Received: 23 November 2023 | Revised: 11 January 2024 | Accepted: 31 January 2024

DOI: 10.1002/ajh.27252

RESEARCH ARTICLE

AJH WILEY

Splenic irradiation for myelofibrosis prior to hematopoietic cell transplantation: A global collaborative analysis

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Abstract

Splenomegaly is the clinical hallmark of myelofibrosis. Splenomegaly at the time of allogeneic hematopoietic cell transplantation (HCT) is associated with graft failure and poor graft function. Strategies to reduce spleen size before HCT especially after

failure to Janus kinase (JAK) inhibition represent unmet clinical needs in the field. Here, we leveraged a global collaboration to investigate the safety and efficacy of splenic irradiation as part of the HCT platform for patients with myelofibrosis. We included 59 patients, receiving irradiation within a median of 2 weeks (range, 0.9–12 weeks) before HCT. Overall, the median spleen size prior to irradiation was 23 cm (range, 14–35). Splenic irradiation resulted in a significant and rapid spleen size reduction in 97% of patients (57/59), with a median decrease of 5.0 cm (95% confidence interval, 4.1–6.3 cm). The most frequent adverse event was thrombocytopenia, with no correlation between irradiation dose and hematological toxicities. The 3-year overall survival was 62% (95% CI, 48%–76%) and 1-year non-relapse mortality was 26% (95% CI, 14%–38%). Independent predictors for survival were severe thrombocytopenia and anemia before irradiation, transplant-specific risk score, higher-intensity conditioning, and present portal vein thrombosis. When using a propensity score matching adjusted for common confounders, splenic irradiation was associated with significantly reduced relapse ($p = .01$), showing a 3-year incidence of 12% for splenic irradiation versus 29% for patients with immediate HCT and 38% for patients receiving splenectomy. In conclusion, splenic irradiation immediately before HCT is a reasonable approach in patients experiencing JAK inhibition failure and is associated with a low incidence of relapse.

1 | INTRODUCTION

Splenomegaly is the clinical hallmark of myeloproliferative neoplasms (MPN).[1,2] Massive splenomegaly is particularly pervasive in patients with myelofibrosis, with 38% of cases having a palpable spleen at least 10 centimeters (cm) below the left costal margin (LCM) and 23% with a spleen extending more than 16 cm.[1,3] Mechanisms underlying this observed clinical manifestation are primarily explained by the occurrence of extramedullary hematopoiesis in progressively fibrotic bone marrows of patients with MPNs.

Janus kinase (JAK) inhibitors and novel agents have shown promising reduction of spleen size in newly diagnosed myelofibrosis.[4–6] However, not all patients will respond, or they eventually progress at some point in their disease course. Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative treatment option,[7] and the numbers of patients eligible for HCT continue to increase worldwide. However, this procedure is associated with relevant morbidity and mortality, posing a particular challenge for patients with significant splenomegaly, who often present with severe symptom burden and resulting biological complications such as anemia or thrombocytopenia. Furthermore, splenomegaly, and in particular massive splenomegaly, is associated with graft failure, poor graft function, and is thought to be associated with an increased risk of relapse after HCT.[8–10] Therefore, strategies to reduce spleen size before HCT in addition to JAK inhibitors represent unmet clinical needs in the field. One approach to reduce spleen size prior to HCT could be splenic irradiation.[3] However, evidence on its role remains scarce, with only single-center experiences of very few patients being reported over the last decade. Main unknowns for splenic irradiation as part of the HCT sequence are efficacy, optimal dose, actual toxicities, as well as factors influencing the outcome of that procedure. Particularly, clinicians have always been reluctant to irradiate massive spleens because of the risk of hemorrhagic complications.

Here, we took advantage of a global collaboration to investigate the role of splenic irradiation as part of the HCT platform for patients with myelofibrosis. We described detailed characteristics, safety, and efficacy of patients receiving splenic irradiation. To determine the role of splenic irradiation, we then compared its efficacy with patients with splenomegaly receiving immediate HCT or those receiving splenectomy in match-adjusted fashion.

2 | METHODS

2.1 | Data collection

We retrospectively collected data from patients with primary myelofibrosis (PMF), post polycythemia vera, and post-essential thrombocythemia myelofibrosis (PPV MF and PET MF) receiving splenic irradiation as part of the HCT algorithm. Patients with secondary acute leukemia at the time of SI were excluded. Radiation therapy had to be given within 3 months prior to or be part of conditioning therapy for HCT. Detailed information on irradiation was collected in addition to usual patient-, disease-, and transplant-related variables. Disease-specific characteristics included diagnosis, presence of portal vein thrombosis,[11] any thrombosis, cytology counts, Dynamic

International Prognostic Scoring System (DIPSS) score,[12] Myelofibrosis Transplant Scoring System (MTSS, calculated at time of HCT for splenectomy and immediate HCT and before irradiation.),[13] prior JAK inhibitor treatment (if any), other therapies, and somatic mutations. These included driver mutations (*JAK2*, *MPL*, and *CALR*), as well as other mutations, including *ASXL1*.

Irradiation-specific variables included: spleen size before irradiation, after irradiation/before the start of conditioning, and after HCT; measurement technology (physical, ultrasound, computed tomography); date of irradiation; fractionation; total dose; and irradiation technology. Safety variables included: blood counts before and after irradiation, as well as at days 50 and 100 after HCT; development of veno-occlusive disease (VOD) or thrombotic microangiopathy (TMA) after HCT; necessity of red blood cell (RBC) or platelet transfusions after irradiation and after HCT; other acute toxicities after irradiation (such as infections, abdominal pain etc.).

2.2 | Statistical analysis

Primary outcomes were spleen size reduction and safety after irradiation. Other outcomes were days until neutrophil engraftment, days until platelet engraftment, relapse incidence, non-relapse mortality, and overall survival. Neutrophil engraftment was defined as the first of 3 consecutive days of achieving a sustained peripheral blood neutrophil count of $>0.5 \times 10^9$/L and platelet engraftment was defined as independence from platelet transfusion for at least 7 days with a platelet count of more than $>20 \times 10^9$/L. Primary graft failure was defined by an absolute neutrophil count $<0.5 \times 10^9$/L by day +28 following stem cell infusion, hemoglobin <8 g/dL, and platelets $<20 \times 10^9$/L.

Descriptive statistics for continuous variables were computed by means of Mann–Whitney test. Categorical variables were compared using the Chi-squared method. Binary logistic regression was used to determine the effects of spleen characteristics on status variables (such as engraftment). Kaplan–Meier estimates were used for calculating survival probabilities, while probabilities of non-relapse mortality, relapse, and incidence of acute and chronic graft-versus-host disease (GVHD) were assessed using the cumulative incidence function, taking competing risks into account. For the development of GVHD, events of relapse and death without relapse were competing events. For outcome of relapse, death without relapse was the competing event. For non-relapse mortality, relapse was the competing event. For multivariate survival analysis, Cox modeling was applied and for competing risks, the model of Fine and Gray was used.

To minimize selection bias and enable a more representative comparison in terms of outcomes after irradiation, a matched-pair analysis of patients with splenomegaly who received irradiation versus no therapy (immediate HCT) versus splenectomy was designed. Patients were matched according to transplant-specific risk (MTSS), using a greedy caliper algorithm.

Variables with a p-value of <.05 were considered significant. All analyses were done with R statistical software version 4.0.5.

3 | RESULTS

3.1 | Patients

This global collaborative study included 59 patients, of whom 71% had PMF, 17% PPV, and 12% PET MF. Median age at HCT was 59 years (range, 32–76 years). Risk category according to DIPSS prior to irradiation was low in 3%, intermediate-1 in 22%, intermediate-2 in 44%, and high in 31%. Driver mutation status was *JAK2* in 44%, *CALR* in 40%, and *MPL* in 3%. Seven patients (12%) had portal vein thrombosis (PVT) before irradiation. Ruxolitinib before irradiation was received by 75% of our cohort whereas 5% were exposed to fedratinib. Two-thirds of patients received reduced-intensity conditioning HCT and 59% of patients were allografted from a matched unrelated donor. (Table 1).

3.2 | Spleen and irradiation characteristics and efficacy

Median time from irradiation to HCT was 2 weeks (range, 0.9–12 weeks) and median spleen size prior to irradiation was 23 cm (range, 14–35). Overall, 24 patients (41%) received irradiation in 1 week prior to HCT, meaning as direct part of conditioning. Spleen size was measured mainly by ultrasound (in 75% of patients). Notable, spleen size did not correlate with blood counts prior or after irradiation.

The median total irradiation dose was 7 Gy (range, 3–12), fractionated in a median of 5 administrations (range, 2–12). Most patients (47%) received involved-field radiation therapy, 22% received helical tomotherapy or volumetric modulated arc therapy, 13% received 3d conformal radiation therapy, and the remaining received other forms of radiotherapy.

Splenic irradiation resulted in a significant and rapid spleen reduction in 97% of patients. The median spleen size reduction was 5.0 cm (95% confidence interval, 4.1–6.3 cm), and there was no significant correlation between spleen size prior to irradiation and absolute spleen reduction ($R = 0.27$, $p = .26$), meaning that larger spleens appeared to benefit from irradiation in a similar fashion to smaller spleens (Table 2). Furthermore, no correlation was found between the total dose and the amount of spleen size reduction ($R = 0.24$; $p = 0.34$; Figure 1). However, patients with ruxolitinib exposure showed higher absolute spleen size reduction (median, 5.0 vs. 2.8 cm; Figure 1), which was not statistically significant ($p = .64$).

3.3 | Safety

Splenic irradiation resulted in a significant decrease in platelet counts from a median of 92×10^9/L (range, 8–722) prior to irradiation to 45×10^9/L (range, 2–400) after irradiation and before the start of HCT conditioning. The median drop of platelets was 50×10^9/L (95% confidence interval, 34–80). Higher platelet

TABLE 1 Patient and treatment characteristics.

Characteristic	Total cohort ($n = 59$)
Age, median (range)	59 (32–76)
Diagnosis at HCT, *n* (%)	
PMF	42 (71)
PET MF	7 (12)
PPV MF	10 (17)
Karnofsky performance status, *n* (%)	
<90%	23 (39)
90%–100%	36 (61)
DIPSS, *n* (%)	
Low	2 (3)
Intermediate-1	13 (22)
Intermediate-2	26 (44)
High	18 (31)
Constitutional symptoms, *n* (%)	37 (63)
Driver mutation, *n* (%)	
CALR	24 (41)
JAK2	26 (44)
MPL	2 (3)
***ASXL1*, *n* (%)**	16 (27)
JAKi exposure, *n* (%)	
Ruxolitinib	44 (75)
Fedratinib	3 (5)
Any thrombosis prior SI, *n* (%)	8 (13)
PVT prior SI, *n* (%)	7 (12)
HLA-match, *n* (%)	
Matched related	14 (24)
Matched unrelated	35 (59)
Mismatched related (haplo)	7 (12)
Mismatched unrelated	3 (5)
Conditioning intensity, *n* (%)	
Reduced	39 (66)
Myeloablative	20 (34)
Time between SI and HCT in weeks, median (range)	2 (0.9–12)
Spleen size measurement	
Physical examination	6 (10)
Ultrasound	44 (75)
Computed tomography	9 (15)
Total dose in Gy, median (range)	7 (3–12)
Fractionation, median (range)	5 (2–15)

counts prior to irradiation correlated with higher counts after irradiation ($r = 0.83$; $p < .001$).

Splenic irradiation resulted also in a significant decrease of leukocytes from a median of 9.5 $\times 10^9$/L (range, 0.1–163.8) to 2.2 $\times 10^9$/L (range, <0.1–55) after irradiation (Table 2). The median drop in leukocytes was 6.4 $\times 10^9$/L. No significant reduction in hemoglobin was observed after irradiation. There was no correlation between irradiation dose and post-irradiation hematological toxicities (Figure 1).

TABLE 2 Efficacy and hemotological toxicity after irradiation.

Characteristic	Pre-irradiation	Post-irradiation/ pre-HSCT	*p*
Spleen size, cm	23 (14–35)	18 (10–29)	.04
Hb, g/dL	8.9 (6.2–13.7)	8.5 (9.0–13.0)	.43
Platelets, $\times 10^9$/L	92 (8–722)	39 (2–400)	.03
Leukocytes, $\times 10^9$/L	9.5 (0.1–163.8)	2.2 (0.1–55)	.03

Only 3 patients had non-hematological adverse events. One patient developed tumor lysis syndrome, which could be controlled to proceed with HCT. Notably, this patient had the highest reduction of spleen size (10 cm, from 32 before to 22 cm after irradiation). Two patients experienced abdominal pain while undergoing irradiation, which was successfully controlled with supportive care and analgesics. Notably, no hemorrhagic complications were registered.

3.4 | Transplant outcomes

Neutrophil engraftment was achieved by 92% within a median of 18 days (range, 11–48 days) after HCT, and platelet engraftment was achieved by 48 patients (81%) within a median of 34 days (**Supplemental Figure 1S**). Patients with severe thrombocytopenia (<50 $\times 10^9$/L) before irradiation showed higher likelihood of graft failure ($p = .07$) and experienced delayed platelet engraftment within a median of 54 days. No other factors on neutrophil or platelet engraftment were identified.

Three patients (5%) developed VOD after HCT after 3 days, 6 days, and late-onset after 31 days, respectively. Both patients with early post-transplant VOD died within 1.2 and 3.6 months after HCT. The patient with late-onset VOD was successfully treated with defibrotide and is disease-free and alive at the last follow-up after 9 months from HCT. No association with total dose and development of VOD was observed, with the 3 cases receiving 5, 6, and 7 Gy, respectively. There was no case of TMA after HCT in the total cohort.

With a median follow-up of 2.7 years (95% confidence interval, 1.7–3.6 years), the 3-year overall survival was 62% (95% CI, 48%–76%). Non-relapse mortality after 1 year was 26% (95% CI, 14%–38%) and cumulative incidence of relapse after 3 years was 13% (95% CI, 3%–22%). Incidence of acute GVHD grade II–IV and chronic GVHD was 25% and 38%, respectively.

3.5 | Impact on transplant outcomes

The complete univariate analysis on survival with cause-specific hazards is shown in **Supplemental Table 1S**. Increased spleen size prior to

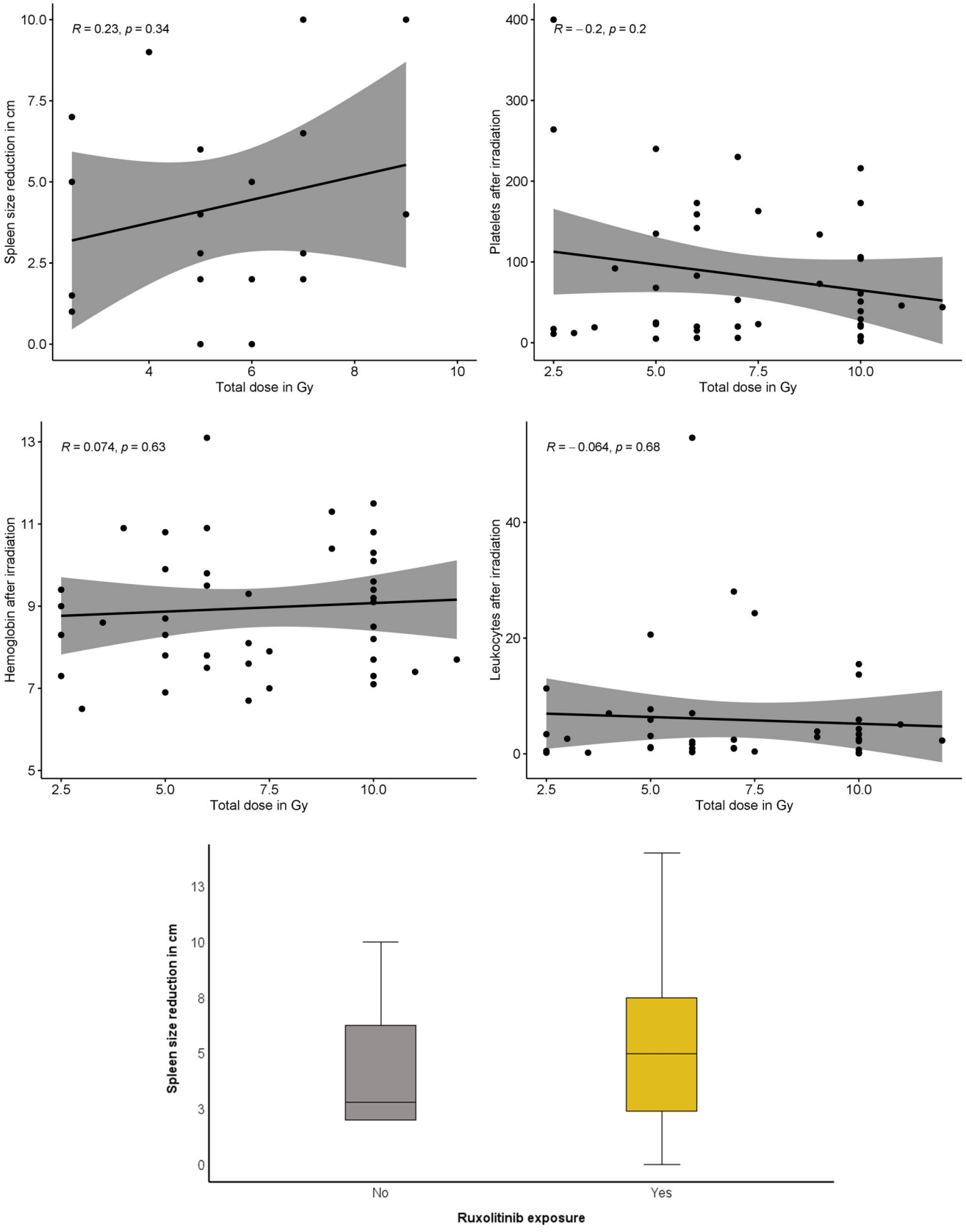

FIGURE 1 Impact of irradiation dose on efficacy and hematological toxicity. [Color figure can be viewed at wileyonlinelibrary.com]

irradiation seemed to have a trend of association with graft failure ($p = .10$) whereas was not significantly associated with worse survival (hazard ratio, 1.06; 95% confidence interval, 0.98–1.16; $p = .16$), nor with non-relapse mortality or relapse incidence. However, further diving into massive splenomegaly by dividing spleen size prior to irradiation into <30 versus ≥30 cm showed 3-year survival of 73% versus 41% ($p = .01$), and non-relapse mortality of 14% versus 58%, respectively ($p = .02$). Furthermore, those patients with massive splenomegaly had markedly lower platelet counts (median, 31 vs. 98 $\times 10^9$/L) and more severe anemia (median, 8.1 vs. 9.4 g/dL) at the time of splenic irradiation. No effect of spleen size after irradiation, total administered dose, or radiotherapy technology on outcomes was observed.

In terms of blood counts, hemoglobin level before irradiation was also associated with survival ($p = .02$), showing a hazard ratio of 0.71 (95% CI, 0.53–0.94). In particular, hemoglobin >10 g/dL associated with a significantly better 3-year OS of 84% (95% CI, 66–100%) vs. 48% (95% confidence interval, 29%–67%) in cases with hemoglobin ≤10 g/dL ($p = .01$). While platelet count did not significantly associate with outcome when investigated as a continuous variable, severe thrombocytopenia of <50 $\times 10^9$/L before irradiation showed significantly worse 3-year OS of 46% (95% CI, 22%–70%) versus 71% (95% CI, 55%–87%) for cases with ≥50 $\times 10^9$/L platelets ($p = .01$).

In addition, the presence of PVT before irradiation was significantly associated with worse survival ($p = .01$), showing a hazard ratio of 3.32 (95% CI, 1.30–8.51; **Supplemental Figure 2S**). This was almost exclusively driven by increased risk of non-relapse mortality ($p = .01$), showing a hazard ratio of 3.26 (95% CI, 1.29–8.24). Portal vein thrombosis did not seem to be associated with response to irradiation (median spleen size reduction, 5.0 vs. 4.5 cm) nor with spleen size prior to irradiation (median, 23 vs. 22 cm).

In terms of transplant-specific variables, we found no impact of donor type on post-transplant survival ($p = .87$). However, there was a significant difference in outcome according to intensity of conditioning, showing 3-year OS of 71% for reduced intensity versus 37% for higher-intensity conditioning ($p = .03$; **Supplemental Figure 2S**). There was also no significant difference in outcome of ATG versus no ATG for GVHD prophylaxis ($p = .94$).

We then tried to validate the MTSS (incorporating age, performance status, driver mutations, *ASXL1*, donor type, and platelet and leukocyte counts) in this cohort of patients. An increase in MTSS score was significantly associated with an increased risk of death (hazard ratio, 1.77; 95% confidence interval, 1.11–2.79; $p = .01$). Furthermore, applying the MTSS to this small cohort of 59 patients, we could adequately distinguish between lower risk (low and intermediate risk group) and higher risk groups (high and very high-risk group), showing 3-year OS of 72% (95% CI, 57%–87%) versus 38% (CI, 12%–63%; $p < .001$; **Supplemental Figure 2S**).[13]

A multivariable model on OS confirmed predictive parameters, showing independent effects for worse outcome of severe anemia (hazard ratio, 3.73; 95% CI, 1.08–12.88; $p = .04$), severe thrombocytopenia (hazard ratio, 2.58; 95% CI, 1.00–6.78; $p = .05$), higher MTSS score (hazard ratio, 1.61; 95% CI, 1.00–2.66; $p = .05$), higher-intensity conditioning (hazard ratio, 3.52; 95% CI, 1.34–9.23; $p = .01$), and PVT (hazard ratio, 1.44; 95% CI, 1.57–11.45; $p = .004$).

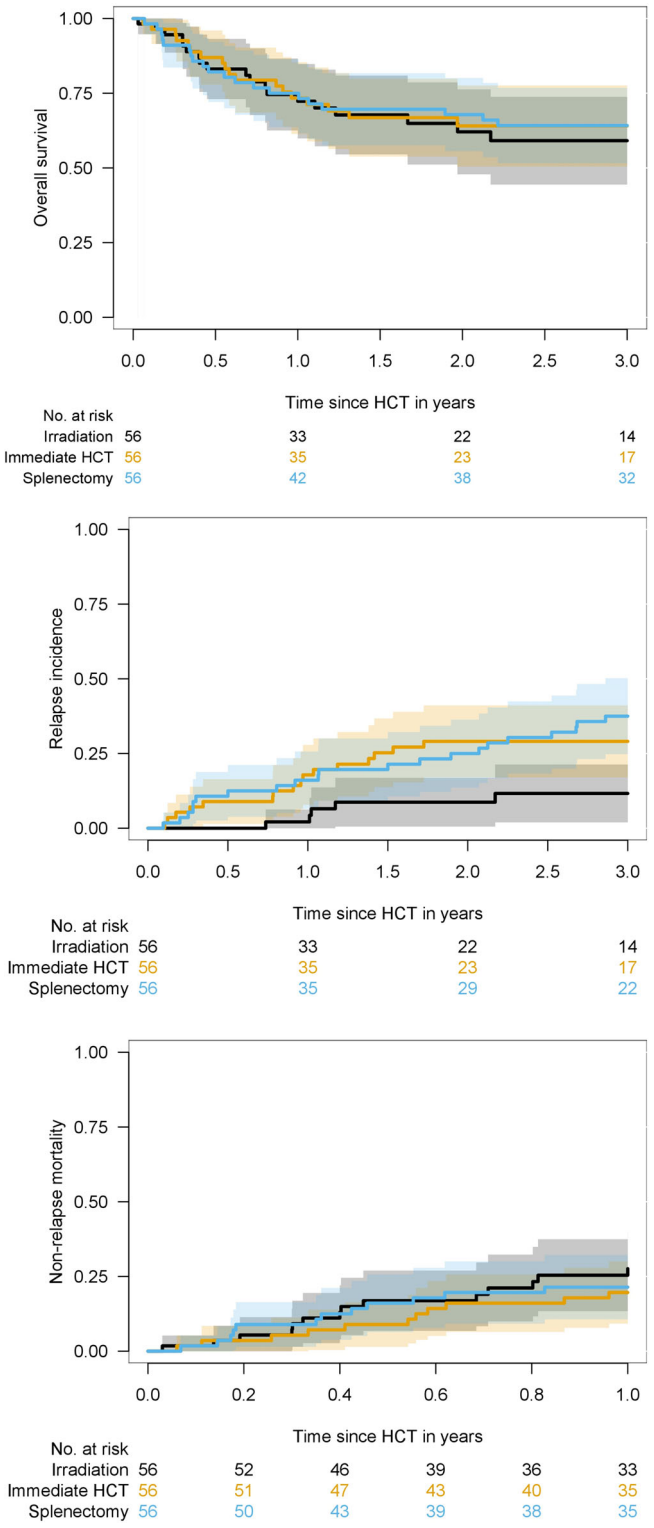

FIGURE 2 Matched comparison of splenic irradiation, immediate hematopoietic cell transplantation (HCT), and splenectomy. [Color figure can be viewed at wileyonlinelibrary.com]

In this model, increased spleen size prior to irradiation was not significantly associated with increased risk of death (continuous hazard ratio, 1.06; 95% CI, 0.97–1.16; $p = .22$).

3.6 | Matched comparison of patients according to transplant-specific risk

We then use a propensity score matching strategy to compare the cohort of irradiated patients with patients with splenomegaly without intervention (immediate HCT) and those who received splenectomy. Matching was done according to their transplant-specific risk (MTSS; **Supplemental Table 2S**). Median spleen size of patients receiving immediate HCT was 20 cm (range, 16–36 cm), which was significantly different from irradiated patients (median, 23 cm; $p = .004$). Distribution according to MTSS lower or higher risk was 75% and 25% for irradiated and 78% and 22% for patients with immediate HCT, and 68% and 32% for patients with splenectomy ($p = .56$). The MTSS was predictive for survival in all three groups ($p = .01$ and .01 and .04, respectively).

Comparing the three groups, neutrophil engraftment was achieved by 92% and 81% for splenic irradiation, 96% and 85% for immediate HCT, and 89% and 79% for splenectomy ($p = .22$ and .31, respectively). The 3-year overall survival was similar ($p = .86$), showing rates of 61%, 63%, and 62%, respectively (Figure 2). There was also no significant difference in non-relapse mortality ($p = .38$). However, splenic irradiation was associated with significantly reduced relapse incidence ($p = .01$), showing 3-year incidence of 12% (95% CI, 2%–21%) for irradiated versus 29% (95% CI, 17%–41%) for patients with immediate HCT versus 38% (95% CI, 25%–50%) for patients receiving splenectomy (Figure 2).

4 | DISCUSSION

This is the first international and largest study to date on splenic irradiation as part of the HCT algorithm for patients with myelofibrosis and splenomegaly. We showed a significant spleen size reduction immediately after irradiation, and most patients developed thrombocytopenia and leukopenia. We showed feasibility of this procedure in terms of safety, survival, and non-relapse mortality, which was comparable to that of non-irradiated patients. Notably, relapse incidence was significantly reduced in irradiated patients compared with patients undergoing immediate HCT and those who received splenectomy. Independent predictors of worse outcomes in patients with splenic irradiation were severe thrombocytopenia and anemia, higher MTSS, PVT, and higher-intensity conditioning therapy before HCT.

Data concerning the mechanism of action of ionizing radiation in myelofibrosis patients with splenomegaly remains scarce. Preliminary examinations of circulating cells in myelofibrosis treated with splenic irradiation found that it may lead to the depletion of splenic myeloid progenitor cells.[1] Small reports suggested that splenic irradiation can achieve a transient spleen size reduction in most patients, which furthermore accompanies improvement in disease-related symptom burden.[3,14,15] However, hematological side effects can be severe with rapid development of severe thrombocytopenia and anemia, while, in addition, partial liver irradiation may not be avoidable, potentially increasing the risk of post-transplant liver toxicity.[16] Our data clearly showed the hematotoxic effect of splenic irradiation, showing drops in platelets and leukocytes across patients after irradiation/before the start of HCT conditioning. However, we did not observe any irradiation-related acute toxicities or deaths in our large case series. We showed a 5% incidence (3 patients) of VOD after HCT, which was not associated with total irradiation dose. This may suggest that early HCT after irradiation may enable mitigation of the cytopenic effect of radiotherapy.

Splenomegaly at the time of HCT is associated with graft failure and poor graft function,[9,17] and may be associated with post-transplant relapse,[8,18] but no studies to date have systematically evaluated comparisons of different interventions to reduce spleen size as part of the HCT platform. First-line treatment for such patients is JAK inhibition (mostly ruxolitinib), while new JAK inhibitors have been recently approved specifically for thrombocytopenic and anemic patients.[5,19] Spleen size per se did not impact the benefit derived by the irradiation procedure. However, massive splenomegaly, which was associated with severe thrombocytopenia and anemia before irradiation, correlated with worse survival and larger spleen size also after HCT (Supplemental Figure 3S), suggesting that irradiation can likely be effective in patients with moderate but not massive splenomegaly. However, although patients with massive splenomegaly had more frequently severe thrombocytopenia, comparison with moderate splenomegaly was not statistically significant, and larger case series are needed to determine the effect of irradiation in this cohort. Remarkably, we clearly observed that engraftment, overall survival, and non-relapse mortality were similar to that of general myelofibrosis populations undergoing HCT.[20–23] We showed remarkable absolute spleen size reduction within a short period of time during splenic irradiation and before the start of pre-HCT conditioning, which was independent of initial spleen size. Although we did not find a correlation between spleen changes upon irradiation and post-transplant outcomes, a reduction of the spleen size may enable symptom relief, especially in massive splenomegaly, a finding that warrants evaluation in future studies with larger sample sizes.

Splenectomy may be another option for patients with massive splenomegaly and significant symptom burden but is also associated with higher relapse incidence when compared with patients without splenectomy.[18,24] Crude comparisons of the splenic irradiation cohort analyzed here with published cohorts undergoing splenectomy suggest significantly reduced relapse incidence in patients receiving irradiation (3-year incidence 13% vs. 30%–40% for patients with splenectomy).[18,24,25] We took advantage of a large multicenter cohort and matched comparison to analyze irradiated patients in a controlled fashion with those who had splenomegaly but underwent immediate

HCT and those who received splenectomy, finding similar survival outcomes but significantly reduced relapse rates for splenic irradiation. These results are in line with findings for JAK inhibitors,[26–30] where response to treatment was significantly associated with reduced relapse rates, pointing towards a crucial role of the spleen within the disease environment, whereby removal of the spleen might not change progressive nature of underlying biology of the patients with massive splenomegaly.[31] On the other hand, increased risk for relapse in patients with splenectomy might rather reflect the onset of more progressive disease of such patients. Although we did not find significant differences as to disease risk based on current prognostic tools between the patient's groups undergoing the various interventions, outcome prediction post-transplant in MF is from being precise. In line with this, we cannot rule out biological differences not accounted for in current prognostication models between splenectomized and irradiated patients.

The optimal dosing for splenic irradiation is still poorly defined and often depends on the baseline hematologic parameters and local experience. The dose fractionation schedule used in hematological patients with splenomegaly varies widely, and a wide range of total doses has been reported (starting from 0.15 Gy to over 30 Gy). The most frequent schedule in our cohort consisted of 5–10 Gy delivered in 1–2 Gy fraction daily. We did not observe a significant effect of total dose or number of fractions on efficacy and safety. Thus, it may be recommended that high doses could be avoided while achieving the same outcomes.

As responses are rapid but non-durable, the conditioning regimen should be initiated promptly after completion of radiotherapy to benefit from maximum spleen volume reduction. This might overcome the onset higher risk for graft failure for patients with splenomegaly, and indeed we found comparable engraftment rates compared with normal populations (91%).[32] Moreover, early HCT allows for mitigation of the cytopenic effect of radiotherapy. This is particularly important, as we identified severe thrombocytopenia and anemia as independent predictors for worse survival. Furthermore, with splenic irradiation being part of the HCT algorithm, this might help risk stratify patients and thus counsel patients, in line with current consensus.[7]

In terms of procedure-related factors with respect to HCT itself, to date, no significant difference in outcome has been shown for the comparison of different conditioning intensities.[33,34] These results were irrespective of underlying disease or molecular features.[33,35,36] We found here, that patients receiving higher-intensity conditioning after splenic irradiation showed significantly worse outcomes after HCT. This was despite the fact, that patients receiving higher-intensity regimens were significantly younger (median, 57 years) compared with patients who received reduced-intensity conditioning (median, 61 years). These results may caution the application of higher-intensity treatment in such a vulnerable population with severe disease burden and frailty, irrespective of age.[37,38]

We acknowledge several limitations, which are mainly due to the retrospective nature of our study. We cannot fully exclude the selection bias of patients receiving splenic irradiation. Only patients fit enough for irradiation and subsequent HCT might have been included, and we did not collect information on whether patients were planned for that treatment but subsequently dropped out due to progressive disease, death or other causes. We applied multivariable modeling to account for possible confounders, finding 5 independent predictors of survival. This might lead to overinterpretation of certain effects in such a limited number of patients and should be interpreted with caution. Duration of JAK inhibition exposure before irradiation was not available in most patients and we could not evaluate its influence on overall outcomes. Furthermore, by matching patients according to their transplant-specific risk, and as the MTSS score was predictive in both the irradiated and non-irradiated cohort, we aimed to minimize potential selection and therefore reporting bias. Despite this, we cannot fully exclude the possibility of selection bias and other confounding factors in the comparison between splenic irradiation and other cohorts, as seen when comparing spleen sizes between patients who received the intervention (irradiation or splenectomy) and those who did not. However, rates of overall survival and relapse for patients with splenomegaly and no intervention or splenectomy appeared to be in line with previous reports. We did not have information on post-HCT spleen size for patients who received immediate HCT, limiting interpretations on spleen outcomes compared with cases receiving splenic irradiation. Furthermore, the median follow-up was 3 years, whereas, in most myelofibrosis HCT studies, follow-up of at least 5 years is reported, limiting interpretation of long-term outcomes of irradiation followed by HCT in this specific patient population. Last, while outcomes appeared to be similar across centers (irrespective of center size or region), we cannot exclude a heterogeneous policy in deciding for splenectomy versus irradiation inherent to multicenter case series of rare disease settings.

In conclusion, this first collaborative study on splenic irradiation followed by HCT myelofibrosis suggests splenic irradiation as a reasonable approach in patients with splenomegaly and JAK inhibition failure. Irradiation was associated with significantly reduced relapse after HCT. In terms of safety, while cytopenias were frequent after irradiation, there was no direct correlation between total irradiation dose and safety as well as efficacy, thus suggesting that high doses could be avoided.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

No funding received.

CONFLICT OF INTEREST STATEMENT

Nothing to disclose related to this work.

DATA AVAILABILITY STATEMENT

Original data may be received upon reasonable request to the corresponding author via e-mail

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gagelmann N, Hobbs GS, Campodonico E, et al. Splenic irradiation for myelofibrosis prior to hematopoietic cell transplantation: A global collaborative analysis. *Am J Hematol*. 2024;99(5):844-853. doi:10.1002/ajh.27252