Low-dose Splenic Irradiation in Conjunction With Ruxolitinib to Provide Symptomatic Relief in Heavily Treated, Advanced Stage Myelofibrosis: A Case Series From a UK Tertiary Referral Center

Alesia Khan1,2, Claire Woodley1, Deepti Radia1, George N. Mikhaeel3, Jessica Brady3, Natalia Curto Garcia1, Patrick Harrington1, Jennifer O’Sullivan1, Shahram Kordasti1,2, Yvonne Francis1, Susan Asirvatham1, Sahra Ali1, Priya Sriskandarajah1, Jamie Saunders1, Hugues de Lavallade1, Donal P. McLornan1, Claire N. Harrison1

Correspondence: Claire N. Harrison (claire.harrison@gstt.nhs.uk).

Progressive splenomegaly is a common characteristic of advancing myelofibrosis (MF). The use of ruxolitinib (Novartis Pharmaceuticals, Basel, Switzerland) has significantly improved the management of symptomatic splenomegaly as well as prolonging survival for many patients. However, effective treatment can be impacted by dose-limiting cytopenia, and ruxolitinib resistance or intolerance. For patients experiencing debilitating splenomegaly despite conventional or novel agents, management strategies remain challenging. We hereby review 4 patient scenarios (Table 1), narratives below, detailing use of low-dose splenic radiotherapy (LDSR) in addition to ruxolitinib continuation and will discuss potential limitations and implications.

Case 1: A 57-year-old female initially presented in August 2012 with primary MF (PMF) and palpable spleen length of 12 cm (longitudinal) below left costal margin (BCM). She was classified as high risk as per the Dynamic International Prognostic Scoring System (DIPSS). Initial therapy was hydroxycarbamide, leading to a reduction in spleen length to 13 cm via ultrasound, and subsequently she enrolled on the phase II ROBUST study evaluating the efficacy of single-agent ruxolitinib. She achieved a partial symptom response but therapy ceased after 7 months following dose-limiting cytopenia and ruxolitinib resistance or intolerance. For patients experiencing debilitating splenomegaly despite conventional or novel agents, management strategies remain challenging. We hereby review 4 patient scenarios (Table 1), narratives below, detailing use of low-dose splenic radiotherapy (LDSR) in addition to ruxolitinib continuation and will discuss potential limitations and implications. Further radiotherapy was administered alongside. Considerable clinical improvement in the splenomegaly and splenic pain was achieved for 10 months. He then demonstrated progressive, symptomatic splenomegaly, with an increase in splenomegaly to 29 cm BCM. The spleen had gradually increased to 25 cm with worsening constitutional symptoms despite optimized dosing density. Four cycles of low-dose cytarabine were administered with minimal response, with an increase in splenomegaly to 29 cm BCM. The patient subsequently received splenic radiotherapy. A total of 3 Gy was delivered, in 2 fractions of 1 and 2 Gy, respectively, with a 2-week gap between treatments. Ruxolitinib 25 mg BD was administered alongside. Considerable clinical improvement in the splenomegaly and splenic pain was achieved for 10 months. He then demonstrated progressive, symptomatic splenomegaly, so received further radiotherapy (1.5 Gy in 3 fractions over 6 weeks) but with little benefit. He unfortunately demonstrated progressive disease and died 6 months following the last treatment.

Case 3: A 67-year-old male with DIPSS high-risk MF and bulky splenomegaly (15 cm palpable BCM) enrolled in the phase II Harmony trial and commenced ruxolitinib 15 mg and buparlisib 60 mg both twice daily. After 7 weeks on therapy, he demonstrated an excellent spleen response (spleen palpable 2 cm BCM). Unfortunately, by week 17, his spleen returned to baseline. Two months later, he withdrew from the trial, and despite ruxolitinib dose escalation, he had marked splenic progression. Initially, planned for 8 Gy radiotherapy, he received a total of 6 Gy, given in 3 fractions over 3 weeks, with a 50% reduction in spleen size evident for 3 weeks. Radiotherapy was terminated due to dose-limiting grade 4 thrombocytopenia. Ruxolitinib
25 mg BD was maintained throughout and he maintained clinical improvement for 6 months. Massive splenomegaly with infarcts necessitated further radiotherapy (4 Gy in 2 fractions given weekly) again with subjective symptomatic improvement. He subsequently passed away due to a spontaneous major cerebral hemorrhage, not related to significant cytopenia.

Case 4: A 64-year-old gentleman was diagnosed with post-polycythemia Vera MF in 2014 (MYSEC-PM intermediate II risk), with a spleen of 33 cm on imaging and was commenced on ruxolitinib 15 mg BD. He achieved a partial spleen response, was not keen for therapy switch, and declined transplantation. In January 2019, he was enrolled in a phase II study exploring the utility of KRT-232, an inhibitor of Mouse double minute (MDM2), in MF patients. He failed to respond and recommenced on ruxolitinib until January 2020, when he came off study due to grade IV neutropenia. In September 2020, imaging reported a spleen of 32 cm craniocaudally, evolving splenic infarct and extensive portal hypertension. Following radiotherapy referral, he was initially scheduled to receive 12 Gy in 6 fractions over 3 weeks. He was felt suitable for twice weekly treatment. He remained on ruxolitinib 20 mg BD and recommenced on ruxolitinib until January 2020, when he was felt suitable for twice weekly treatment. He remained on ruxolitinib 20 mg BD and prednisolone 10 mg throughout. Unfortunately, he developed grade 4 cytopenia and treatment was stopped after 4 fractions. He failed to mount any significant splenic response and became heavily red cell and platelet transfusion dependent, with varical bleeds and infectious complications. He opted for ongoing palliative management and passed away 2 months after the completion of radiotherapy.

Symptomatic, debilitating splenomegaly in patients with advanced MF who have failed conventional and novel agents remains challenging. Due to the risk of mortality and indeed morbidity, splenectomy is not usually a viable option in these high-risk patients with bulky splenomegaly despite more recent outcome improvements. Our cases, over an 8-year period, highlight that many MF patients in the current era receive multiple lines of therapy. We demonstrate that for those who had exhausted such approaches, patients could potentially receive LDSR in conjunction with ongoing ruxolitinib, with clinically significant, albeit transient, spleen responses, duration ranging from 6 to 10 months in the 3 responders.

There is a paucity of literature and prospective monitoring of derived responses following LDSR in MF, with most of the literature from the pre-JAK inhibitor era. Greenberger et al initially described splenic irradiation as a successful symptom-relieving treatment for “myeloid metaplasia” >40 years ago. Bouabdallah et al evaluated splenic irradiation in 15 MF patients failing conventional therapies, utilizing a median irradiation dose per treatment course of 9.8 Gy (range, 0.6–30.5), in daily fractions of 0.4–1.0 Gy. The overall response rate was 59% with a median response duration of 10 months (1–19 mo). Optimal responses were observed when the red cell transfusion burden was low and full planned course could be delivered. Frederico et al administered splenic irradiation to 14 patients, previously treated with cytoreductive therapy but with resistant symptomatic splenomegaly. Treatment schedules utilized were varied, with patients receiving total doses between 2 and 10.8 Gy per course, in fractions of 0.2–1.4 Gy over a 2-week period. Significant spleen reductions were achieved in 82% of radiotherapy courses, with 94% of courses leading to splenic pain improvement. This team compared 3 groups based on the total dose received—low-dose patients (n = 6) receiving 2–4 Gy in 10 fractions, intermediate-dose patients (n = 4) 5 Gy in 10 fractions, and high-dose patients (n = 4) receiving 9.8–10.8 in 10 fractions. No significant clinical benefit associated with higher treatment radiotherapy dosages and hematological toxicities were greater. No hematological toxicity was recorded in the low-dose group, compared to 50% grade 4 cytopenias in the high-dose group.

The median duration of benefit following 1 course was 5.75 months.
Thus, enhancing anti-MF cell-mediated effects. Exact mechanisms of cytokine release, potentiating a secondary immune response, eradication of CD8+ suppressor T cells and radiation-induced hematopoiesis, additional postulated effects of LDSR include small series.

Side effects of JAK inhibitors would be impossible to ascertain in this unknown at present. Potential survival benefits of LDSR along-course. How this will be modulated by JAK inhibition remains unknown at present. Potential survival benefits of LDSR alongside JAK inhibitors would be impossible to ascertain in this small series.

Mechanistically, in parallel to direct abrogation of splenic hematopoiesis, additional postulated effects of LDSR include eradication of CD8+ suppressor T cells and radiation-induced release of cytokines, potentiating a secondary immune response, thus enhancing anti-MF cell-mediated effects. Exact mechanisms, however, remain undetermined. The potential of JAK inhibitors alongside LDSR to enhance radiotherapy-mediated cell death in MF has not, to the best of our knowledge, been described. Alternatively, ruxolitinib-mediated immunosuppressive properties may paradoxically counter LDSR immune-mediated effects, hence requiring evaluation.

In conclusion, we demonstrate that LDSR alongside ruxolitinib in 3/4 advanced phase, heavily pretreated patients, provided objective, measurable splenic responses for a median of 7.5 months accompanied by symptom improvement. Optimizing dosing schedules remains paramount. Patients require individually tailored dose scheduling based upon spleen volume, initial radiotherapy response, hematological reserve, and transfusion requirements. The value of our series lies in describing potential clinical benefit in the “end-stage” MF representing the current therapeutic landscape, compared to the older literature, and potential observed value, previously undescribed, in combinatorial use of LDSR and continued JAK inhibition (specifically ruxolitinib).

Disclosures

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References

1. Harrison CN, McLornan DP. Current treatment algorithm for the management of patients with myelofibrosis, JAK inhibitors, and beyond. *Hematology Am Soc Hematol Educ Prog*. 2017;2017:489–497.
2. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115:1703–1708.
3. Mead AJ, Milojkovic D, Knapper S, et al. Response to ruxolitinib in patients with intermediate-1-, intermediate-2-, and high-risk myelofibrosis: results of the UK ROBUST Trial. *Br J Haematol*. 2015;170:29–39.
4. Passamonti F, Giorgino T, Mora B, et al. A clinical–molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31:2726–2731.
5. Mesa RA. How I treat symptomatic splenomegaly in patients with myelofibrosis. *Blood*. 2009;113:5394–5400.
6. Cervantes F. How I treat splenomegaly in myelofibrosis. *Blood Cancer J*. 2011;1:e37.
7. Randhawa J, Ostojcic A, Vrhovac R, et al. Splenomegaly in myelofibrosis–new options for therapy and the therapeutic potential of Janus kinase 2 inhibitors. *J Hematol Oncol*. 2012;5:43.
8. Santos FP, Tam CS, Kantarjian H, et al. Splenectomy in patients with myeloproliferative neoplasms: efficacy, complications and impact on survival and transformation. *Leuk Lymphoma*. 2014;55:121–127.
9. Greenberger JS, Chaffey JT, Rosenthal DS, et al. Irradiation for control of hypersplenism and painful splenomegaly in myeloid metaplasia. *Int J Radiat Oncol Biol Phys*. 1977;2:1083–1090.
10. Bouabdallah R, Coso D, Gonzalez-Casabianca L, et al. Safety and efficacy of splenic irradiation in the treatment of patients with idiopathic myelofibrosis: a report on 15 patients. *Leuk Res*. 2000;24:491–495.
11. Federico M, Pagnucco G, Russo A, et al. Palliative splenic irradiation in primary and post PV/ET myelofibrosis: outcomes and toxicity of three radiation schedules. *Hematol Rep*. 2011;1:e37.
12. de la Pinta C, Fernández Lizarbe E, Montero Luis Á, et al. Treatment of symptomatic splenomegaly with low doses of radiotherapy: retrospective analysis and review of the literature. *Tech Innov Patient Support Radiat Oncol*. 2017;3–4:23–29.
13. Weinmann M, Becker G, Einsele H, et al. Clinical indications and biological mechanisms of splenic irradiation in chronic leukaemias and myeloproliferative disorders. *Radiother Oncol*. 2001;58:235–246.