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Case reports and case series

Treatment of symptomatic splenomegaly with low doses of radiotherapy: Retrospective analysis and review of the literature

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ABSTRACT

Objectives: To evaluate the effectiveness of low doses of radiation therapy for symptomatic splenomegaly in malignant and benign diseases.
Patients and methods: 5 patients with symptomatic splenomegaly were treated with low doses of radiation in our centre (January 2008–December 2016). 4/5 patients had malignant neoplasia (acute myeloid leukemia, non Hogdkin lymphoma and prolymphocytic B cell leukemia) and splenomegaly was caused by extramedullary hematopoiesis. 1/5 patient had benign disease (HBV liver cirrhosis) and splenomegaly was caused by vascular ectasia. Median age was 73 years (range 61–86 years). There were 4 females and 1 male. These patients had exclusively splenic pain or abdominal discomfort in 20%, exclusively cytopenias 40% and both 40%. Patients needed radiation therapy for symptomatic control. Dose per fraction was 0.5 Gy every two days; total dose initially prescribed 10 Gy. IGRT were performed in all patients to ensure an appropriate position and to adapt the treatment volume to the changes in the spleen volume along the treatment. Median craneocaudal length size of the spleen was more than 26 cm (range 15.2–34.9 cm).
Results: Median radiation doses were 4.85 Gy (range 2.5–10). Median craneocaudal spleen size reduction was 4.6 cm (0–8 cm). Splenic pain and abdominal disturbances improved in all patients. Median increase of haemoglobin and platelets levels was 1.6 mg/dl and 27.950 cells respectively in the first week after the end of radiotherapy.
One patient had to interrupt her treatment due to grade II neutropenia. No other toxicities were described. With a median follow-up of 39 months (16–89 months), only one recurrence was described at 24 months and consisted of thrombocytopenia. The patient received a second course of radiotherapy with excellent response.
Conclusion: Low doses of radiation therapy for treatment of symptomatic splenomegaly were effective, with a low rate of side effects. Splenic pain and abdominal discomfort completely improved and cytopenias rised to secure levels.

Introduction

The spleen is an abdominal hematopoietic organ, usually not palpable, involved in different functions such as blood pathogen elimination, aged blood-cell destruction and extramedullary hematopoiesis. Splenomegaly refers to a pathological enlargement of the spleen, and is generally defined as craneocaudal growth of spleen more than 11 cm. Splenomegaly is the leading clinical sign of various lymphoid and myeloid malignancies, but also can occur as a secondary manifestation of a broad spectrum of benign non-neoplasic diseases. Splenomegaly can be developed in malignant myeloproliferative and lymphoproliferative diseases like myelofibrosis, prolymphocytic leukemia, hairy cell leukemia, non-Hodgkin's lymphoma or chronic lymphocytic leukemia, but also due to benign conditions like liver cirrhosis, amyloidosis or Gaucher's disease.

Splenomegaly physiopathology includes four mechanisms. First, reticuloendothelial and lymphoid-system hyperplasia, typically present in autoimmune diseases such as autoimmune hemolytic anemia. Spleen in this illness accumulates large number of

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defective red blood cells, which results in an enlarged hyperfunctioning spleen (splenomegaly). Second, extramedullary hematopoiesis in myeloproliferatives syndromes, including anemia and leukoerythroblastic reaction. Third, portal hypertension and passive congestion in cirrhotic patients. Last, infiltration of proteins (amyloidosis and Gaucher disease) or tumor cells [1]. The symptoms of an enlarged spleen can include pain cause by Gerota capsule distension, a sense of fullness, discomfort in the left upper quadrant, early satiety and diarrhea due to organ compression and cytopenias due to hypersplenism [5,6]. In some patients the spleen becomes so enlarged that its lower pole protrudes into the pelvis or crosses the midline into the lower right or upper right abdominal quadrants. In these patients with a massively enlarged spleen symptoms could be ischemia and pain due to splenic infarction.

Treatment of symptomatic splenomegaly depends on its etiology: chemotherapy in haematologic tumors [6,7], transjugular intrahepatic portosystemic shunt (TIPS) used for reducing portal venous pressure [8,9], radiofrequency [10,11], splenic embolization [12,13], splenectomy [14,15] or radiotherapy. Effectiveness of splenic irradiation for palliation of splenomegaly symptoms is well known since beginning of the 20th century, both in malignant and non-malignant disorders. Underlying mechanism of splenic irradiation seems to be related to a reduction of tumor burden in the spleen as well as to splenic reticuloendothelial system suppression.

In this paper, we present 5 patients who received splenic low-dose irradiation for malignant and non-malignant conditions. The indications, setting, results and toxicity profile are discussed.

Material and methods

We have retrospectively analyzed the outcomes of 5 patients with splenomegaly referred to our department to consider splenic irradiation for symptomatic splenomegaly between January 2008 and December 2016.

There were 4 females and 1 male, with a median age of 73 years (range 61–86 years). Primary diseases were malignant neoplasms [(acute myeloid leukemia ($n = 1$), non Hogdkin lymphoma ($n = 2$) and prolymphocytic B cell lymphoma ($n = 1$)]. One patient had splenomegaly due to vascular ectasia with liver cirrhosis. Symptoms and signs of splenomegaly included pain or abdominal discomfort in 20%, cytopenia in 40% and both in 40%. At first medical appointment patients and physicians evaluated pain presence (present/absent). If present, pain was referred as mild, moderate or severe. No specific pain-tools were used, because the pain had visceral characteristics and its evaluation in numeric scales was difficult to asses. Median size of the spleen determined by craneocaudal length was 26 cm (range 15.2–34.9 cm).

All patients and treatment parameters are summarized in Table 1. Patients needed radiotherapy for symptomatic control.

Radiation is delivered after three dimensional computer tomography based treatment planning (CT-plan). All patients were planned with non contrast-enhanced computerized tomography (CT scan) because no enhancement of any lesion was mandatory and the whole organ was delimited. CT-plan images are acquired in supine position, every 3 mm CT slice thickness and sent to a Pinnacle® planning system. CT plan images to define treatment volume (spleen) in all slices, surrounded by 1 cm safety margin (to compensate internal organs movements and uncertainties of technique) to create the planning target volume (PTV). We contour bowel, stomach, kidneys and liver as organs at risk to avoid adverse effects. A total dose of 10 Gy in 0.5 Gy fractions was prescribed, and treat two or three fractions per week. In some cases we were able to interrupt treatment before achieving the total prescribed dose due to good response at even lower doses.

In our center, it is used a volume-adaptative technique for splenic irradiation. This technique allows to avoid radiation to surrounding organs such as liver, bowel, stomach or kidneys. During the delivery of the treatment, every two fractions we perform a CT conebeam, obtained by the linac right before treatment. This CT conebeam is registered with CT-plan and has two purposes: first, it is used for image-guided radiotherapy (IGRT) to assure the administration of treatment in the accurate site; second, to monitor spleen volume changes between fractions. Once we detect a volume reduction in the organ, the spleen is recontoured the spleen, recreating a new and smaller PTV and redesign the treatment for this new scenario. It is possible to proceed so because the spleen is an organ with a capsule and all its content stays inside the capsule. With this reduction in volume we achieve better dose-volume histograms for organs at risk and, therefore, less toxicity. We believe that the use of this advantageous technique contribute to a better tolerance of treatment.

Besides pain, diarrhea and sickness evaluation, blood counts are monitored once per week, and supportive treatment prescribed when necessary.

Results

Median radiation doses were 4.85 Gy (range 2.5–10 Gy). The causes for stopping the treatment before 10 Gy are summarized in the Table 1. Median craneocaudal spleen size reduction was 4.6 cm (0–8 cm). Splenic pain and other abdominal disturbances improved in all patients. Median increase of haemoglobin and platelets levels was 1.6 mg/dl and 27.950 cells respectively in the first week after the end of radiotherapy. On Table 2, we reported pre-treatment leukocyte and thrombocyte counts, nadir values and post-treatment values. In consecutive visits both patients and physicians assessed changes in pain intensity as worse, stable, improve or absent. One patient had to interrupt the treatment due to grade II neutropenia. This patient received treatment with ruxolitinib concomitant to radiation therapy and this drug can

Table 1
Patients characteristics and cause of interruption.

Pathology	Gender	Age	Volume pre-treatment (cm)	Symptoms	Dose (Gy)	Response	Interrupt treatment	Cause of interruption
Acute myeloid leukemia	F	61	25	Pain and anemia	5.5	Yes	Yes	Neutropenia Grade II
Non Hogdkin lymphoma	F	77	29	Pain, thrombopenia and anemia	3	Yes	No	Increase platelets, clinical response and reduce of spleen volume
Liver cirrhosis	F	61	13.2	Thrombopenia	3	Yes	No	Increase platelets
Prolymphocytic B leukemia	F	80	23	Anemia and thrombopenia	2.5	Yes	No	Increase platelets and clinical response
Non Hogdkin lymphoma B	M	86	27.5	Pain and thrombopenia	10	Yes	No	Clinical response and reduce of spleen volume

Table 2
Pre-treatment leukocyte and thrombocyte counts, nadir values and post-treatment values.

	Platelets pre-treatment	NADIR platelets	Platelets post-treatment	Leukocytes pre-treatment	NADIR leukocytes	Leukocytes post-treatment
Acute myeloid leukemia	419,000	21,000	125,000	26,000	1900	750
Non Hogdkin lymphoma	95,000	93,000	105,000	14000	2630	2160
Liver cirrhosis	62,300	53,300	92,900	1700	1470	3300
Prolymphocytic B leukemia	42,000	40,000	88,000	1440	1460	5370
Non Hogdkin lymphoma B	34,000	32,000	44,200	6400	4700	6680

cause neutropenia and infections. No grade II-IV diarrhea or sickness were described and the patients present good tolerance. No other toxicities were described.

With a median follow-up of 39 months (16–89 months), only one recurrence was described at 24 months and consisted of thrombocytopenia. This patient underwent a second course of radiotherapy up to a total dose of 2 Gy, 0.5 Gy per fraction. Excellent response and no toxicities were described in re-irradiation. Planning dosimetry and radiologic evaluation is showed in Figs. 1 and 2.

Discussion

Splenic irradiation with low doses of radiotherapy is a treatment option that can improve splenomegaly symptoms such as pain and cytopenia. Although low dose radiotherapy is a well-known effective and safe approach for splenomegaly of malignant and non-malignant conditions, it has traditionally been used only when other treatments have failed or are contraindicated. Several hypotheses have been described in order to explain treatment response mechanism. The main event is a direct radiation-induced cell death, which leads to elimination of malignant cells located in the spleen. On the other hand, an inmuno modulation to cause a redistribution of circulating lymphoid subpopulations with reduction of normal T-suppressor lymphocytes and increased anti-tumor activity. Third, a radiation-induced release of cytokines is believed to potentially stimulate a secondary immune modulation enhancing anti-neoplasic cell-mediated effects [7,29]. The exact mechanism how splenic irradiation exerts its effects in splenomegaly is poorly understood. The cellular death depends on the type of tumor and varies with tumoral biology [7].

A wide variety of approaches have been described for splenomegaly and subsequent hypersplenism, both of malignant and non-neoplasic processes. Systemic chemotherapy is an effective alternative in tumoral illnesses, but with adverse effects such as nausea, vomiting and diarrhea, together with more severe ones, for instance, thrombotic complications or cytopenias. Placement of TIPS involves the creation of a low-resistance channel between the hepatic vein and the intrahepatic portion of the portal vein using angiographic techniques. It is an effective technique, but it can be associated with a number of complications that includes: capsular punction, cardiac arrhythmias, intraperitoneal bleeding, fistula, thrombosis, sepsis, hepatic encephalopathy, intravascular hemolysis or hemodynamic instability, risk of puncture of extrahepatic organs, catheter damage, wire damage, even fracture or stent migration [8,9]. The radiofrequency ablation (RFA) is relatively well tolerated, but severe and potentially fatal complications can arise [10,11]. The splenic embolization consists of placing a catheter in the splenic artery followed by repeated injection of particles until splenic blood flow is reduced by about 50% [11]. The embolization is limited by complications such as splenic abscess, splenic injury, sepsis, portal vein thrombosis, pneumonia, atelectasis, pleural effusion and damage of renal and/or liver function, have been reported as 30% [12,13,19]. Total splenectomy may be an effective treatment for hypersplenism, but it impairs the body's ability to produce antibodies against encapsulated microorganisms and predisposes patients to sepsis. This technique has several complications as postoperative bleeding, gastric perforation, vascular thrombosis, pancreatic fistula, postsplenectomy sepsis or perioperative mortality [14]. Other techniques are the high-intensity focused ultrasound (HIFU) ablation. Complications are abdominal pain (25%), low fever (10.7%) and hydrothorax (7.1%) [20].

Radiation therapy for splenomegaly in hematologic diseases has been widely studied. Senn made the first description of the technique in 1903, when he treated a 30-years old male with diagnosis of leukemia [17]. Kriz et al. [32] analyzed 122 hematologic patients

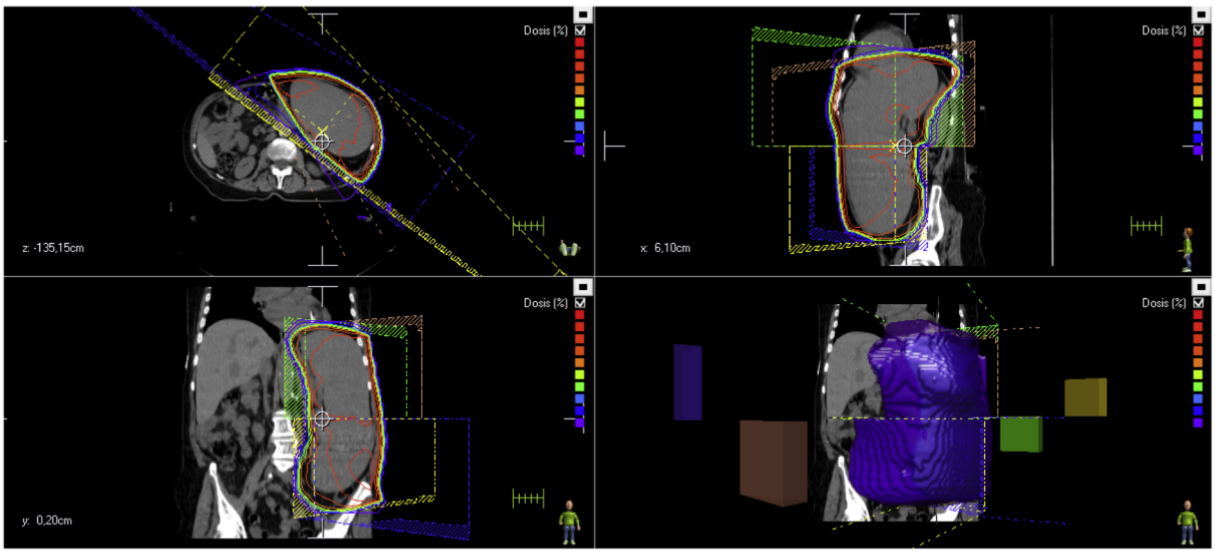

Fig. 1. Planning isodoses and field incidences.

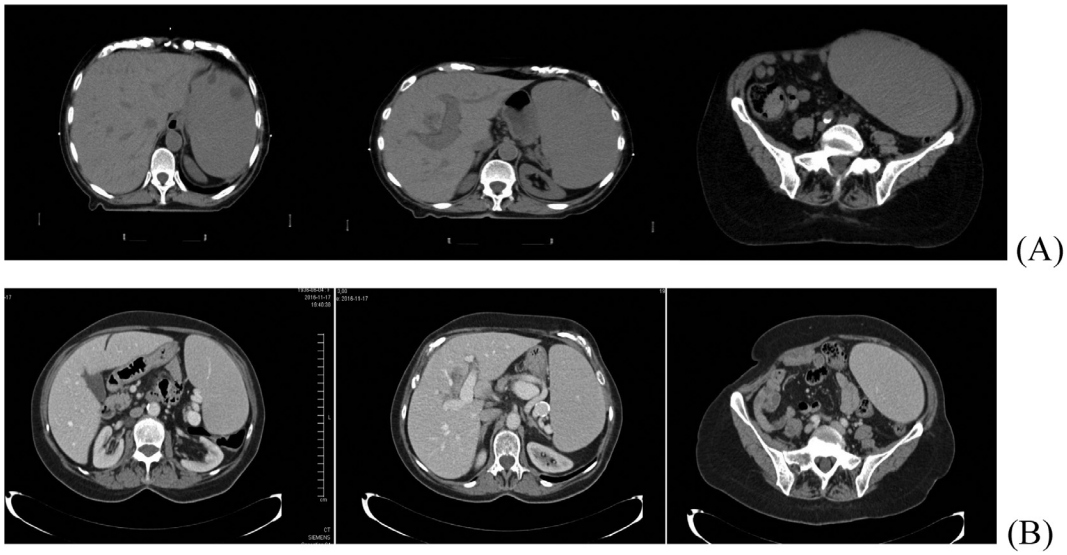

Fig. 2. Radiologic response to treatment. A. Spleen volume before radiotherapy. B. Spleen volume after low-dose radiotherapy.

in twenty years with excellent response. Pain relief was observed in 74% and improve in hematological disease was observed in 78%. No important toxicities were described. Symptomatic response of splenic irradiation is around of 50% and 90% and count blood cell is around 14% and 78% depends on series, according to Weinman et al's review [7]. Liu, Kenawi and Bruns reported around 100% of pain relief and 37–100% increase of platelets counts in benign splenomegaly [4,30,31]. Radiotherapy takes place usually in refractory splenomegaly or when the patient refuses other treatments [21–28], although we consider it should be used sooner in the natural history of this affection. Cervantes et al. [35], refuse treatment because it is not durable, but in some studies it is demonstrated the possibility to repeat treatment with similar toxicity as the first time. In our series we reported a low rate of toxicities, only one patient present toxicity as grade II neutropenia. Non-gastrointestinal or skin toxicities were described; neither splenic infarction nor more than grade II hematological toxicities were described. Comparing with toxicities developed after invasive techniques, this excellent tolerance should convert radiotherapy in a first line treatment.

Techniques for spleen radiotherapy are varied. Nazmy et al. [34] described that two parallel opposite posterior-anterior fields as the most accepted, but single direct anterior field technique could be a good option. Two-field technique showed correct coverage and homogeneous dose distribution. However, the best option to protect the organs at risk was the single direct anterior field technique. In the same way, Ibáñez-Villoslada et al. [3] used parallel and opposed fields with 6 or 15 Mv photons, depending on the patient's thickness. Similar to this series, in our institution, we used two parallel opposite postero-anterior fields or oblique fields.

Doses and fractionation in case reports series are variable. In most of the cases, doses were between 2.7 and 23 Gy, with dose per fraction between 0.1 Gy to 3 Gy. In Soldic et al. study [33] they used total dose of 10 Gy with 0.5 Gy to 1 Gy for fraction daily and twice-weekly treatment schedule similar to Namzy et al. [34]. These reports have applied low total doses and low fraction dose, similar to our serie, with a total dose between 2 and 10 Gy with 0.5 Gy for fraction.

Despite using similar doses, the range of toxicities is very different. Mc Farland et al. [2] analyzed 17 patients with hematologic diseases who received radiation treatment with 0.5 Gy in two fractions the first week, 0.75 Gy in two fractions the second week, and 1 Gy in two fractions the third week. These patients had important complications such as nauseas, fatigue, cytopenia, and heart attack by anemia. Chen et al. reported severe myelosuppression between 10% and 30% due to irradiation. Treatment plan in these studies was with 6 or 18 mV photons, with parallel fields with 3D planning using TC or clinical evaluation. No decrease of volume guided by response to treatment was applied, no control with IGRT and, in Mc Farland study [2], radiation oncologist increased the weekly dose. The most common side effects in Soldic et al. [33] study were thrombocytopenia and anemia, this toxicities increase in patients that had received chemotherapy and the authors described difficulties distinguishing progression from toxicity. Kriz et al. [32], used fraction between 0.1 and 2 cGy, total was dose 0.3–16 Gy and showed important symptomatic response with low rate of toxicities. The most frequent toxicity in Larenkov et al. [36] study was thrombocytopenia (25%), leukopenia in 13.5% and anemia in 9.6%. In this study they described the possibility of kidney toxicity in dose more than 20 Gy in 40% of volume. We were able to avoid kidney irradiation applying the oblique fields instead of the postero-anterior ones. Intensity-modulated radiation therapy and volumetric-modulated arc therapy (VMAT), have enabled even more conformal radiation delivery limited organ at risk. These techniques are effective but also more expensive. Additionally not all centers dispose of these techniques, so opposite fields and adaptative radiotherapy is a good alternative for these centers.

In the same way, Ibáñez-Villoslada et al. [3] reported severe neutropenia and sickness. In this study neither IGRT nor decrease of volume according to response are applied. A few studies had used adaptative volume, the most of this with ultrasonography or clinical exam [33]. In our study, we use CT-plan, radiotherapy imaging guided daily with decrease of volume and re-planning if it is necessary. We only observed grade II neutropenia in one patient. The treatment was stopped and patient has response after 5.5 Gy (11 fractions) with 50% spleen decrease. No other toxicities were described. Our low rates of toxicities or complications might be achieved with adaptative-volume radiotherapy. Due to the low number of patients in our cohort and the design, retrospective case-series, we cannot establish definitive recommendations.

All important studies and toxicities are summarized in Table 3.

Table 3
Splenic irradiation: toxicities and response in the literature.

Authors	Number of patients (type of disease)	Total dose (Gy)	Doses/fraction (Gy)	Response	Duration	Toxicities
Greenberger et al. [37]	25p MMM RT = 14 p	6 (0.4–17.2)	0.25(0.1–0.5) daily	95% SS 100% PC 28% CR 67% PR	1–73 m	No
Bouroncle et al. [28]	82p HCL RT = 24 p	4–9	0.5 daily	6 p NR 1 p CR 16 p PR	3–12 m 1 p 3y	No
Aabo et al. [38]	22p CLL (RT)	10 (2.5–24)	0.5–1 daily	77% PR SS 84% SR	1y (2–36)	6p gastrointestinal grade I-II
Wagner et al. [39]	17 p CML (RT)1 1 p chemo previously	0.15–6.5	0.25–0.5cGy/2–3 times weekly	71% PC 76% SS	Not reported	Better with intermittent schedule
Sciascia et al. [26]	14p IMF (RT)	16.2 Gy(7–24)	1 (0.5–10) daily	100% PC 13p decrease more than 50%	6 m (2–15)	Neutropenia Thrombocytopenia 4p severe anemia
Guiney et al. [23]	22p CLL (RT)	5.5 Gy(1.25–24)	0.25–0.5 Gy/3 per week or 1–2 Gy 1 per week	61% SS 96% SR	14 m (3–116)	Leukopenia Thrombocytopenia
Paulino et al. [22]	25p hematologic diseases RT = 14 p	4.5 Gy(0.5–10)	0.25–1 daily >500 cGy more effective in CLL	60% SS 91% PC	Splenomegaly <12 m Pain > 6 m	2p interrupt treatment
Elliott et al. [26]	23p MMM	2.77 Gy (0.95–13.65)	0.35 (0.2–1.3)	93.9% SS 93.9% PC	Median 6 m (1–41)	43.5% cytopenia26% pancytopenia13% sepsis or haemorrhage
Bouabdallah et al. [18]	15p IMF	9.8 Gy (0.6–30.5 Gy)	0.1–1 Gy/day	59% More in previously transfused	Median 10 m (1–19)	No
Van Mook et al. [24]	23p B-CLL Complete treatment 20 p	10 Gy	1 Gy	14p PR Stable 9p SR: platelet	–	Nausea, slight diarrhea, pleuropneumonia, granulopenia with fever (all = 1), urinary tract infection, high fever (n = 1), thrombocytopenia (2p) Transfusion for bleeding in 1p
Mc Farland et al. [2]	17p Hematologic disease	4.5 Gy	0.5 Gy 2 fractions first week2 fraction 0.75 cGy second week 2 fractions 1 Gy third week	22/25 PC 6/9p SR		Nauseas, fatigue, cytopenia, heart attack by anemia. 5p re-irradiation
Shrimali et al. [40]	19p	4.5 Gy (1.5–8 Gy)	0.25–1 Gy	85% SS 25% SR		
Namzy et al. [34]	18p 13p CML 5 CLL	1.25 Gy-12 Gy	0.25–1 Gy	100% PC SR (Hb)	–	4p re-irradiation
Kriz et al. [32]	122p 31p CML 37p CLL 23p OMF 17 PV 5p myelogenous leukemia 4p idiopathic thrombocytopenic purpura 3p NHL 2pMM	0.3–16 Gy	0.1–2 Gy	74.8% PC 50% splenic reduction in 77% 73.6% SR	–	Hematologic ⇐ grade 2 EORTC/RTOG
Soldic et al. [33]	11p 6p NHL 4p CLL 1p myelofibrosis	7 Gy (1–10 Gy)	0.5–1 Gy	71% PC	–	Thrombocytopenia (27.3%) Anemia (36.4%) 2p re-irradiation

(*continued on next page*)

Table 3 (*continued*)

Authors	Number of patients (type of disease)	Total dose (Gy)	Doses/fraction (Gy)	Response	Duration	Toxicities
Lavrenkov et al. [36]	32p 21p myeloproliferative 5p malignant lymphoma 5p CLL 1p HHC	6–10 Gy	0.5 Gy daily	78.8% SS SR: 75% anemia 63.5% thrombopenia	19 m (4–42)	Severe complication in more than 10 Gy Non myelosuppression
Bruns et al. [4]	5pAutoimmune hepatitis (n = 2) Cystic fibrosis (n = 1) Granulomatosis liver disease (n = 1) M. Werlhof with liver cirrhosis (n = 1)	3 Gy	0.5 Gy two or three times a week	4p PC 2p decrease splenic size: 10% SR: 4p	20 m (2–36)	No toxicities
Pistevou-Gombaki et al. [16]	17p CML 3p idiophatic polycythaemia Chemotherapy previously	5.8Gy 6 Gy 9.8Gy 3.6 Gy	580cGy/5fr 600cGy/6fr 980cGy/14fr 360cGy/6fr	Good response	12 m	Well tolerated

SS: spleen size. PC: Pain control. SR: systemic response. NR: No response. CR: Complete response. PR: partial response.
MMM: myeloid metaplasia. HCl: hairly cell leukemia. CLL: chronic lymph leukemia. IMF: Idiopathic myelofibrosis. B-CLL: B-cell prolymphocytic leukemia. CML: chronic myeloid leukemia. OMF: osteomyelofibrosis.

Conclusion

Low doses of radiotherapy in symptomatic splenomegaly treatment are effective with low rate of adverse effects for malignant or non-malignant diseases. As we compare our treatment and results with those radiation treatments published at literature, we found less toxicity, better tolerance and similar final doses and efficacy. We considered that the use of our advantageous volume-adaptative technique could reduce toxicities with CT planning, IGRT and adaptative dose. Pain and abdominal discomfort improved completely and count blood cells recovered security levels. Therefore, we consider splenic irradiation as first line treatment in symptomatic splenomegaly.

Conflict of interest

The authors declared that there is no conflict of interest.

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