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Case Report
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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

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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.[1] However, effective treatment can be impacted by dose-limiting cytopaenia, 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).[2] 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.[3] She achieved a partial symptom response but therapy ceased after 7 months following dose-limiting cytopaenia and progressive splenomegaly. Successive treatments with fedratinib, combination ruxolitinib and danazol, then pacritinib ensued with short-lived responses. She declined allograft. The spleen measured 20 cm craniocaudally on imaging accompanied by significant splenic pain. Subsequently, she received 5 Gy splenic irradiation in 5 fractions (1 Gy weekly, with a 6-week break between fractions 3 and 4 due to grade 4 thrombocytopenia) demonstrating an overall reduction in spleen size by 10 cm. Ruxolitinib 25 mg twice daily (BD) was continued throughout. She remained cytopenic (the maximum grade 4 thrombocytopenia) but maintained marked symptomatic benefit for approximately 6 months before splenic progression. Prednisolone and thalidomide were sequentially added for palliation and she died thereafter.

Case 2: In 2012, a 64-year-old male with DIPSS-Intermediate 2 MF was referred, the spleen was palpable 8 cm BCM while receiving hydroxycarbamide and danazol. Progressive splenomegaly ensued reaching 17 cm palpable BCM. Dose-attenuated ruxolitinib was commenced with an initial partial spleen response (11 cm BCM), yet by month 15 on treatment, 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 splenic 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

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Table 1.

Summary of Patient Characteristics and Response to Therapy.

	Case 1	Case 2	Case 3	Case 4
Diagnosis	PMF	PMF	PMF	PPV MF
Sex	Female	Male	Male	Male
Prognostic score	DIPSS high	DIPSS intermediate 2	DIPSS high	MYSEC-PM intermediate 2
Age at time of LDSR (yrs)	61	67	67	64
Time from center review to radiotherapy (mo)	49	46	29	86
Size of spleen at time of referral	12 cm BCM	8 cm BCM	15 cm BCM	20 cm BCM
Size of spleen at time of LDSR	20 cm longitudinal (imaging)	29 cm BCM	23 cm BCM	32 cm longitudinal (imaging)
Radiotherapy dose (details in text)	5 Gy in 5 fractions	1. 3 Gy in 2 fractions 2. 1.5 Gy in 3 fractions	1. 6 Gy in 3 fractions 2. 4 Gy in 2 fractions	8 Gy in 4 fractions
Size of spleen following radiotherapy	10 cm on imaging	Not available after course 2	11 cm BCM	No response
Maximum hematological toxicity	Grade 3 anemia Grade 4 thrombocytopenia	Grade 3 anemia Grade 4 thrombocytopenia	Grade 4 thrombocytopenia	Grade 4 neutropenia and thrombocytopenia
Time to maximal hematological toxicity	Day 25	Course 1. Day 20 Course 2. Day 54	Course 1. Day 29 Course 2. Day 29	Day 12
Duration of hematological toxicity	Treatment break required, persistent Grade 4 thrombocytopenia Anemia supported with transfusion ongoing	1. At day 137 resolved to Grade 2 thrombocytopenia and anemia 2. At day 121 thrombocytopenia resolved Grade 3, anemia ongoing	1. At day 152 resolved to Grade 2 thrombocythemia 2. RIP at D32 (unrelated)	No recovery, RIP day 77
Duration of response (mo)	6	Course 1. 10 Course 2. No response	Course 1. 6 Course 2. NA	No response
Concurrent dose of ruxolitinib	25 mg BD	25 mg BD	25 mg BD	20 mg BD
Previous treatments	HU, fedratinib, pacritinib, danazol	HU, danazol, LD AraC, EPO	BKM120	HU, KRT-232, fedratinib Prednisolone
Subsequent treatments	Prednisolone and thalidomide	Nil	Nil	Nil
Survival from time of first LDSR (mo)	19	6	7 (from course 1)	2

AraC = cytosine arabinoside; BCM = below costal margin; BD = twice daily; DIPSS = Dynamic International Prognostic Scoring System; HU = hydroxycarbamide; LD = low dose; MYSEC-PM = myelofibrosis secondary to PV and ET-prognostic model; NA = not applicable; PMF = primary myelofibrosis.

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 cytopaenia.

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.[4] 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 2 homolog (MDM2), in MF patients. He failed to respond and recommenced on ruxolitinib until January 2020, when he enrolled on the phase III Freedom trial, receiving fedratanib but 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 prednisolone 10 mg throughout. Unfortunately, he developed grade 4 cytopaenia 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 variceal 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.[5–8] 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[9] initially described splenic irradiation as a successful symptom-relieving treatment for "myeloid metaplasia" >40 years ago. Bouabdallah et al[10] 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[11] 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, but longer in those in the lower-dose categories who were retreated (21 mo from initial course; range 10–44 mo). Lower doses appeared iso-effective in reducing splenomegaly compared with higher dosing. The authors suggested a regimen of 2 Gy (10 fractions over 2 wks) appeared well tolerated, avoided severe hematologic toxicity and in some patients permitted further retreatment.

The optimal radiotherapy dose/fractionation schedule to provide measurable relieve of splenic symptoms, while trying to minimize significant hematological toxicity remains unclear. This is clearly determined by each individual case, as demonstrated by the dosing and fractionation range for these 4 patients with convenient scheduling. Hematological toxicity can be difficult to quantify in an already fragile population, many of whom are already transfusion dependent with progressive disease, but must be considered during planning and during each 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.[12,13] 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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