly can be a life-threatening procedure. However, those patients with CGL and refractory splenomegaly but without hematologic evidence of blastic leukemia may benefit from splenectomy, especially with improvement in the platelet count. In this study an attempt was made to use intraarterial splenic infusion to reduce massive splenomegaly. Reduction of size and palliation of symptoms were achieved without significant serious compromise of blood counts. The benefit, although dramatic, was transient, and spleen size was noted to increase in the weeks following cessation of intraarterial infusion. This can be attributed to the short duration of action of cytosine arabinoside in the face of highly proliferative leukemic blast cells. The technique might be more useful for reduction of spleen size in those patients who might benefit from subsequent splenectomy. Marked changes in peripheral blood counts were not seen, except in the two instances where the patients had massive splenomegaly accompanied by elevations of white cell counts above 100,000/cu mm. The latter circumstance suggests that splenic production of granulocytes was contributing significantly to the circulating peripheral cell mass. The absence of systemic toxicity may be due to deamination of cytosine arabinoside by cytidine deaminase in both splenic and hepatic tissues.

Patients with painful splenic enlargement due to leukemic cell infiltration who otherwise cannot be palliated might benefit from the technique. It offers a safer alternative to the toxic potential of attempting to reduce spleen size with high doses of systemic cytotoxic agents.
ACKNOWLEDGMENT

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REFERENCES

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