SPLENIC IRRADIATION IN HEMATOLOGIC MALIGNANCIES AND OTHER HEMATOLOGIC DISORDERS – SINGLE INSTITUTION EXPERIENCE

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SUMMARY – Splenic irradiation has long been known as a palliative treatment modality in patients with various malignant hematologic diseases aiming to ameliorate clinical symptoms of splenomegaly as well as clinical sequels of hypersplenism. It provides considerable effect with low toxicity although exact radiotherapy dose and fractionation schedule are not known. During the 1996-2010 period, eleven patients were treated at our institution with splenic irradiation. They received 16 courses of fractionated radiotherapy. There were six patients with non-Hodgkin's lymphoma, four with chronic lymphocytic leukemia, and one patient with myelofibrosis. The median of the dose received was 7 Gy, while the median of dose received per fraction was 1 Gy. Both parallel opposed anterior-posterior fields and tangential fields were used. Due to the clinical target volume shrinkage, the treatment field was reduced in 44% of courses. Of the courses initiated for symptom control, 71% resulted in effective palliation, whereas of the courses started to treat hematologic sequels of hypersplenism 50% produced desirable effects. The most common side effects included thrombocytopenia and anemia. Splenic irradiation provides effective and low-toxic palliation of symptoms but it is much less successful in treating hematologic disorders caused by hypersplenism.

Key words: *Splenic neoplasms – radiotherapy; Palliative care; Lymphoma, non-Hodgkin; Leukemia; Myelofibrosis*

Introduction

Splenic irradiation is the oldest known treatment for various neoplastic hematologic diseases. It was first applied in leukemias one century ago and remained the only effective treatment for years[1]. The advent of potent anti-neoplastic drugs restricted the use of splenic irradiation merely to palliative treatment of splenomegaly, treatment of rare lymphoproliferative diseases like prolymphocytic leukemia, hairy cell leukemia or some cases of mantle zone non-Hodgkin's lymphoma (NHL), and treatment of refractory chronic lymphocytic leukemia (CLL).

Splenomegaly is the leading clinical sign in various lymphoid and myeloid malignancies. Splenic irradiation is effective in palliation of symptoms associated with splenomegaly such as abdominal tumor, pain, anemia, and thrombocytopenia[2]. Favorable effects of splenic irradiation are mainly connected with two mechanisms: reduction of spleen tumor burden (decreasing splenomegaly) and suppression of splenic reticuloendothelial system. There are a number of studies showing therapeutic effect of splenic irradiation in a variety of hematologic malignancies[3-7]. The main reason for using splenic irradiation is the fact that it is a low-toxic and easily applicable palliative treatment. Lymphoid tumor tissue is sensitive to therapeutic ra-

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diation and very low doses of 0.05-0.5 Gy are capable of inducing apoptosis in thymic or splenic tissue[8]. So, for splenic irradiation, low total doses and small fractions of fractionated radiotherapy have been successfully used.

In this paper, we present 11 patients that received splenic irradiation (six patients with NHL, four patients with CLL and one patient with myelofibrosis). The indications, setting, results and toxicity profile are discussed.

Patients and methods

During the 1996-2010 period, 11 patients were treated with splenic irradiation at our institution and their case records were reviewed. All patients had splenomegaly with secondary hypersplenism, and were referred for palliative splenic irradiation at our department. Hematologists were responsible for cytotoxic treatment and follow up of these patients. When splenic irradiation was considered as the treatment of choice, patients were presented to radiation oncologist for further radiation treatment.

Radiotherapy was delivered with cobalt unit. Depending on spleen size, a direct field or two opposite fields were used to cover palpable splenomegaly in most patients. During the treatment, each patient was closely monitored before each fraction of radiotherapy with complete blood count and clinical examination to assess changes in the spleen size. Both were used to assess toxicity. In some cases, even ultrasonography was used to modify target volume. The treatment was administered until achieving the desired splenic shrinkage, withdrawal of symptoms, or the occurrence of unacceptable toxicity.

Clinical outcomes were divided as follows: clinical response implied amelioration of symptoms, while hematologic response included improvement of blood count.

Results

Patient characteristics are shown in Table 1. There were 11 patients in total, six male and five female, median age 73, considered as high age. The leading underlying diagnosis was CLL, followed by NHL, and only one patient with myelofibrosis. The great majority of patients with hematologic malignancy were referred for radiotherapy at an advanced stage of the disease and only one patient had received no prior chemotherapy. Some details regarding previous chemotherapy were not recorded in the chart, as follows: primary chemotherapy in NHL patients consisted of 6-8 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) protocol, whereas primary chemotherapy in CLL patients predominantly included chlorambucil, then CVP (cyclophosphamide, vincristine, prednisone) and protocols containing fludarabine and cyclophosphamide. The patients with myeloproliferative diseases received treatment with hydroxyurea, interferon alpha and corticosteroids for a short time.

Table 1. Patient characteristics

Number of patients	11
Age (yrs, median)	35-81 (73)
Sex, n (%)	
Male	6 (54.5)
Female	5 (45.5)
Primary diagnosis, n (%)	
CLL	4 (36.4)
NHL	6 (54.5)
Myelofibrosis	1 (9.1)
Stage, n (%)	
CLL	4 (100)
Rai II	1 (25 %)
Rai IV	3 (75%)
NHL	6 (100)
Stage IV	6 (100)
Previous treatment, n (%)	
One line of chemotherapy	3 (27.3)
Two lines of chemotherapy	3 (27.3)
Three lines of chemotherapy	2 (18.2)
No chemotherapy	1 (9.1)
Unknown	2 (18.2)
Splenomegaly, n (%)	11 (100)

CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin's lymphoma

All patients had pronounced extensive splenomegaly with apparent consequential clinical symptoms.

These 11 patients treated with splenic irradiation received 16 courses of fractionated radiotherapy (Ta-

Table 2. Radiotherapy details

Number of courses	16
Treatment frequency, n	
Daily fractionation	8
Thrice-weekly fractionation	8
Number of fractions *per* patient (median)	1-15 (9)
Portal arrangement, n (%)	
AP-PA parallel opposed	7 (43.8)
Direct anterior	2 (12.5)
Tangential	7 (43.8)
Field area range, cm^2 (median)	60-234 (154)
Field area reduction, n (%)	7 (43.8)
Dose/fraction range, Gy (median)	0.5-1 (1)
Total dose range, Gy (median)	1-10 (7)

ble 2). Nine patients had only one course of splenic irradiation, while two patients were re-irradiated (received more than one course of splenic irradiation). More precisely, one patient had four courses of splenic irradiation within the period of two years, and another one had two courses of splenic irradiation at two-year intervals.

Regarding the cause of referral for splenic irradiation, 6 of 16 treatment courses were started in order to relieve clinical symptoms (painful splenomegaly, abdominal tumor, discomfort and pain accompanied by 'B' symptoms, i.e. weight loss and night sweats). Only one course was initiated to treat severely impaired blood tests caused by hypersplenism. The remaining 9 courses were carried out to treat both clinical symptoms and impaired blood tests.

Both daily fractionation and thrice-weekly treatment schedule were used. The median of fractions delivered per patient was 9. Furthermore, parallel opposed (AP-PA) or tangential fields were most commonly used.

Total radiation dose delivered varied from 1 to 10 Gy, median dose 7 Gy, while fraction size varied from 0.5 to 1 Gy, median 1 Gy. In 4 courses, the treatment was initiated with fraction size of 0.5 Gy. Afterwards, during the treatment, the dose was increased to 1 Gy per fraction.

Regarding initial radiotherapy portal field area, the largest area was 13x18 cm (234 cm^2). Out of 16 courses, in 7 fields these areas were reduced due to spleen shrinkage. The results of radiotherapy applied are summarized in Table 3.

Satisfactory clinical responses were recorded in 5 of 6 courses initiated for symptom relief, whereas 1 course led to no response (a patient with CLL). Out of 9 courses initiated for both symptom relief and amelioration of hematology findings, satisfactory clinical response was achieved in 7 (four NHL and three CLL patients), and satisfactory hematologic response in 5 (three CLL and two NHL patients) cases. In this group, there were 2 and 4 non-responders, respectively. The four non-response courses referred to three CLL patients and one NHL patient. One course was applied for abnormal hematology findings resulting from hypersplenism only, but induced no response (NHL patient). Only one patient had myelofibrosis

Table 3. Results

Radiotherapy courses applied for symptom relief, n (%)	6 (37.5)
Satisfactory clinical response	5
Not responded	1
Radiotherapy courses applied for symptom relief and abnormal hematology findings, n (%)	9 (56.3)
Satisfactory clinical response	7
Not responded	2
Satisfactory hematologic response	5
Not responded	4
Radiotherapy courses applied for abnormal hematology findings, n (%)	1 (6.3)
Not responded	1
Total courses, n (%)	16 (100)

Table 4. Toxicity

	n (%)
Anemia	3 (27.3)
Thrombocytopenia	4 (36.4)
Pancytopenia	1 (9.1)
Temporary radiotherapy course interruption	2 (18.2)
Permanent radiotherapy course interruption	1 (9.1)
Erythrocyte transfusions	3 (27.3)
Platelet transfusions	2 (18.2)
Total patients	11 (100)

and received one course of successful splenic irradiation to treat excessive splenomegaly (extramedullary hematopoiesis) and consequential abdominal pain and discomfort.

The majority of courses initiated for symptom control resulted in effective palliation (71%), while a significant number of courses started to treat hematologic sequels of hypersplenism failed to produce desired effects (50%).

Toxicity

Toxicity data are presented in Table 4. Special precaution was taken to monitor peripheral (complete) blood count and general status of the patient before each fraction of splenic irradiation. Sometimes, it is hard to distinguish features of advanced and deteriorating underlying malignant hematologic disease in patients referred for splenic irradiation and side effects of splenic irradiation itself.

In our sample, the most common side effect was thrombocytopenia in four patients (two of them required platelet transfusion), followed by anemia requiring red blood cell transfusion in three patients. Two patients had temporary radiotherapy course interruption due to thrombocytopenia. Only one patient had pancytopenia. In four patients, hematologic toxicity seemed to be dose limiting.

In one patient, the treatment was stopped at just 1 Gy since there was no benefit and the patient was considered as a non-responder to splenic irradiation.

Discussion

In our series of patients, splenic irradiation caused favorable palliative effect, which is comparable with other reports. There was no intent to cause complete response, rather to achieve hematologic response and relief of splenomegaly symptoms, although even complete systemic remissions in all types of lymphoproliferative disorders have been observed after splenic irradiation[9].

Regarding the effects of splenic irradiation, they are mostly comparable with splenectomy, depending on the total dose of fractionated radiotherapy. Splenic irradiation is considered a local treatment, causing the kill of neoplastic cells homed in the spleen and a small proportion of circulating neoplastic cells occurring in splenic vessels at the time of radiotherapy, but it can also induce systemic effects, probably due to the release of chemokines and other autocrine and paracrine regulatory molecules. Cell kill reduces the proportion of neoplastic cells in the spleen with consequential decrease of tumor burden and amelioration of splenomegaly[10]. When considering therapeutic outcome of splenic irradiation, it should be noted that there are several types of response, e.g., regression of spleen, reduction of white blood count (WBC), normalization of RBC and platelet counts, or complete remission. The majority of studies with splenic irradiation in CLL analyzed only few of these features, but all studies demonstrated the efficacy of splenic irradiation through relief of symptoms associated with splenomegaly. Therefore, most cited responses were reduction of spleen size or relief of pain and abdominal discomfort. The response rate using these criteria in reported studies was 50%-90%[3,4,6,7,9,11-13]. Regarding these clinical outcomes, our results are completely comparable. Another study outcome was reduction of increased WBC, recorded in a great proportion of CLL patients. In some studies, a considerable proportion of patients (22%-38%) achieved complete hematologic remission (remission in bone marrow, liver or lymph nodes), but this result could be achieved predominantly in the population of patients with prolymphocytic and hairy cell leukemia, and in some cases of splenic lymphoma[7,9]. In our study, the above mentioned hematologic remission was not analyzed because the respective data were lacking. All our patients had a large tumor mass, most of them had bone marrow infiltration, therefore complete tumor regression was impossible. The results of splenic irradiation regarding treatment of anemia and thrombocytopenia are opposing, ranging from very good to modest[7,12]. A great variety of radiotherapy treatments have been reported. Most studies used single doses between 0.5 and 1 Gy given daily or 1-3 times a week. Radiation therapy was applied until remission or significant reduction of spleen size. Total doses were 5-10 Gy and doses higher than 10 Gy provided no further spleen reduction[3,14].

The most effective dose and fractionation schedule in splenic irradiation is still unknown and is a matter of debate. Depending on the underlying disease, total

doses between 4 and 10 Gy, mostly in 1-Gy fractions, are used. Since there is no adequate evidence based data, different fractionation schemes have been successfully used: daily, weekly, twice weekly and thrice weekly fractionation[3,11,12]. The total radiation dose delivered in our study varied from 1 to 10 Gy, with median dose of 7 Gy, while fraction size varied from 0.5 to 1 Gy, with median of 1 Gy. The doses in our study were comparable with previous reports. There are several mechanisms responsible for the effects of splenic irradiation. These are direct cell kill, immune modulation, or 'radiotherapeutic' splenectomy[10]. In this setting, splenic irradiation is the cause of hyposplenism and immunization with pneumococcus vaccine might be warranted. Our patients were pretreated with chemotherapy and almost all were older than 65, which is appropriate for splenic irradiation. The majority of reports on CLL patients recommend the use of splenic irradiation in elderly patients with predominant bone marrow lymphocytosis, in patients with previous extensive chemotherapy or radiotherapy, and in patients with poor marrow reserve. Splenic irradiation is considered as a non-toxic treatment, therefore subsequent treatment is not compromised[4]. The main clinical indications for splenic irradiation are CLL, prolymphocytic leukemia, hairy cell leukemia, various types of NHL, and myeloproliferative syndromes. Furthermore, splenic irradiation could synergistically improve therapeutic response in primary chemotherapy resistant hairy cell leukemia[15].

In our series, patients with NHL, all in stage IV, predominated. Since NHL is the most common hematologic malignancy infiltrating the spleen and demanding local and systemic therapy, these patients account for the largest share of all patients treated with splenic irradiation[16]. The second group were patients with CLL. Such a distribution is in accordance with other reported series of splenic irradiation.

One patient from our series had myelofibrosis.

Another specific female patient with CLL had splenic irradiation in four courses (one primary treatment and 3 re-irradiations for relapse). These treatments were not associated with any major side effects.

In some patients with excessive splenomegaly and lymphoproliferation predominantly restricted to the spleen, splenectomy could be the therapy of choice. Splenectomy is performed in patients with symptomatic splenomegaly refractory to chemotherapy, but it carries a substantial surgical risk[17,18]. Splenic irradiation is an effective alternative, with a considerably lower risk. All our patients had irradiation fields encompassing the whole spleen. Clinical target volume was defined by computerized tomography (CT), abdominal ultrasonography and clinical examination. Enlarged spleen can fill the whole left hemiabdomen, with an increasing risk of spleen rupture.

Enlarged spleen shrinks during the radiotherapy course, so it is necessary to adjust the target volume. It this case, palpation can be very easily performed and informative. In complicated cases, ultrasonography is needed. In our series, a meaningful proportion of patients had shrinkage of treatment field due to diminution of spleen during radiotherapy.

The acute toxicity of splenic irradiation is low, especially when compared with cytotoxic chemotherapy. In our patient series, toxicity was acceptable and they had completed their radiotherapy course mainly without serious side effects. The most common side effects included thrombocytopenia, anemia and pancytopenia. Toxicity profile in our patients was in concordance with other reports[10,14,19].

There were some limitations of our study. It was a retrospective study focused on treatment-related toxicity profile, feasibility and clinical setting rather than systemic response and survival because data regarding longer follow up and clinical outcome were lacking. It should be noted that splenic irradiation is a very rare and decreasingly required procedure, so it takes a long period to collect greater number of patients. In the future, we plan to acquire all necessary data to assess the real clinical value and effect of splenic irradiation in our setting and to compare it with other reports.

Conclusion

In properly selected patients, splenic irradiation can provide effective and low-toxic palliation. It can compensate for the shortcomings of systemic treatment in various hematologic malignancies, especially in cases when splenectomy is neither possible nor necessary. Although splenic irradiation is not so frequent treatment, in a multidisciplinary clinical setting including hematologist and radiation oncologist it can

be considered as the treatment of choice, taking into account regular assessments, adequate fractionation, field reduction and monitoring of blood count.

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Sažetak

OZRAČIVANJE SLEZENE U BOLESNIKA SA ZLOĆUDNIM I DRUGIM HEMATOLOŠKIM BOLESTIMA – ISKUSTVA JEDNE BOLNIČKE USTANOVE

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Ozračivanje slezene je najstariji poznati način palijativnog liječenja bolesnika s različitim zloćudnim hematološkim bolestima. Ima za cilj umanjiti kliničke simptome splenomegalije, kao i posljedice hipersplenizma. Ozračivanje slezene ima značajan učinak uz nisku toksičnost, ali točna radioterapijska doza kao i način frakcioniranja nisu poznati. Između 1996. i 2010. godine 11 bolesnika je liječeno u našoj ustanovi ovim postupkom. Ti bolesnici su primili ukupno 16 aplikacija frakcioniranog zračenja. Šest bolesnika je imalo ne-Hodgkinov limfom, četiri kroničnu limfatičnu leukemiju, a jedan bolesnik je imao mijelofibrozu. Medijan aplicirane tumorske doze bio je 7 Gy, a medijan aplicirane doze po frakciji 1 Gy. Korištena su nasuprotna paralelna te tangencijska radioterapijska polja. Zbog smanjenja kliničkog ciljnog volumena terapijsko polje je tijekom postupka radioterapije smanjeno u 44% radioterapijskih aplikacija. Od radioterapijskih postupaka započetih s ciljem kontrole simptoma 71% ih je rezultiralo uspješnom palijacijom, dok je od postupaka koji su započeti radi popravka hematoloških posljedica hipersplenizma njih 50% izazvalo željeni učinak. Najčešće nuspojave bile su trombocitopenija i anemija. Ozračivanje slezene omogućuje učinkovitu i nisko toksičnu palijaciju simptoma, ali je manje uspješno u liječenju hematoloških poremećaja uzrokovanih hipersplenizmom.

Ključne riječi: *Slezena, tumori – radioterapija; Palijativna skrb; Limfom, ne-Hodgkinov; Leukemija; Mijelofibroza*