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IV. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Splenic irradiation provides transient palliation for symptomatic splenomegaly associated with primary myelofibrosis: a report on 14 patients

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Abstract We retrospectively analyzed the outcomes of 14 patients with primary myelofibrosis who were treated with splenic irradiation (SI) for symptomatic splenomegaly between January 2000 and December 2012 at 12 hospitals. Median age at the time of SI was 67 years (range 47–76). The median dose of radiation per course was 5 Gy, administered in a median of eight fractions. Spleen size was reduced in 93 % of patients, and persisted for a median of 2.2 months (range 0.1–13.8). Symptom relief occurred in 86 % of patients, and lasted for a median of 2.5 months (range 0.1–16.5). Although SI provided a high rate of palliation for patients with symptomatic splenomegaly, the responses were transient. Significant thrombopenia (<25 × 10^9/L) occurred in eight patients (57 %), and neutropenia (<0.5 × 10^9/L) was observed in seven (50 %). Nine patients (64 %) required an increased number of red blood cell transfusions after SI. Five patients (36 %) developed serious infections, with two deaths (14 %), as a result of SI-induced cytopenia. The median survival for all patients after SI was 18.5 months (range 0.1–71.9). The Dynamic International Prognostic Scoring System model effectively distinguished the prognosis after SI between patients in the intermediate-2 and high-risk groups.

Keywords Myelofibrosis · Splenomegaly · Splenic irradiation · Palliation

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Introduction

Myelofibrosis (MF) is characterized by bone marrow fibrosis, progressive anemia, extramedullary hematopoiesis, splenomegaly, and the presence of disease-associated symptoms such as fatigue, night sweats, body weight loss, fever, and abdominal discomfort [1]. MF can present as a primary disease (primary MF or PMF) or can arise from antecedent polycythemia vera (PV) (post-PV MF) or essential thrombocythemia (ET) (post-ET MF). PMF, PV, and ET are categorized as myeloproliferative neoplasms (MPNs), and gene mutations in *JAK2*, *MPL*, or *CALR* are frequently observed in these three diseases [2–9].

MF-associated splenomegaly is often associated with early satiety, abdominal pain, or abdominal discomfort; in one study these symptoms occurred in 75.5, 63.0, and 71.7 % of MF patients, respectively [10]. Hydroxyurea has been found to be effective for splenomegaly and its associated symptoms. One study reported that 40 % of MF patients exhibited a reduction in spleen size and 45 % experienced relief of symptomatic splenomegaly; the median duration of these responses was 13.2 months, and most MF patients with symptomatic splenomegaly became drug resistant [11]. Splenic irradiation (SI) is useful for such patients; in one report 94 % of patients achieved an objective decrease in spleen size following SI, and all patients experienced symptomatic relief [12]. We assessed the

usefulness of SI for PMF treatment in terms of response rate and duration, toxicities, and survival after SI.

Materials and methods

The Research Committee for Idiopathic Hematopoietic Disorders in Japan conducted a retrospective survey of SI for PMF in collaboration with hematologists at 587 medical institutes throughout Japan, all of which were approved as designated institutes by the Japanese Society of Hematology. We sent a questionnaire to hematologists to collect information on patients treated with SI for PMF from 2000 to 2012. The diagnosis of PMF was made by each attending physician using the conventional or most current criteria [1, 13, 14]. This study was approved by the Research Ethics Committee of the University of Miyazaki.

The radiation treatment techniques used in these patients were determined by radiologists at each institute, and for this study we collected data on total radiation dose and its fractions.

Responses were evaluated based on a subjective relief of abdominal pain and tightness, and an objective decrease in spleen size on physical examination after SI. For cases in which no accurate measurements were documented, objective responses were recorded only if a significant reduction in spleen size was documented by the attending physician.

To predict survival after SI, we applied the Dynamic International Prognostic Scoring System (DIPSS) [15] using parameters obtained within 10 days before SI. It utilizes five risk factors to predict survival: age older than 65 years, hemoglobin lower than 10 g/dL, leukocytes higher than 25 $\times$ 10^9/L, circulating blasts $\geq$1 %, and constitutional symptoms.

Statistical analyses were performed using the statistical software SPSS ver. 20.0 (SPSS Inc, Chicago, IL, USA), and a p value <0.05 was considered significant.

Results

Patient characteristics

Patient characteristics are listed in Table 1. There were nine males and five females, with a median age of 67 years (range 47–76) at the time of SI. The median duration of disease from the diagnosis of PMF to SI was 73.7 months (range 3.1–255.2).

Radiation

The median duration of treatment was 15 days (range 5–24). The median dose of radiation per course was 5 Gy (range 2–10.8), administrated in a median of eight fractions (range 5–10) (Table 2).

Response

Reduction of spleen size was obtained in 13 of 14 patients (93 %), and it persisted for a median of 2.2 months (range 0.1–13.8). Relief of symptoms associated with PMF was reported by 12 of 14 patients (86 %), and it lasted for a median of 2.5 months (range 0.1–16.5). The overall response (spleen size reduction and/or relief of symptoms) rate was 100 %, with a median duration of 2.8 months (range 0.1–16.5) (Table 2).

Nine patients required regular RBC transfusions before SI; of these, one achieved a positive response, with an 88 % reduction in transfusion requirements.

Toxicity

SI-associated toxicity was limited to myelosuppression. Thrombopenia (<25 $\times$ 10^9/L) occurred in eight patients (57 %), and neutropenia (< 0.5 $\times$ 10^9/L) was observed in seven (50 %). Five (36 %) patients developed serious infection, four of whom experienced febrile neutropenia or sepsis. Two patients (14 %) experienced hemorrhage. There was no statistical correlation between the baseline neutrophil count before SI and the development of neutropenia (<0.5 $\times$ 10^9/L) ($p = 0.88$), or between the baseline platelet count before SI and the onset of severe thrombopenia (<25 $\times$ 10^9/L) after SI ($p = 0.44$). There was no statistical correlation between radiation dose and the post-SI development of either neutropenia ($p = 0.53$) or severe thrombopenia ($p = 0.22$). Among nine patients who were RBC transfusion dependent, five required increased transfusions after SI. Furthermore, four patients who did not require regular RBC transfusions before SI became RBC transfusion-dependent after SI, needing more than two blood products per month.

Survival

The median survival of all patients after SI was 18.5 months (range 0.1–71.9). Two patients died as a result of SI-induced complication, at 0.1 and 1.6 months after SI, respectively. Nine patients died, four as a development of acute myeloid leukemia, three as a result of progressive disease, one of cardiac failure, and one for unknown reasons. At the time of last follow-up, three patients were alive. We applied DIPSS [15], a widely used prognostic model in PMF, to the patients in this study to evaluate its ability to predict survival after SI. Of 14 patients, two, nine, and three patients were assigned to the intermediate-1, intermediate-2, and high-risk groups, respectively. Of

Table 1 Characteristics of patients prior to splenic irradiation (SI)

Case	Age/sex	Duration from diagnosis to SI (months)	Previous treatments	Initial symptoms	DIPSS risk before SI	Palpable spleen size (cm)	Prior RBC transfusion (units/month)	WBC ($\times 10^9$/L)	ANC ($\times 10^9$/L)	Hb (g/dl)	Platelet ($\times 10^9$/L)
1	58/F	5.7	Steroids	Anemia, early satiety	Intermediate-2	13	4	2.2	1.0	4.7	388
2	76/M	92.4	Anabolic steroids	Early satiety, portal hypertension	Intermediate-2	Not precisely measurable	0	8.0	4.3	6.8	244
3	69/F	47.2	Anabolic steroids, hydroxyurea	Early satiety	Intermediate-2	Extending downwards on a level with the navel	0	17.8	10.1	9.3	92
4	67/M	138.5	No therapy	Early satiety, portal hypertension	Intermediate-2	4	0	8.1	5.1	9.0	154
5	64/F	3.1	Anabolic steroids, transfusion	Anemia, early satiety, pain, thrombocytopenia	Intermediate-1	10	4	1.7	1.4	5.5	10
6	71/M	89.3	Anabolic steroids, transfusion	Anemia	Intermediate-2	20	18	14.6	13.1	6.5	151
7	63/M	53.2	Hydroxyurea	Early satiety, pain, portal hypertension	High	12.5	0	36.8	30.9	8.6	478
8	72/M	54	Anabolic steroids, transfusion	Pain	Intermediate-2	18	2	14.9	6.8	7.4	261
9	67/M	100.6	Melphalan, steroids, transfusion	Early satiety	High	30	16	75.8	6.8	5.2	176
10	62/M	255.2	Hydroxyurea	Early satiety, portal hypertension	Intermediate-2	15	0	2.0	0.9	6.8	88
11	47/M	156.2	Hydroxyurea, transfusion	Abdominal discomfort related to splenomegaly	Intermediate-1	Extending to the pelvic cavity	8	12.4	6.3	6.9	218
12	63/F	138.4	Transfusion	Pain, splenic infarction	Intermediate-2	20	8	1.0	0.4	5.8	16

Table 1 continued

Case	Age/sex	Duration from diagnosis to SI (months)	Previous treatments	Initial symptoms	DIPSS risk before SI	Palpable spleen size (cm)	Prior RBC transfusion (units/month)	WBC ($\times 10^9$/L)	ANC ($\times 10^9$/L)	Hb (g/dl)	Platelet ($\times 10^9$/L)
13	67/F	29.5	Transfusion	Abdominal discomfort related to splenomegaly, portal hypertension	Intermediate-2	24	24	11.6	8.6	4.6	33
14	67/M	58	Hydroxyurea, transfusion	Early satiety, pain, thrombocytopenia	High	10	8	21.8	12.2	6.5	31

DIPSS dynamic international prognostic scoring system, *RBC* red blood cell, *WBC* white blood cell, *ANC* absolute neutrophil count, *Hb* hemoglobin

the two patients at intermediate-1 risk, one was still alive 67 months after SI at the time of last follow-up, and the other died 71.9 months after SI. The median survival times of patients in the intermediate-2 and high-risk groups were 18.5 and 2.9 months, respectively, and the former was significantly longer than the later ($p = 0.022$).

Discussion

We showed here that SI ameliorated abdominal symptoms associated with MF, resulting in spleen size reduction and/or relief of symptoms in almost all patients. These results were comparable with those of previous reports with relatively large sample sizes. In the report of Elliott et al. of 50 courses of SI in 23 patients, objective spleen size reduction was observed in 94 %, and relief of symptoms was obtained in 96 % [12]. In the Bouabdallah et al. study of 15 patients, 90 % of patients reported complete resolution of splenic pain, and 81 % showed an objective reduction in spleen size [16]. In our cases, the median total radiation dose was 5 Gy in a median of eight fractions, compared to total doses of 2.8 and 9.8 Gy in previous reports. SI using less than 10 Gy seems to be sufficient to ameliorate splenomegaly and its associated symptoms. In spite of the high efficacy, however, the duration of response has been short: a median of 2.8 months in our study, and 6 or 10 months in previous reports [12, 16].

The major toxicity of SI in MF is myelosuppression. In our study, grade 4 thrombopenia was observed in 57 % of patients, and 14 % of patients experienced bleeding. Grade 4 neutropenia occurred in 50 % of patients, and 29 % of patients demonstrated febrile neutropenia or sepsis. Furthermore, 14 % of patients died as a result of SI-induced cytopenia. These frequencies were almost same as those in previous studies; in one report [12], prolonged cytopenia was observed in 26 % of patients, and 13 % of patients died from sepsis or bleeding, while in a second report [16], grade 4 thrombopenia or neutropenia occurred in 12 and 35 % of patients, respectively, while 6 % of patients died from cerebral bleeding. No previous reports have identified pretreatment variables that might predict life-threating cytopenias. In agreement with previous studies, we found that neither neutrophil counts before SI nor radiation dose was associated with grade 4 neutropenia, and neither pre-SI platelet counts nor radiation dose was associated with grade 4 thrombopenia.

In general, the outcomes after SI were not favorable, although symptoms associated with splenomegaly were effectively resolved. The median post-SI survival in our study was 18.5 months, similar to the 22 months found in a previous report [12]. In our series, five of 14 patients died within 100 days after SI. The benefits of SI for these

Table 2 Responses and toxicity to the splenic irradiation (SI)

Case	Dose of SI (Gy)	Number of fractions	Maximum decrease in palpable spleen size (cm)	Relief of symptoms (controlled symptoms)	Neutropenia ($<0.5 \times 10^9$/L)	Thrombopenia ($<25 \times 10^9$/L)	Overall response duration (months)	Survival after SI (months)
1	5	10	10	+ (Early satiety)	+	−	0.6	34.9
2	10.8	9	Significant*	−	−	+	1.6	1.6
3	10.8	6	Significant**	+ (Early satiety)	+	+	4.9	25.2
4	3.2	8	4	+ (Early satiety, portal hypertension)	−	−	2.2	6.8 +
5	2.1	7	Significant*	+ (Early satiety, portal hypertension)	−	−	13.8	71.9
6	3.5	7	9.4	+ (Mechanical discomfort)	−	+	5.9	18.9
7	7	7	12.5	+ (Portal hypertension)	+	+	0.1	0.1
8	10	10	18	+ (Pain)	+	+	4.5	4.5 +
9	5	10	15	+ (Anemia, early satiety)	−	−	0.7	2.9
10	3.5	7	10	−	+	+	2.7	18.5
11	5	8	Significant***	+ (Abdominal discomfort)	+	+	2.2	67 +
12	2.4	8	0	+ (Pain)	+	+	16.5	16.5
13	9	5	Significant*	+ (Abdominal discomfort, portal hypertension)	−	−	0.3	0.3
14	2	10	4	+ (Early satiety, pain)	−	−	2.8	3.1

* Determined by each attending physician

** Spleen had decreased to one third of the initial size

*** Using computed tomography, spleen size measured in the long axis has changed from 28 cm before SI to 22 cm after SI

patients seem small. Therefore, it is important to be able to predict, before starting treatment, which patients might benefit from SI. Several prognostic scoring systems for PMF have been reported to be useful for predicting survival from any given point in time. DIPSS is one of these [15], and in our SI series, the median survival time after SI in the high-risk groups was 0.2 years, which was significantly shorter than that in intermediate-2 risk groups as 1.5 years. DIPSS high-risk patients at the time of SI would little benefit from SI.

The discovery of the *JAK2* mutation in MPNs led to the development of new class of drug, JAK inhibitors, for MF patients. Ruxolitinib, the first JAK inhibitor, has excellent efficacy against splenomegaly and symptoms of MF compared with placebo or the best available therapy [17–20]. Ruxolitinib is also expected to have a favorable impact on survival [21, 22]. Regarding the current treatment strategy for MF, it seems optimal to choose ruxolitinib therapy before SI for splenomegaly and its associated symptoms. In the future, SI may be chosen for patients who are resistant or intolerant to ruxolitinib.

In conclusion, SI provides excellent palliation for symptomatic splenomegaly associated with MF, and reduces spleen size in most patients. Is should be noted, however, that these responses are transient, and SI can cause potentially fatal complication. The use of prognostic models such as DIPSS may help us select patients who would benefit from SI.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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bjh research paper

Long-term outcome of patients with acquired chronic pure red cell aplasia (PRCA) following immunosuppressive therapy: a final report of the nationwide cohort study in 2004/2006 by the Japan PRCA collaborative study group

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Summary

Immunosuppressive therapy has been employed as the initial treatment for acquired chronic pure red cell aplasia (PRCA), such as idiopathic, thymoma-associated, or large granular lymphocyte (LGL) leukaemia-associated PRCA, which is thought to be immune-mediated. To explore the overall long-term outcome following immunosuppression and to identify the risk factors for death in these disorders, we conducted nationwide surveys in Japan 2004 and 2006, and identified a total of 185 patients with acquired chronic PRCA, including 72 idiopathic, 41 thymoma-associated and 14 LGL leukaemia-associated cases of PRCA for whom data was available. The present study evaluated 127 patients with these three subsets of PRCA. The median overall survival has not yet been reached in idiopathic PRCA. The estimated median overall survival times in patients with thymoma-associated and LGL leukaemia-associated PRCA were 142·1 and 147·8 months, respectively. Twenty-two deaths were reported, and the response to induction therapy and relapse of anaemia were found to be associated with death. The major causes of death were infection in seven patients and organ failure in another seven patients. The results suggest that maintenance therapy and the management of infectious complications are crucial for improving the prognosis of chronic PRCA.

Keywords: pure red cell aplasia, idiopathic, thymoma, large granular lymphocyte leukaemia, immunosuppressive therapy.

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Pure red cell aplasia (PRCA) is characterized by severe normochromic, normocytic anaemia associated with reticulocytopenia and absence of erythroblasts in otherwise normal bone marrow (Dessypris & Lipton, 2004). The acquired form of chronic PRCA may present as a primary haematological disorder in the absence of any other diseases or secondary to lymphoproliferative disorders, infections and collagen vascular diseases or after exposure to a wide variety of drugs or chemicals. Idiopathic PRCA and secondary PRCA not responding to the treatment of the underlying diseases are generally treated as an immune-mediated disorder (Krantz *et al*, 1973; Clark *et al*, 1984; Lacy *et al*, 1996; Go *et al*, 2001; Dessypris & Lipton, 2004).

We previously conducted nationwide surveys for adult-acquired chronic PRCA by sending questionnaires to haematology departments in Japan in 2004 and 2006. One-hundred and eighty-five patients were enrolled, and we reported the efficacy of immunosuppressive therapy in patients with idiopathic PRCA, thymoma-associated PRCA and large granular lymphocyte (LGL) leukaemia-associated PRCA (Sawada *et al*, 2007; Fujishima *et al*, 2008; Hirokawa *et al*, 2008). In these studies, we demonstrated that treatment containing ciclosporin is effective for inducing remission and preventing relapse in idiopathic PRCA and thymoma-associated PRCA, and that LGL leukaemia-associated PRCA shows a good response to either cyclophosphamide or ciclosporin, although it is not clear whether haematological responses can be maintained without continuation of immunosuppressive therapy (Sawada *et al*, 2007, 2008; Fujishima *et al*, 2008; Hirokawa *et al*, 2008).

We have also reported that the discontinuation of maintenance immunosuppressive therapy is associated with relapse of anaemia in patients with idiopathic PRCA (Sawada *et al*, 2007). Re-induction therapy is effective in some patients, but subsequent remission may not be achieved in other patients. It remains uncertain whether life-long immunosuppression is justified because of its adverse effects, such as opportunistic infections. In order to address this question, we have investigated the overall long-term response and outcome following immunosuppression in patients with idiopathic, thymoma-associated, or LGL leukaemia-associated PRCA, and identified the risk factors for death in these disorders using the PRCA patient cohort of 2004 and 2006.

Patients and methods

Patients

Surveys from 185 patients with chronic PRCA were collected from 45 institutions in Japan by the nationwide survey conducted by the PRCA collaborative study group in 2004 and 2006. Diagnoses of PRCA had been made between 1990 and 2006. Details of the procedure and eligibility criteria were described previously (Sawada *et al*, 2007; Fujishima *et al*, 2008; Hirokawa *et al*, 2008). The classification of PRCA was based on the criteria proposed by the Haematopoietic Organs Research Committee of the Ministry of Health, Labour and Welfare of Japan in 2005 (Sawada *et al*, 2007), which was fundamentally based on the criteria proposed by Dessypris and Lipton (2004).

Seventy-two patients with idiopathic PRCA, 41 with thymoma-associated PRCA, and 14 with LGL leukaemia-associated PRCA were included in the present study; patient characteristics are shown in Table I. The age of the patients at the onset of PRCA ranged from 18 to 89 years (median age, 62 years) and there was a 51:76 male to female ratio of

Table I. Patient characteristics.

	Idiopathic PCRA	Thymoma-associated PCRA	LGL leukaemia-associated PCRA
Number of patients	72	41	14
Age, years: median (range)	60·5 (18·0–89·0)	65·0 (27·0–82·0)	63·0 (44·0–85·0)
Gender: male/female	25/47	18/23	8/8
Response to induction therapy			
CR/PR	25/36	24/3	5/8
NR	9	8	1
Not evaluable	2	6	
Outcome			
Alive	58	32	12
Dead	13	7	2
Unknown	1	2	
Observational period, months: median (range)	86·8 (0·5–274·3)	61·4 (3·1–178·5)	104·0 (7·7–157·2)
Cause of death			
Organ failure	5 (2 liver, 1 cardiac, 1 renal, 1 NOS)	1 (cardiac)	1 (NOS)
Infection	1 (marrow failure)	5 (4 pneumonia, 1 CMV)	1 (ATG-associated)
Malignancy	2 (1 lymphoma, 1 myelofibrosis)	1 (thymoma)	
Cerebral infarction	1		
Diabetes mellitus	1		
Unknown	3		

LGL, large granular lymphocyte; PRCA, pure red cell aplasia; CR, complete remission; PR, partial remission; NR, no response; NOS, not otherwise specified; CMV, cytomegalovirus; ATG, anti-thymocyte globulin.

cases. The last questionnaires for 109 patients, excluding the patients who had already died or had been lost to follow-up at the previous analysis, were sent to the institutions in December 2012 for collection of data on relapse, subsequent treatment and efficacy, iron chelation therapy, transformation to some other form of haematological disorder and outcome. The median observation period of this patient cohort was 87·6 months (range: 0·5–274·3 months).

This study was approved by the institutional review board, and performed according to the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan.

Definition of responses and data analysis

Definitions of the haematological responses to immunosuppressive therapy were previously described (Sawada *et al*, 2007; Fujishima *et al*, 2008; Hirokawa *et al*, 2008). Briefly, complete remission (CR), partial remission (PR) and no response (NR) were defined as the achievement of normal haemoglobin levels without transfusion, the presence of anaemia but without transfusion dependence, and continued dependence on transfusions, respectively. The date of remission was defined as that of the final transfusion after the initiation of remission induction therapy. The minimum period required before evaluation of response to agents was set at 2 weeks. The agent for maintenance therapy was defined as that used or tapered off after successful induction of remission. Relapse was defined as new requirement for transfusion.

All statistical analysis was performed using PASW Statistics 18 (SPSS, Tokyo, Japan). Survival time was estimated using the Kaplan–Meier method, and comparison between two groups was made by the log-rank test (Kaplan & Meier, 1958). Given that treatment response and relapse following successful treatment are time-dependent covariates, comparisons of survival time according to these categories were made using the Mantel-Byar method (Anderson et al, 1983; Mi et al, 2013). As the patients were alive during the time between diagnosis and the date that treatment response obtained, we classified those patients as NR until the date of achieving remission, and the subsequent follow-up time was classified as the survival time for the patients in response. The time between the date of treatment response and relapse of anaemia was also considered to be a guarantee time, and we analysed the survival time in patients who remained in remission and those in relapse of anaemia according to the Mantel-Byar method. Comparison of parametric data was made with non-paired two-tailed *t*-tests after the equality of variance was determined by Levene's test. Comparison of categorical data was made with Person's chi-square test, unless otherwise stated. Multivariate analyses were performed using the multiple logistic regression model. The statistical significance level of the tests was 5% in the present study.

Results

Overall survival

The median overall survival has not yet been reached in patients with idiopathic PRCA. The mean survival time of