

## Locoregional intrasplenic chemotherapy for hypersplenism in myelofibrosis

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**Summary.** A 79-year-old patient with post-polycythaemic myelofibrosis presented with severe hypersplenism. After splenic artery catheterization, cytosine arabinoside was given intrasplenically from November 1999 to March 2000 for 5 d/month at 10 mg/m<sup>2</sup> and increased each month by 10 mg/m<sup>2</sup>. It was then administered by continuous infusion until June 2000, starting at 20 mg/m<sup>2</sup>/d and tapering by 5 mg/m<sup>2</sup> every 2 weeks to a final daily dose of 5 mg/m<sup>2</sup>/d. The drug was then stopped. The

spleen had decreased to one third of the initial volume. Clinical conditions and haematological indices improved substantially. Intrasplenic therapy could be a new therapeutic tool for hypersplenism in chronic idiopathic and post-myeloproliferative myelofibrosis.

**Keywords:** myeloproliferative disease, myelofibrosis, hypersplenism, locoregional chemotherapy, cytosine arabinoside.

Myelofibrosis with myeloid metaplasia (MMM) is a clonal disease of the haemopoietic stem cell presenting with hypercellular bone marrow, collagen deposition in the extracellular marrow spaces and extramedullary haemopoiesis (Anastasi & Vardiman, 2000). The post-myeloproliferative form results from the fibrotic transformation of polycythaemia rubra vera (PRV) and essential thrombocythaemia.

Treatment of severe hypersplenism in chronic idiopathic and post-myeloproliferative MMM is largely unsatisfactory. When conventional therapy fails, splenectomy and splenic irradiation remain the only therapeutic options.

Intra-arterial chemotherapy through percutaneous arterial catheters is well established for the treatment of solid tumours (Aigner, 1998), but has no applications in neoplastic blood diseases. Following the same principle, we speculated that locoregional chemotherapy through the splenic artery might reduce spleen size and revert to haematological and systemic toxicity of hypersplenism. On this assumption, we treated a patient with post-myeloproliferative myelofibrosis and severe hypersplenism using intrasplenic infusion of cytosine arabinoside.

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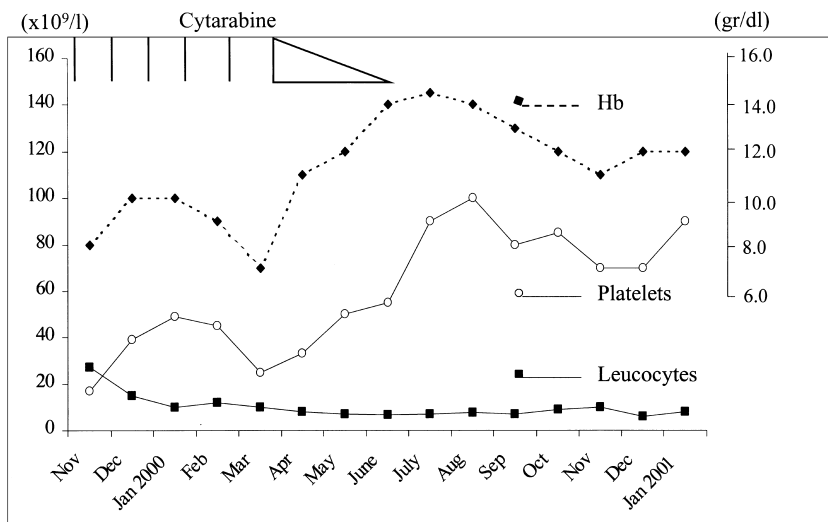
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### CASE REPORT

A 79-year-old man presented in October 1999 with anaemia, thrombocytopenia, leucocytosis and splenomegaly. PRV had been diagnosed 23 years earlier and treated with venesections alone until November 1998. Since that time, haemoglobin and platelet counts had gradually decreased and the spleen had enlarged rapidly causing abdominal discomfort, hypercatabolic symptoms, health deterioration and weight loss. Physical examination showed widespread skin bruises and a massive spleen, reaching the left iliac fossa and crossing the midline. The peripheral blood showed immature granulocyte precursors, occasional blast cells and the typical morphological red cell abnormalities of MMM. A bone marrow biopsy was consistent with a myeloproliferative disorder with fibrotic evolution. An abdominal ultrasound scan confirmed the massive splenomegaly; the liver was of normal size and structure. The mean spleen volume measured by spiral computerized tomography was calculated at 3 l.

### MATERIALS AND METHODS

Informed consent for surgery and locoregional chemotherapy was obtained. After packed red cell and platelet transfusion, the left axillary artery was punctured under local anaesthesia and ultrasound guidance using the Seldinger technique; the splenic artery was catheterized and the splenic vascular anatomy was highlighted angiographically.



**Fig 1.** Haematological findings during and after treatment with intrasplenic cytosine arabinoside. The haemoglobin drop in October and November 2000 was as a result of extended bruises caused by a fall and a subdural bleed following a car accident, from which the patient has fully recovered.

A 6-French hydromer-coated polyurethane catheter was inserted and attached to a self-sealing silicone reservoir (Port-a-Cath, Deltec, USA). This was implanted in a subcutaneous pocket of the upper chest wall and connected to a CADD infusion pump (Deltec). From November 1999 to March 2000, intra-arterial cytosine arabinoside was given overnight for 5 d/month starting at a dose of 10 mg/m<sup>2</sup>; the dose was increased each month by 10 mg/m<sup>2</sup>. From April to June 2000 the drug was administered by continuous infusion at the initial dose of 20 mg/m<sup>2</sup>/d, then tapered by 5 mg/m<sup>2</sup> every 2 weeks to a final daily dose of 5 mg/m<sup>2</sup>/d. The infusion was then stopped and the catheter flushed with a heparin solution (100 units/ml) every 2 weeks.

## RESULTS

### Spleen size

Following intermittent cytosine arabinoside, the spleen size changed little on examination; however, the calculated spleen volume decreased from 3 l to 2.5 l and the abdominal discomfort was much improved. During the following period of continuous infusion, the spleen volume shrank steadily to 1.05 l and remained so in a repeat scan 3 months later.

### Haemopoiesis

The patient received blood and platelet transfusions again in March 2000. The haemoglobin ceased to fall thereafter and the patient became transfusion independent. Red cell macrocytosis appeared, probably due to the effect of the drug on erythropoiesis. Nucleated red cells were no longer detected in the peripheral blood, although the morphological red cell abnormalities persisted. The white cell counts returned to normal levels and immature granulocyte precursors were no longer observed. The platelet counts rose but became inaccurate because of the appearance of platelet clumps. A modest effect on the cell counts was apparent at the higher doses of monthly cytosine arabino-

side (Fig 1). A bone marrow biopsy, taken 6 months following initiation of chemotherapy, was unchanged.

### Performance status

Systemic and hypercatabolic symptoms remitted within a few weeks of starting treatment and long before the reduction of the spleen. The patient gained 5 kg in weight and was able to resume a normal active life.

## DISCUSSION

The patient's recent clinical deterioration and spleen enlargement was not due to leukaemic transformation: flow cytometry analysis with myeloid and lymphoid markers (data not shown) and bone marrow histology did not show excess of blasts. He was a healthy and active man, but became homebound and transfusion-dependent within few months. A treatment aimed mainly at reducing the spleen volume with little systemic and haematological toxicity therefore seemed appropriate, also taking the patient's age into account.

Treatment of MMM is aimed mainly at alleviating signs and symptoms of hypersplenism and bone marrow failure and has included hydroxyurea, corticosteroids, androgens, blood and platelet transfusion, erythropoietin and alpha interferon (Barosi, 1999); some patients have benefited from allogeneic or autologous bone marrow transplantation (Guardiola *et al*, 1999; Tefferi, 2000).

Symptomatic hypersplenism in myelofibrosis partially responds to conventional treatment with hydroxyurea, which is effective not only in reducing spleen size, leucocytosis and thrombocytosis but also in improving hypercatabolic symptoms (Tefferi, 2000). Refractory hypersplenism is commonly treated with splenectomy or spleen irradiation. Splenectomy has a mortality and a morbidity rate of nearly 10% and 30%, respectively, as a result of bleeding, infections and thrombosis (Tefferi *et al*, 2000). Further, disease acceleration and rapid progression to acute leukaemia can occur (Barosi *et al*, 1998). Spleen irradiation,

although less harmful, has only a transient effect and is occasionally followed by prolonged and life-threatening cytopenias (Elliott *et al*, 1998).

Intra-arterial indwelling catheters carry a low morbidity risk; no fatal events have been described; complications, although rare, are mainly vascular thrombosis and catheter displacement (Grosso *et al*, 2000; Aldrighetti *et al*, 2001). Severe bone marrow depression is not usually a problem, given the low dosage of drugs used.

Other haematological conditions with inoperable hypersplenism, such as lymphoproliferative disorders, may benefit from such therapeutic modality. Finally, intrasplenic treatment could be viewed as a preliminary step to splenectomy once the reduction of the spleen size has been achieved.

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