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BRIEF ARTICLE

Helical tomotherapy and systemic targeted therapies in solitary plasmacytoma: Pilot study

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Abstract

AIM: To assess the feasibility of the combination of helical tomotherapy® (HT) and a concurrent systemic targeted therapy in patients with solitary plasmacytoma (SP) with the aim to decrease toxicity while improving therapeutic efficacy.

METHODS: Six patients with biologically, histologically, and radiologically confirmed SP were treated using HT and a systemic targeted treatment concomitantly. Total dose was 40 Gy/20 fractions. Four patients received 4 cycles of concurrent lenalidomide-dexamethasone combination and two patients were treated with concomitant bortezomib-dexamethasone. All toxicities were described using the Common Terminology Criteria for Adverse Effects v3.0.

RESULTS: Five patients had a bone tumor and one patient had an isolated pancreatic mass. Five patients presented with pain, one had neurologic symptoms related to medullary compression, which was treated by an emergency surgery. Median age was 59.5 years (range, 50-74 years). All patients had initial positron emission tomography-computed tomographys, three patients had total body bone magnetic resonance imaging examination, and three patients had computed tomodensitometry scans. The toxicity profile was excellent with no higher than grade 1 toxicity. Four of the six patients experienced a partial radiological response, four had complete response on positions emission tomography and 5/6 patients experienced a complete relief of their symptoms 4 mo after treatment. At a median follow-up of 18 mo, 5/6 patients were controlled clinically, radiologically, and biologically.

CONCLUSION: Using HT, we could deliver a highly conformal irradiation concurrently with a molecularly targeted therapy. This association yielded in a high response rate and a low toxicity. A prospective study with longer follow-up will help determining the true benefit of such strategy.

Key words: Plasmacytoma; Radiation therapy; Targeted treatment; Tolerance; Lenalidomide; Bortezomib

Core tip: Solitary plasmacytomas consist of a localized collection of malignant plasma cells without evidence of a systemic plasma cell proliferative disorder. It accounts for about 5% of all plasma cell neoplasms and may present with a single bone lesion (single bone plasmacytoma) or as a single extramedullary or extra-

osseous lesion. Using helical tomotherapy®, we could deliver a highly conformal irradiation concurrently with a molecularly targeted therapy. This association yielded in a high response rate and a low toxicity. A prospective study with longer follow-up will help determining the true benefit of such strategy.

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INTRODUCTION

Solitary plasmacytomas (SPs) consist of a localized collection of malignant plasma cells without evidence of a systemic plasma cell proliferative disorder. It accounts for about 5% of all plasma cell neoplasms and may present with a single bone lesion single bone plasmacytoma (SBP) or as a single extramedullary or extra-osseous lesion. The main symptoms presented by patients with SBPs are pain, soft tissue swelling, or pathological fractures, which can occasionally lead to significant neurological symptoms when the axial skeleton is affected. Diagnosis of a SP requires ruling out the presence of a systemic plasma cell disorder[1]. In addition to pathological confirmation of the plasmacytoma, complete bone examination should be conducted, including computed tomodensitometry (CT), magnetic resonance imaging (MRI), and 18-fluorodeoxyglucose positions emission tomography-computed tomodensitometry (PET-CT)[2]. Serum or urine can demonstrate the presence of a monoclonal protein, but these tend to be small.

Helical tomotherapy® (HT) (Accuray Incorporated, Sunnyvale, CA, United States) is a new intensity-modulated radiation treatment combined with megavoltage CT imaging allowing an accurate patient positioning. This technique reduces the doses received by critical normal organs and has been already used successfully against hematologic diseases[3-6].

MATERIALS AND METHODS

Inclusion criteria

Between September 2009 and September 2011, six patients with proven solitary plasmocytomas were treated with helical tomotherapy concomitantly with a systemic targeted treatment. Medical records of the patients were analyzed for demographics, tumor description, treatment, toxicity and outcomes. Diagnosis of SP was confirmed through a complete biological, radiological, histological, and clinical evaluation. The possibility of multiple myeloma was eliminated. All patients met the following criteria: a biopsy-proven plasma cell tumor, a bone marrow biopsy showing less than 10% plasma cells without evidence of clonality as established by flow cytometry analysis, a single pathologic lesion in the imaging work up (PET-CT, X-ray bone scan, MRI of total body bones), no biological abnormalities attributable to myeloma, and low concentration of urine or serum monoclonal protein, if present[1].

Treatments

Helical tomotherapy was used to deliver 40 Gy in 20 fractions concomitant with a targeted antineoplastic agent. Treatment planning was performed as previously reported[4,5]. A treatment planning CT scan was performed then images were transferred to treatment planning system (Eclipse 3D, Varian Medical Systems Inc., Palo Alto, United States). The gross tumor volume (GTV) was contoured then a 0.5 cm margin was added to the GTV to generate the clinical target volume; a margin of 0.5 cm was added to obtain the planning target volume (PTV), to account for internal organ motion and setup errors. Dose calculation was performed using the helical tomotherapy treatment planning system (TomoTherapy HI-ART version 3.1.2.3; TomoTherapy Inc., Madison, United States), using a jaw width of 2.5 cm, a pitch of 0.286 and a modulation factor of 2.5. Dose constraints were placed on both PTV and organs at risk (Figure 1).

Four patients received lenalidomide and dexamethasone, two of whom also receiving zoledronic acid. The two other patients were treated with bortezomib and dexamethasone. Lenalidomide was administered at a dose of 25 mg/d for 21 d per cycle for four cycles with a 1-wk break between cycles. Dexamethasone was given at 40 mg on d1 to d4 and d9 to d12 of the first cycle, and then only from d1 to d4 during the remaining cycles. Bortezomib was administered at the usual regimen of 1.3 mg/m^2 on d1, d4, d8, and d11, every 3 wk for 4 mo. Lenalidomide and bortezomib were initiated at the same time as the tomotherapy treatment.

Follow-up

Clinical, biological, and radiological follow-ups were performed at week 6, month 4, and month 12 after the initial therapy. The primary end point of this study was the acute toxicity profile of this treatment combining radiotherapy with novel targeted agents. We also analyzed the clinical, biological, and radiological response to the treatment. Radiological responses were defined as complete response, partial response, or stable disease according to the Response Evaluation Criteria in Solid Tumors.

RESULTS

Patients

Five patients had a bone tumor and one patient had an isolated pancreatic mass. Five patients presented with pain, one had neurologic symptoms related to medullary compression, which was treated by an emergency surgery. Median age was 59.5 years (range, 50-74 years). Patients'

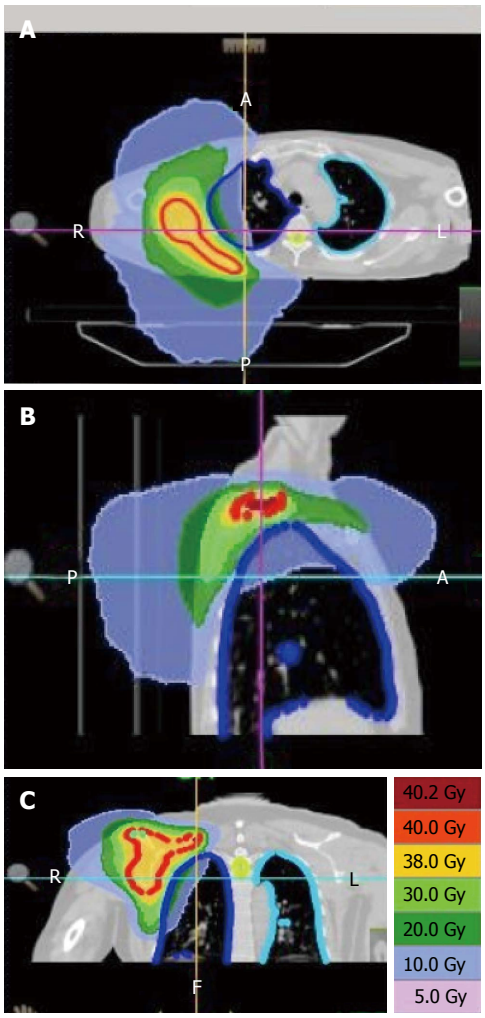

Figure 1 Example of highly conformal irradiation allowed by helical tomotherapy: Irradiation of a scapular bone plasmacytoma. A: Transverse view; B: Sagittal view ; C : As shown by isodoses curves, radiation doses to the ipsilateral lung could be significantly reduced while target coverage was excellent. A: Anterior; R: Right; L: Left; P: Posterior.

and tumors' characteristics are shown in Table 1. All patients had initial PET-CTs, three patients had total body bone MRI examination, and three patients had CT scans. All of them had an abnormal focal uptake on PET/CT imaging and abnormalities on MRI and CT scans. Two patients had no monoclonal protein, two had monoclonal immunoglobulin IgG Lambda at a low level, and two patients had monoclonal light chains.

Treatment outcome

Four patients experienced complete radiological response and four had partial response on PET/scan. Of the five patients who initially suffered from pain, three experienced a complete relief of symptoms 6 wk after treatment and all of them were relieved after 4 mo. Of the two patients who had monoclonal light chains, we observed a stable monoclonal chain ratio in one case with normalization of plasma gamma globulin and decrease of the ratio in the other case. Among the patients who had monoclonal immunoglobulin IgG Lambda, one had a complete disappearance of this immunoglobulin and the other one had a large drop in the value of the peak.

Table 1 Patients' characteristics

Characteristics	Value
Patients (*n*)	6
Median age, yr (range)	59.5 (50-74)
Gender (*n*)	
Female	1
Male	5
PS (*n*)	
0	2
1	4
2	0
Tumor site (*n*)	5
Bone (*n*)	
Scapula	1
Spine	3
Pelvis	1
Extra osseous	1
Symptoms (*n*)	
Pain	5
Compression	1
Neurological symptoms	2
Surgery (*n*)	1
Targeted treatment	
Lenalidomide, DXM	2
Bortezomib, DXM	2
Lenalidomide, DXM, zoledronic acid	2
helical tomotherapy, 40 Gy (*n*)	6

DXM: Dexamethasone; PS: Performance status.

With a median follow-up of 18 mo (range, 11-22 mo), five of the six patients were free of clinical, radiological, or biological progression. Furthermore, four patients had achieved a radiological response and five patients had a complete relief of symptoms 4 mo after treatment.

Toxicity

No acute or delayed toxicity more than grade 1 was reported at 6 wk, 4 mo, and 12 mo after treatment.

DISCUSSION

In this study, we evaluated six cases of proven SPs treated with HT concomitantly with a targeted molecular therapy. We found an excellent acute toxicity profile for the combination of highly conformal intensity-modulated radiotherapy delivered through HT and lenalidomide or bortezomib. No acute toxicity and no treatment disruption were reported. No delayed toxicity was reported with a median follow-up of 18 mo.

Although local response to radiotherapy is very good[7-10], about half of patients with SPs eventually develop a multiple myeloma[11-17]. Prescription doses used to irradiate this type of tumors are discussed in the literature. Some authors recommend more than 40 Gy while others have reported no dose-response relationship beyond 35-40 Gy[18-22]. Therapeutic decisions are

usually based on risk factors for recurrence, such as the tumor size[23-29].

The high risk of evolution toward myeloma encouraged new strategies for SPs. Lenalidomide is a thalidomide derivative. It exerts direct antitumor effect (apoptosis induction), immunomodulatory action, and antiangiogenic activity. Lenalidomide plus dexamethasone was shown superior to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma[30]. Bortezomib inhibits proteasome and thus prevents degradation of proapoptotic factors. Combination of bortezomib with melphalan-prednisolone was shown superior to melphalan-prednisolone alone in patients with diagnosed myeloma who were ineligible to high-dose therapy[31].

There is a growing interest in the literature for combining these agents and others with radiation for treatment of solitary plamacytoma. Some authors have thus recommended combined-modality therapy, especially for patients with a high risk of recurrence or systemic evolution[28]. Co-administration of radiotherapy and these new systemic treatments, including lenalidomide and bortezomib, for a short period of time, could enhance local control and could potentially eradicate subclinical disease at the time of diagnosis, in order to prevent or delay further escalation to myeloma. However, these targeted molecular agents carry a theoretical risk of increasing radiation-induced toxicity and the addition of molecular targeted agents to radiotherapy warrants a careful consideration[32]. Thus, it was demonstrated that bortezomib could enhance radiation-induce apoptosis in sold tumors, suggesting also a risk of enhancing radiation-induced toxicity[33]. There are scarce data on the combination of lenalidomide with irradiation but preclinical data have reported radio-sensitizing effects in normal hematopoietic bone marrow[34].

As we previously reported[4,5] and as illustrated in Figure 1 for one of the patients included in this study, helical tomotherapy could deliver adequate target coverage while minimizing doses to critical organs. Incorporation of this highly conformal irradiation modality could help delivering effective radiation therapy and concurrent targeted molecular agent while minimizing the risk of local adverse effects.

These preliminary results showed an excellent acute toxicity profile for helical tomotherapy combined with lenalidomide or bortezomib. Although further follow-up is warranted for ensuring the lack of delayed toxicity, these data encourage further assessment of new combined schedules with radiotherapy in order to improve response rate in plasmacytomas, with the possibility to rapidly achieve pain control and suppress or delay subsequent development of other bone lesions or multiple myeloma.

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COMMENTS

Background

Solitary plasmacytomas (SPs) consist of a localized collection of malignant plasma cells without evidence of a systemic plasma cell proliferative disorder. It accounts for about 5% of all plasma cell neoplasms and may present with a single bone lesion single bone plasmacytoma (SBP) or as a single extramedullary or extra-osseous lesion.

Research frontiers

Diagnosis of a SP requires ruling out the presence of a systemic plasma cell disorder In addition to pathological confirmation of the plasmacytoma, complete bone examination should be conducted, including computed tomography (CT), magnetic resonance imaging (MRI), and 18-fluorodeoxyglucose positions emission tomography (^{18}FDG-PET). Serum or urine can demonstrate the presence of a monoclonal protein, but these tend to be small. The high risk of evolution toward myeloma encouraged new strategies for SPs. Lenalidomide is a thalidomide derivative. It exerts direct antitumor effect (apoptosis induction), immunomodulatory action, and antiangiogenic activity. Lenalidomide plus dexamethasone was shown superior to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma. But no data is available in SP.

Innovations and breakthroughs

There is a growing interest in the literature for combining these agents and others with radiation for treatment of solitary plamacytoma. Some authors have thus recommended combined-modality therapy, especially for patients with a high risk of recurrence or systemic evolution.

Applications

These preliminary results showed an excellent acute toxicity profile for helical tomotherapy combined with lenalidomide or bortezomib. Although further follow-up is warranted for ensuring the lack of delayed toxicity, these data encourage further assessment of new combined schedules with radiotherapy in order to improve response rate in plasmacytomas, with the possibility to rapidly achieve pain control and suppress or delay subsequent development of other bone lesions or multiple myeloma.

Peer review

This subject is of paramount importance for oncologists, radiologists, and neurosurgeons alike. The paper is well written and comprehensible with clear figure and good discussion.

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