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ORIGINAL ARTICLE

Splenic irradiation as palliative treatment for symptomatic splenomegaly due to secondary myelofibrosis: a multi-institutional experience

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Summary

Purpose: *To evaluate the impact of splenic irradiation as a palliative treatment for symptomatic splenomegaly due to secondary myelofibrosis.*

Methods: *Seventeen patients with chronic myelogenous leukemia and 3 with idiopathic polycythaemia presented with splenomegaly, splenic pain and anemia. Due to symptomatic splenomegaly, despite first-line treatment, the patients underwent splenic irradiation. Two patients received two different schedules of external radiotherapy (580 cGy in 5 fractions and 600 cGy in 6 fractions). Eight patients received 980 cGy in 14 fractions. Ten patients received two courses of 360 cGy in 6 fractions, 3 months apart. Median follow-up was 12 months post irradiation.*

Results: *The patients showed excellent response to treatment one month post-radiotherapy, while treatment was well tolerated without severe toxicity. The dimensions of the spleen decreased significantly. Pain-related Visual Analogue Score (VAS) regressed after completion of irradiation. During 12-month follow-up all patients maintained the benefit of radiotherapy.*

Conclusion: *This study indicates that splenic irradiation could be a safe and effective palliative treatment for symptomatic splenomegaly due to secondary myelofibrosis*

Key words: *palliative treatment, secondary myelofibrosis, splenic irradiation, splenomegaly*

Introduction

Splenomegaly presents frequently in patients with idiopathic myelofibrosis or chronic myelogenous leukemia, indicating significant splenic metaplasia [1,2]. Splenic irradiation for symptomatic splenomegaly has been electively delivered in patients with idiopathic myelofibrosis, when other therapies were inefficient or not indicated, while the appropriate irradiation schedule remains to be defiined. Radiotherapy may improve the quality of life of patients with splenomegaly, reducing the splenic pain and often the splenic size, but literature remains rare in this field [3-5].

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Although the optimal radiation dose for splenic irradiation in patients with myelofibrosis is still unclear, median dose schedules reported in the literature range from 9.8 to 7.7 Gy, in daily fractions of 0.4-1 Gy, depending on both clinical response and hematological toxicity [6,7]. Symptom relief was observed in up to 100% of patients, which was not accompanied by a reduction of splenic size in all of the cases [7].

The purpose of this study was to evaluate the potential role of splenic irradiation as a palliative treatment for symptomatic splenomegaly in patients with secondary myelofibrosis due to chronic myelogenous leukemia and idiopathic polycythemia, respectively.

Table 1. Patient characteristics

Characteristics	
Age median, years (range)	49 (31-67)
Male/female	13/7
History	
Myelogenous leukemia, N (%)	17 (85)
Idiopathic polycythemia, N (%)	3 (15)
Spleen dimensions (in cm, CT scans)	
Mean X (±SD)	29.2 (±1.8)
Mean Y (±SD)	22.8 (±1.4)
Mean Z (±SD)	11.8 (±1.5)
Mean VAS (±SD)	7.5 (±0.8)

Methods

Patients and procedure

Twenty patients with splenomegaly due to secondary myelofibrosis were included in the present retrospective study. Patient characteristics are shown in Table 1. On clinical examination the spleen was palpable in all patients, extending to the anterior iliac ruga, while abdominal computed tomography (CT) showed enlarged spleen. Before study enrollment all patients were treated with hydroxyourea 500 mg x3/per day, corticosteroids (methylprednizolone 16 mg twice daily), folic acid and allopurinol (100 mg daily), without response. Patients with chronic myelogenous leukemia had also been treated with interferon alfa 2b (IFN-a2b 3 miu 3 times a week) for a year, without response, in contrast with the positive results of other studies about the beneficial effect of IFN in patients with myelofibrosis and myeloid metaplasia [8].

Due to persisting pain despite first-line treatment, we went on second-line treatment with external beam splenic irradiation, as long as the hematological and blood chemistry results were normal (time range: 2000-2010). Abdominal CT images of the first 2 patients were digitized using a flat bed 8-bit scanner and were stored in DICOM III format, while a 2-D treatment planning system was used to set up opposed anterior-posterior fields and subsequently patients received palliative external beam radiotherapy with 60Co unit. Eighteen patients received 3D conformal radiation therapy with 6MV LINAC. Two patients received 2 different schedules of external radiotherapy (580 cGy in 5 fractions and 600 cGy in 6 fractions). Eight patients received 980 cGy in 14 fractions. Ten patients received 2 courses of 360 cGy in 6 fractions, 3 months apart.

To evaluate toxicity and response to treatment, patients underwent clinical examination and blood chemistry tests at least once a week during irradiation and monthly thereafter. ECOG performance status (PS) was evaluated before and after irradiation. Discomfort related to splenomegaly was evaluated with VAS, in a scale from 0 (none) to 10 (maximum discomfort).

Statistics

Differences either in spleen dimensions, in ECOG PS or in VAS score were evaluated with the Wilcoxon non parametric test. Significance level was set at 0.05. The whole analysis was performed with the SPSS vers. 10 software (SPSS Inc., Chicago, Ill, USA)

Results

Patients showed excellent response to treatment one month post-irradiation. In particular, constitutional symptoms, such as malaise, anorexia, weight loss or sweats and splenic pain, were eliminated in all of the patients post-irradiation. Patients showed significant improvement of their mean value of ECOG PS, from 2.95±0.51 to 1.05±0.39 ($p<0.01$, Wilkoxon test). Furthermore, requirements in transfusions reduced after irradiation (from 3-4 to 1-2 units of red blood cell transfusion per month), while spleen size significantly reduced in 3 patients (>85%) in contrast to 40-50% reduction of splenic size in the rest of our patients. VAS was significantly reduced from 7.5±0.8 to 2.2±0.8 ($p<0.01$, Wilcoxon test).

In general, splenic irradiation was well tolerated, without severe toxicity. However, 7 patients (35%) required transfusional support (2 units of red blood cell transfusion per week) during splenic irradiation. The dimensions of the spleen (in cm), decreased significantly: X-axis, from 29.2±1.8 to 14.7±4.0; Y-axis from 22.8±1.4 to 9.1±3.0; Z-axis from 11.8±1.5 to 7.6±2.9 ($p<0.01$, Wilcoxon test).

During 12 months of follow-up, all patients maintained the benefit of splenic irradiation and remained in an excellent performance status (asymptomatic state).

Discussion

Myelofibrosis is a disease of hematopoietic stem cells, and may be either a primary (idiopathic) or secondary disorder, which is characterized by bone marrow fibrosis, extramedullary hematopoiesis and circulating peripheral leukoerythroblastic blood cells [9-12]. Marrow fibrosis results from increased deposition of various interstitial and basement membrane glycoproteins, such as collagene types I, III, IV, V and VI, fibronectin and laminin [1,9-12]. Accumulation and growth of circulating myeloid progenitors in the spleen leads to pathologic enlargement of the organ, with resulting mechanical discomfort, hypercatabolic symptoms, anemia, thrombocytopenia, and portal hypertension, all of which cause the severe morbidity seen in myelofibrosis [4,5].

Today, no other therapy than allogeneic bone marrow transplantation has been shown to cure or to prolong survival of patients with myelofibrosis [13,14]. Thus, current treatment options are palliative and include: red cell transfusional support and androgen therapy for anemia, chemotherapeutic agents to control thrombocytosis, leukocytosis, and hypermetabolic symptoms, with hydroxyurea (most widely used drug), and splenectomy or splenic irradiation for symptomatic splenomegaly [4-5,13-15]. Other patients may also respond to prednisolone, while experimental therapies, such as vitamin D, interferon-alfa, or erythropoietin have also been tested, but they did not show a real efficacy [4,8,12-17].

The role of radiotherapy in patients with myelofibrosis has been often evaluated in selected patients with idiopathic myelofibrosis [18]. Indication for splenic irradiation is left upper quadrant discomfort related to massive splenomegaly in patients who were poor candidates for surgery and when other therapies were inefficient. According to reports, splenic irradiation effectively palliates myelofibrosis-related symptoms (62-100% relief of splenic pain), leads to moderate reduction of the size of spleen (up to 80% of patients with at least 50% regression of splenic size), which is associated with symptomatic relief and finally constitutes an alternative modality for patients refractory to usual treatment options [2-7,19-27].

However, literature is poor as far as the role of splenic irradiation is concerned, for patients with secondary myelofibrosis, on the grounds of other hematological diseases such as chronic myelogenous leukemia or idiopathic polycythemia [19-27]. Moreover, the appropriate dose schedule and timing of irradiation for patients with secondary myelofibrosis has not been fully defined. Splenic irradiation is of greatest utility for patients with considerable symptoms and an adequate platelet count who, due to age or comorbidities, probably would not undergo splenectomy in the future. Moreover, irradiation does not preclude subsequent splenectomy. Studies have been already published concerning splenic irradiation in different myeloproliferative syndromes. In Table 2, published studies are shown, all with small series of patients [2,5-7,20-27]. Radiation therapy doses generally ranged between 2.7 and 16.2 Gy in 0.1-2 Gy daily fractions. Beyond pain relief and reduction of splenic size, effective treatment is associat-

Table 2. Studies of splenic irradiation in myeloproliferative disorders

First author	*N*	*Local response (%). (1) splenic size; (2) pain*	*Irradiation schedule. Total dose (mean total dose per fraction, Gy)*
Gonzaque-Casabianca [2]	24	50 (1) 75 (2)	9.8 (0.4-1)
Elliot [5]	23	94 (1) 94 (2)	2.7 (0.35)
Sciascia [6]	14	84 (1) 88 (2)	16.2 (1)
Slanina [7]	25	71 (1) 76 (2)	3.4 (0.3)
Parmentier [19]	9	66 (1)	4 (0.25)
Greenberger [20]	14	95 (1) 100 (2)	6 (0.25)
Hukku [21]	25	100 (1)	4.5 (0.4-1.2)
Wagner [22]	17	76 (1) 71 (2)	4 (0.1-1)
Paulino [23]	14	43 (1) 87.5 (2)	4.5 (0.25)
Schratter-Sehn [24]	49	-	20.75 (1-2)
Soldic [25]	11	44 (1) 71 (2)	7 (1)
Kriz [26]	122	50 (1) 74.8 (2)	3-16 (0.1-2)
Lavrenkov et al [27]	32	78.8 (1)	6-10 (0.5)
Current study			
Schedule 1	2	51 (1) 71 (2)	
Schedule 2	8	59.9 (1) 78.9 (2)	
Schedule 3	10	37.6 (1) 62.8 (2)	
Overall	20	48.4 (1) 70.5 (2)	

ed with stabilization of body weight and improvement of performance status. A major drawback, as long as the radiation therapy is concerned, was the short mean duration of remission, between 3 and 6 months, reported in most cases. Moreover, splenic irradiation can result in prolonged myelosuppression in certain patients. This calls for cautious radiation dose fractionation schedules, due to individual sensitivity of patients, which vary and cannot be predicted.

Patients presented with severe morbidity due to secondary myelofibrosis for at least 12 months, on the grounds of long-lasting chronic myelogenous leukemia or idiopathic polycythemia, which were refractory to first-line treatment (blood transfusions, hydroxyourea, corticosteroids, interferon, erythropoietin). Due to persisting pain and despite the absence of clear data, patients went on to receive second-line treatment with splenic external beam radiation therapy. Dose schedule, according to median dose reported in other studies in patients with idiopathic myelofibrosis, ranged between 9.8 and 10.5 Gy [1,5-7]. Although only 3 of our patients showed more than 75% reduction of the splenic size post-radiotherapy, constitutional symptoms and splenic pain were alleviated in all of them, a finding in accordance to other studies in patients with idiopathic myelofibrosis [7].

Furthermore, radiotherapy was well tolerated in all of the patients, without severe toxicity, in contrast to the majority of other studies, reporting severe and sometimes prolonged, life-threatening myelosuppression [5-7]. However, 7 patients required transfusional support (2 units of red blood cell transfusion per week) during splenic irradiation, without further clinical significance.

Allthough the median duration of response after splenic irradiation for idiopathic myelofibrosis reported in the literature was only 6 months, our patients maintained the beneficial effect of splenic irradiation for more than 9 months [5].

The rationale of the role of splenic radiotherapy in a myeloproliferative disorder is based in part on the data concerning total body irradiation in myeloid leukemias [20,28]. It was previously demonstrated that myeloid cells respond to low doses of radiotherapy [29,30]. Thus, radiotherapy may lead to a reduction of myeloid metaplasia in the spleen which probably corresponds to clinical improvement seen in our patients. However, this favorable result depends on the degree of marrow fibrosis, and splenic irradiation seems less effective when fibrosis is already established [20,28,29].

Due to the positive impact of splenic radiotherapy in our patients, along with limited data from the literature concerning the role of splenic irradiation in the course of idiopathic myelofibrosis, we consider that splenic radiotherapy is a well-tolerated, safe and effective treatment modality for palliative management of secondary myelofibrosis in patients with severe noncontractable splenomegaly, refractory to standard treatment options, such as transfusions, prednizolone or oral chemotherapy. In these patients, splenic irradiation may lead to local control, improvement of quality of life and a new phase of asymptomatic state as in idiopathic myelofibrosis [1-5].

Splenic irradiation is used as first treatment option for chronic leukaemia, but with the emergence of effective drugs its utility has been more and more restricted to advanced cases presenting with splenomegaly. In selected patients, who do not respond to first-line treatment or are not suitable for drug treatment, splenic irradiation may offer an effective, low toxic and cost-effective palliative therapy. However, further studies are necessary to determine the optimal role, dose schedule, appropriate patient selection and timing of external beam radiotherapy as a palliative treatment modality for secondary myelofibrosis.

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