The role of splenectomy in children with juvenile myelomonocytic leukemia

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Splenectomy has been performed as a palliative treatment both in adults and children with myelodysplastic syndrome (MDS). However, there is no report describing the course after splenectomy in children with MDS. The aim of this study was to evaluate the impact of splenectomy on the outcome of six children with juvenile myelomonocytic leukemia (JMML) who had no HLA identical donor and who became unresponsive to chemotherapy. Persistent thrombocytopenia, increased erythrocyte transfusion requirement and massive splenomegaly were the indications for splenectomy. Hemoglobin values and platelet counts improved following splenectomy in five out of the six patients. Erythrocyte transfusion requirements decreased and none of the patients who responded received erythrocyte transfusion for at least six months. More importantly, the quality of life improved markedly. No mortality related to splenectomy was observed. In conclusion, splenectomy may be considered as a safe supportive treatment approach for some children with JMML.

Key words: juvenile myelomonocytic leukemia, splenectomy, children.

Juvenile myelomonocytic leukemia (JMML) is a clonal stem cell disorder characterized by ineffective hematopoiesis. Childhood JMML is classified as a bridging disorder between myelodysplastic syndrome (MDS) and myeloproliferative diseases[1]. More than 95% of JMML patients are diagnosed under the age of six years. Children with JMML mostly present with hepatosplenomegaly, lymphadenopathy, bleeding, anemia, fever, recurrent infections, rash, failure to thrive and pulmonary disease[1,2]. Stem cell transplantation (SCT) is the only effective therapy that has produced sustained remission in JMML. The patients who have no donor are treated with either low-dose or intensive acute myeloblastic leukemia (AML) chemotherapy protocols[2,3]. In some patients, splenectomy has also been performed as a palliative treatment both in adults and children with MDS[4-8]. However, there is no report describing the course of the disease after splenectomy in children with JMML.

We report regarding the impact of splenectomy on the outcome of six children with JMML.

Material and Methods

We retrospectively evaluated the medical records of six children (2 girls, 4 boys) with JMML who were splenectomized. Some of the clinical features of children at the time of splenectomy are shown in Table I. At initial diagnosis, their ages ranged between 7 and 48 months (median 18 months). They clinically presented with pallor, recurrent pneumonia, fever, rash, hepatosplenomegaly and anemia. The criteria proposed by Hasle et al.[1] were used for the diagnosis of JMML. Test for in vitro spontaneous colony growth was carried out in three patients and their Philadelphia chromosome was negative (Cases 4, 5 and 6). Because of technical failures, cytogenetic analyses were not available in the other three cases. However, we excluded other causes of myelodysplasia including infectious (bacterial, viral, protozoal), collagen tissue diseases and other malignancies. None of the children had HLA identical donor.

Since high-dose methylprednisolone (HDMP; 20-30 mg/kg) treatment has been shown to induce terminal differentiation and apoptosis

Table I. Some of the Clinical and Laboratory Features of Children with JMML

Patient No.	Age (months)* gender	Liver/spleen size* (cm)	Cytogenetics	Interval from diagnosis to splenectomy (months)
1	91, M	1/18	NA	80
2	31, M	9/10	NA	22
3	57, F	10/17	NA	9
4**	32, F	17/17	-7	14
5**	21, M	10/14	-7	14
6**	44, M	10/20	46, XY	2

JMML: Juvenile myelomonocytic leukemia. NA: Not available.
* At the time of splenectomy.
** Test for in vitro spontaneous colony growth was positive.

of myeloid leukemic cells in different subtypes of children with AML in vivo and in vitro[9,10], they were put on high-dose steroid- and low-dose cytosine arabinoside-containing AML chemotherapy regimens described previously[11]. Following chemotherapy, with the exception of one child (Case 6) who had massive splenomegaly and severe thrombocytopenia at diagnosis, hemoglobin (Hb) level and platelet count improved in all patients. However, splenectomy was considered between 2 and 80 months after diagnosis of JMML because of the worsening of the initial incomplete clinical and hematological response (Table I). Criteria for the indications of splenectomy consisted of persistent thrombocytopenia, increased transfusion requirement due to anemia and mechanical symptoms (abdominal discomfort, early satiety, and inability to move comfortably) attributed to increased spleen size. In addition, they had reduced physical activity, bodily pain, and were troubled and anxious. All children received pneumococcal vaccination before splenectomy, and penicillin prophylaxis following the operation.

Results

Following splenectomy, improvement in platelet counts and Hb levels were observed in all children except in Case 6. Before splenectomy, the Hb values of the patients ranged between 3.3 and 7 g/dl despite their having been given frequent blood transfusions. Hb values in patients who responded were found above 10 g/dl in all four to six months after splenectomy without necessitating blood transfusions. Effect of splenectomy on erythrocyte transfusion requirement is shown in Table II. Following the operation, none of these patients received erythrocyte transfusion for six months. However, with the exception of Case 6, the remaining children began requiring erythrocyte transfusion between 6 and 14 months after splenectomy.

Although the platelet counts were below $30.0x10^9$/L, only three children (Cases 3, 4 and 6) required platelet transfusions before the splenectomy. With the exception of Case 6, platelet counts of all patients improved within one week ($>60.0x10^9$/L) following splenectomy. Active bleeding continued only in Case 6.

Table II. Effect of Splenectomy on Erythrocyte Transfusion Requirement and Survival in Children with JMML

Patient No.	Number of monthly transfusion requirements: Splenectomy Before[a]	After	Survival after splenectomy (months)
1	3	1 (14)*	14
2	3	1 (13)	22
3	2	2 (6)	14
4	1	1 (6)*	8
5	2	1 (9)*	12
6	3	4	2

JMML: Juvenile myelomonocytic leukemia.
[a] Within last three months before splenectomy.
* Number in parentheses indicates the interval between splenectomy and transfusion requirement.

An elevation in white blood cell (WBC) count was observed in all patients after splenectomy. Preoperative mean values of WBC count increased from 10.7±9.4 x 10^9/L to 45.0±35.3 x 10^9/L. One to three months following the operation these values ranged between 14.0-70.4 x 10^9/L.

Before the splenectomy, the spleens were of massive size (≥10 cm) in all patients (Table I). Splenomegaly was associated with hepatomegaly (>9 cm) with the exception of one patient (Case 1). After splenectomy, a mild decrease in liver size was observed in three (Cases 2, 4 and 5) of the six patients.

Following the operation, the quality of life improved dramatically in all cases except Case 6. They became free of mechanical symptoms attributed to massive splenomegaly and they were able to conduct daily activities normally. Moreover, they improved emotionally to a more comfortable state. After removal of the spleen, the survival of these children improved markedly, ranging between 8 and 22 months (median 14 months) (Table II). However, Case 6, who did not respond to splenectomy, died two months after the operation. No complication related to splenectomy was observed.

Discussion

There are few studies indicating the role of splenectomy in the management of patients with MDS. Although appropriate indications for splenectomy are not properly settled in MDS, in previous studies it was indicated if persistent thrombocytopenia and mechanical symptoms attributed to increased spleen size were present[4,6]. In a few studies, splenectomy was performed before SCT to reduce leukemic cell burden if splenomegaly persisted below the umbilicus or to reduce the requirements of platelet transfusion[7,8,12,13]. In the present study, persistent thrombocytopenia, increased erythrocyte transfusion requirement and massive splenomegaly were the indications for splenectomy in children with JMML.

In childhood MDS series, splenectomy was reported only in patients receiving SCT[7,8]. Indication of splenectomy before SCT is not clear. It is also not clear whether the splenectomy before SCT reduces the risk of relapse. In two studies of children with JMML, since splenectomy did not influence the outcome, the benefit of splenectomy before SCT was reported as questionable[7,8]. On the other hand, three recent studies suggested that splenectomy before SCT was important for disease control in these children[12,13,14].

In the present study, a rapid improvement in hematological findings was observed following splenectomy in five of the six children with JMML who became unresponsive to chemotherapy. In addition, erythrocyte transfusion requirement decreased significantly. Resolution of anemia following splenectomy was also noted in adult MDS patients who previously required erythrocyte transfusions[4]. The rapid resolution of hematological parameters indicates that spleen trapping of blood elements may have significant contribution for the occurrence of cytopenias in JMML. The pathological studies in adult patients with chronic myelomonocytic leukemia (CMML) have shown that splenomegaly is associated with marked infiltration of monocytes and immature myeloid cells, hemophagocytosis, and extramedullary trilineage hematopoiesis[5,6]. Improvement of the thrombocytopenia in JMML may also be related to destruction of the platelets by the spleen through immune mechanisms[4].

The survival of children with JMML who had no opportunity for SCT was poor. Previous studies showed that about half and one-quarter of these patients were alive at the end of one and two years after presentation, respectively[15-17]. In the present study, following splenectomy, a better quality of life and prolonged survival, ranging between 8 and 22 months, were achieved in five of the six children with JMML who were unresponsive to chemotherapy and had no chance for SCT.

In contrast to the adult MDS patients, no splenectomy-related mortality was observed in children in the previously reported and the present study[5,6]. Based on these results, splenectomy appears to be a safe procedure in children with JMML.

In conclusion, splenectomy may be considered in certain conditions as a safe supportive treatment approach to provide better quality of life and to decrease requirement of transfusions in children with JMML who become unresponsive to chemotherapy and have no opportunity for SCT.

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