TOTAL MARROW IRRADIATION WITH HELICAL TOMOTHERAPY: A CASE REPORT

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A 53-year-old Asian woman with plasma cell myloma with IgG/kappa stage IIIa post chemotherapy was selected for autologous hematopoietic cell transplantation (HCT). Total marrow irradiation (TMI) tomotherapy was planned as a preconditioning regimen of HCT. A total dose of 800 cGy (200 cGy/ fraction) was delivered to the bone marrow. More than 10 months post transplant without evidence of active disease for the patient was noted. Except for Grade 1 nausea and vomiting there were no significantly adverse effects during TMI. The preconditioning regimen for the bone marrow transplant with helical tomotherapy targeting the bone marrow of the whole body is potentially less toxic and as efficacious in the patient. Antiemetics should be prescribed for the whole course of TMI for emesis prevention.
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Key words: Helical tomotherapy, Multiple Myeloma, Total Bone Marrow Irradiation

INTRODUCTION

Multiple myeloma is characterized by neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. The diagnostic evaluation includes serum and urine protein electrophoresis with immunofixation, bone marrow biopsy and aspiration, and an evaluation for end-organ damage. The indications of treatments for plasma cell disorder are anemia, hypercalcemia, renal insufficiency, lytic bone lesions or severe osteopenia, and extramedullary plasmacytomas [1]. The main treatment options for standard risk multiple myeloma are chemotherapy or hematopoietic cell transplantation (HCT). Overall survival is markedly shortened for patients who experienced disease progression at 6 or 12 months.

Total body irradiation (TBI) has been widely used as part of an autologous hematopoietic cell transplantation (HCT) preparative regimen [3]. However, long-term complications following TBI and HCT from non-hematopoetic tissues receiving potentially unnecessary irradi-

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ation are common. One study reported the most common complications include [11] cataracts (15%); Sicca syndrome (13%); hypothyroidism (6.5%); thyroiditis (3%) and asymptomatic alterations in pulmonary function (19%) [4].

Helical tomotherapy (HT) is a new CT-based rotational intensity modulated radiotherapy that can deliver highly conformal dose distributions [7,6]. According to the properties of HT, HT could be attributed to total marrow irradiation (TMI) with a dose reduction to non-hematopoetic tissues to achieve preliminary feasible results and decrease toxicities more than TBI [12,5].

Here, we present the first successful multiple myeloma patient using TMI to the bone and bone marrow spaces along the entire axis as part of an HCT regimen.

CASE REPORT

A 53-year-old woman with a history of hepatitis-C positive, heart failure syndrome, vascular heart disease with moderate tricuspid regurgitation and degenerated joint disease visited our hospital because of lower back pain for one month in February 2007. The compression fracture of T9-12 was impressed by T-spine x-ray. Bone scan showed metastatic, traumatic or infectious bone lesions at the T spine and bilateral anterior ribs. Laboratory data revealed anemia (hematoglobin: 9.4 g/dl), negative urine Bence-Jones protein, reticulocyte count (1.2%) and hypergammaglobulinemia (Ig G: 7720 mg/dl). Multiple myloma was suspected. Bone marrow study showed plasma cell myloma with IgG/kappa stage IIIa [2]. Then, she received modified arm A of IFM 9502 trial treatment [8] (Figure 1). After 3 cycles of the vincristine-adriamycin-dexamethasone (VAD) regimen without tumor progression (>25% increase in tumor mass) and systemic toxicities, peripheral blood stem cells (PBSCs) were collected and pre-HCT evaluation was done. Then, the patient received TMI 8 Gy with helical tomotherapy technique delivered in 4 fractions over a 4-day period (days -6, -5, -4, -3) plus HDM140 administered on day -2 by infusion over 30 minutes. PBSC transplantation was carried out on day 0. Hematopoietic growth factor support

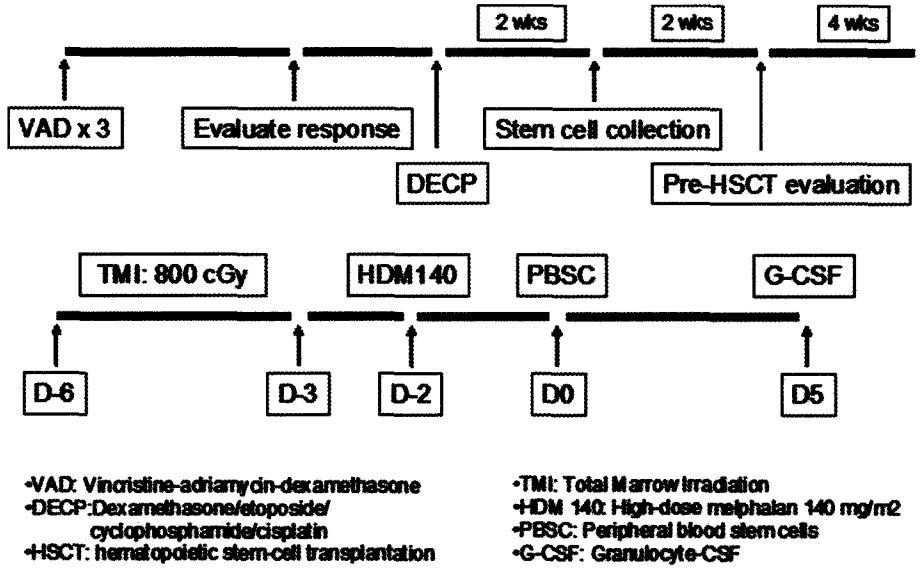

Fig 1. Modified IFM 9502 Trial auto- hematopoietic cell transplantation treatment plan: change total body irradiation to total marrow irradiation.

with granulocyte- CSF (G-CSF) was prescribed on day 5 after transplantation until granulocyte recovery.

Before TMI treatment, all treatment modalities and treatment room were sterilized by Ultraviolet-C within 30min. The patient was transferred by a separate elevator to the treatment room at 7:30 a.m. with antiseptic dressing. The operator was also dressed with antiseptic dressing to contact and to setup the patient. During the treatment, the operators waited with antiseptic dressing in the separate room without touching anything until the treatment finished. Then, the operators went into the treatment room to help the patient re-dress with germless dressing and sent the patient back to her separate room. During TMI, patient was lying supine on the couch and fixed with AccuFix™ Cantilever Board™ and BlueBag™ (Medical Intelligence). AccuFix ™ Cantilever Board™ was used for the fixation of head and neck. BlueBag™ was used for immobilizing body and limbs. There was no extra order to limit patient's respiratory pattern. The patient was scanned in a large bore CT scanner (Siemens, SOMATOM Definition, Dual source computed tomography system) with two image sets. The level at 15 cm above the knee was used as a reference point to separate the upper and lower set. The upper PTV was delineated to the slice from the reference point back two slices. The lower PTV was targeted from the slice of the reference point in the lower image set. The upper PTV in the last targeting slice (from the slice of the reference point back two slices) and the lower PTV in the first slice (reference point) were given 100% of the dose. Then, the dose in the junction would be received 150% of the dose. Both image sets used the Philips Pinnacle[3] treatment planning system

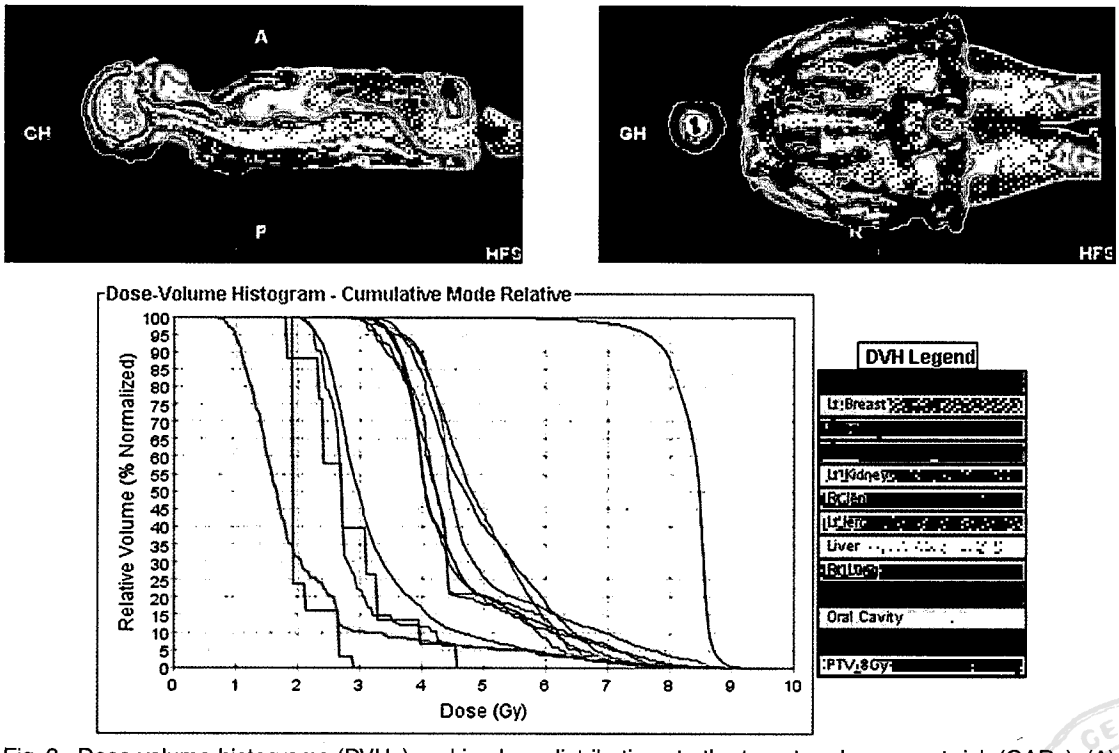

Fig. 2 Dose volume histograms (DVHs) and isodose distributions to the target and organs at risk (OARs). (A) Isodose dose distribution for total marrow irradiation (TMI): segital view. (B) Isodose dose distribution for total marrow irradiation (TMI): coronal view. (C) DVHs for total marrow and OARs. Red, Green, pink and white represent the area of PTV received 8 Gy, 7.2 Gy, 6.4Gy and 4 Gy, respectively.

for contouring. Then, the plan was transferred to the Tomotherapy *Hi Art* Planning system (Tomotherapy, Inc., Madison, Wisconsin, USA). The clinical target volume (CTV) included the entire skeletal system. A planning target volume (PTV) was generated with a 0.5 cm margin for CTV_{spine}, 0.5 cm margin for CTV_{pelvic} and 0.8 cm for $CTV_{extremities}$, respectively. For the ribs, inspiration, expiration and shallow breathing of CT scan were performed. The slice thickness and pitch of Dual source computed tomography system for chest scanning was adjusted to 5 mm and 1.5, respectively. Time spent chest scanning was 5 seconds. It was adapted for the patient holding breath without difficulty during the chest scanning process. The shallow breathing scan was used as the reference scan, and the inspiration and expiration scans were used to determine the margins for the planning target volume. The prescription dose was 200 cGy per fraction (for 4 fractions) for a total dose of 800 cGy to the PTV. The normal tissue dose constraints utilized were based on the results of the survey of the clinical outcome of the target dose and dose limits to various organs at risk (OARs) of the head, chest and abdomen. The field width, pitch, and modulation factor (MF) used for the treatment planning optimization were 2.5 cm, 0.32 and 3.0 for the upper part and 5.0 cm, 0.4 and 2.0 for the lower part, respectively. The dose volume histograms (DVHs) were calculated for the target and individual OARs. Toxicity of treatment was scored according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0).

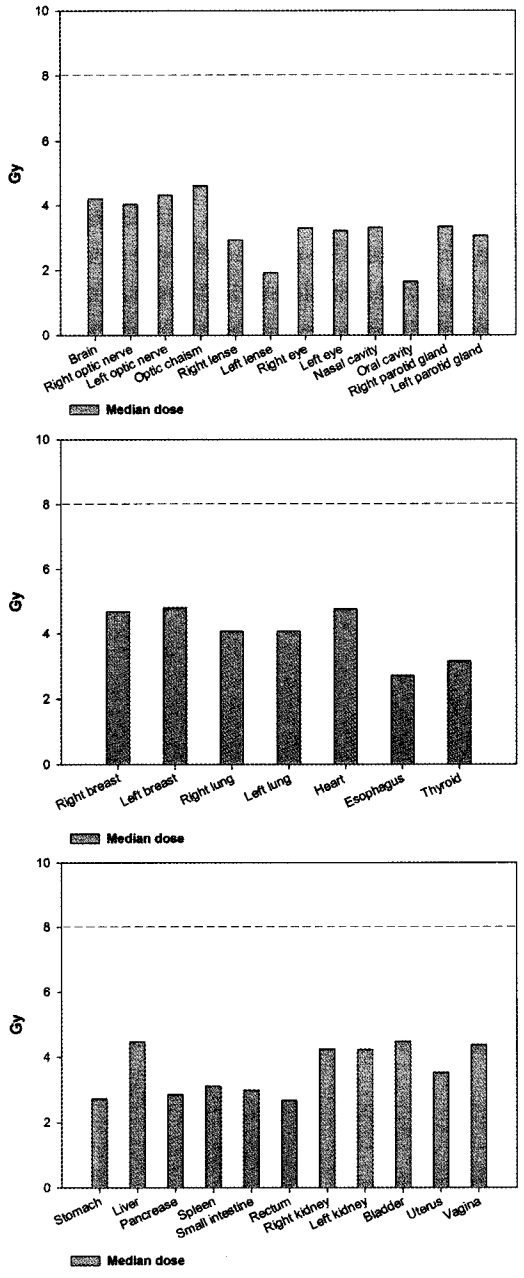

Fig. 3 Total marrow irradiation (TMI) of mean dose to various organs at risk (OARs) (A) Head and neck. (B) Chest. (C) Abdomen.

Daily check of patient positioning was performed by the MVCT system integrated in the tomotherapy machine. Three sets of MVCT scan (scan 1, orbits to T4; scan 2, T10 to the ischial tuberosities; scan 3, 15 cm above knee to 15 cm below knee) were performed with a coarse condition to the check the patient's whole body alignment. The average of 3 sets of setup error was applied. The tolerance of setup error allowed only a 5 mm in any of the three translation directions and 1° of difference in roll. If the setup error was larger than the criteria that re-setup must be done.

More than 10 months post-transplant, the patient was alive with no evidence of disease.

Grade 1 nausea and vomiting were noted after the first fraction of tomotherapy TMI and grade 1 mucositis was noted after the treatment course had finished. Other than the above, there were no adverse effects of TMI tomotherapy and the overall treatment course of the patient was similar to others treated with this conditioning regimen.

The conformal index (CI) for PTV was calculated using the formula CI = TV_{RI}/TV, where TV_{RI} was the target volume covered by the reference isodose and TV was the entire target volume [10]. The homogeneity index is defined as HI = D_{max}/D_{Rx}, where D_{Max} was the maximum dose in the PTV and D_{Rx} was the prescription dose [9]. The conformal index (CI) of $PTV_{Bone\ marrow}$ achieved 95%. The H-index of the entire skeletal system was 1.1 to 1.2. Dose volume histograms (DVHs) and isodose distributions to the target and OARs are shown in Figure 2A, 2B and 2C. The dose of TMI tomotherapy to various OARs of head, chest and abdomen varied from 2.09 Gy to 4.79 Gy, 2.90 Gy to 4.96 Gy and 2.88 Gy to 4.92 Gy, respectively (Figure 3A, 3B and 3C).

The mean value of registration for tomotherapy with pretreatment and post-treatment using kVCT- MVCT fusion are shown in Table 1. The average treatment time for the upper and lower part in beam-on time, setup time and MVCT registration time took roughly 48 min and 11min, 15 min and 10 min, 10 min and 5 min, respectively.

DISCUSSION

This female patient was the first successful Asian case of TMI treated with HT to the entire skeletal system of a multiple myloma as part of autologous hematopoietic cell transplantation regimen. Until presentation, she was well without evidence of active disease and was receiving oral thalidomide for maintenance-therapy. During TMI tomotherapy, only grade 1 nausea was noted.

TMI achieved is at least as effective as marrow suppression with less toxicity. By successfully reducing dose accumulation in the oral cavity, esophagus, stomach and small bowel, only grade 1 mucositis and nausea were noted during TMI (Figure 3A, 3B and 3C). To account for set-up variability and breathing motion, a planning target volume (PTV) was generated with a 0.5 cm margin for CTV_{spine}, 0.5 cm margin for CTV_{pelvic} and 0.8 cm for $CTV_{extremities}$, respectively. According to the report by Hui SK and others [5], a 1cm margin around the bone marrow to account for breathing motion and uncertainty could result in successful treatment . In our experience, using 0.5 cm, 0.5 cm and 0.8 cm margin respectively for CTV_{spine}, CTV_{pelvic} and $CTV_{extremities}$ could achieve the same result.

TMI tomotherapy could achieve high conformity, and homogeneity without compromise of critical organs. The CI of $PTV_{Bone\ marrow}$ achieved 95% and the H-index for the bone and

Table 1. Mean of registration for tomotherapy with pretreatment and post-treatment using kVCT- MVCT fusion.

Shift	Pretreatment		Post-treatment		
	Upper part	Lower part	Chest	Abdomen	Knee
Lateral (mm)	1 ± 0.6	1.5 ± 0.6	1.5 ± 1.0	0.4 ± 0.7	0 ± 0.1
Longitudinal (mm)	10.6 ± 1.2	4.5 ± 2.3	0.8 ± 0.9	1.2 ± 1.1	1.3 ± 1.0
Vertical (mm)	3.3 ± 1.5	2.9 ± 1.9	1.7 ± 2.2	3.1 ± 0.6	0.7 ± 0.5
Roll (degree)	0.3 ± 0.1	0.5 ± 0.4	0.5 ± 0.6	0.4 ± 0.1	0.7 ± 0.3

bone marrow spaces along the entire axis was around 1.1. It is helpful to use various sections of the body in MVCT scans for the pretreatment patient setup. We repeated the MVCT scan after the treatment to monitor the patient's moving condition during the long treatment procedure. The registration time for upper and lower part scanning with MVCT took 10 and 5 minutes, respectively. For pretreatment registration, only the longitudinal direction needed 10.6 mm correction and other directions were less than 5 mm in the upper part. For post-treatment image scans from the pretreatment position, the maximal correction occurred in the vertical direction of abdomen took only 3.1 mm and all the others were limited to 2 mm in sections of the chest, abdomen and knee (Table 1). As mentioned earlier, this was well within our PTV margin design as mentioned before.

Because most critical organs are located in the central part of the body, two image sets were scanned and separated at the level of 15 cm above the knee. Thus, this approach led to different weights in the upper and lower part. The table tilted down slightly when the table moved forward and caused 10.6 mm movement for longitudinal registration. However, post-treatment registration data revealed longitudinal correction in the chest, abdomen and knee sections of 0.8 mm, 1.2 mm and 1.3 mm, respectively. The stabilization during treatment was reliable.

To the best of our knowledge, this is the first report of a preconditioning regimen for bone marrow transplant with helical tomotherapy targeting the bone marrow of the whole body in an Asian patient. It is potentially less toxic and equally as effective. Antiemetics should be prescribed in the whole course of TMI tomotherapy for emesis prevention. This combination treatment needs to be validated by clinical trials.

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以導航螺旋刀進行全骨髓放射線治療：病例報告

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一位第三期多發性骨髓瘤之 53 歲亞洲女性經化學治療後決定接受自體骨髓移植治療。而自體骨髓移植治療前則接受全骨髓放射線治療。整個療程之劑量共計 800 cGy 分成四天，每天接受 200 cGy 之全骨髓照射劑量。接受移植後，歷經十個多月追蹤，無證據顯示其復發。全骨髓照射治療療程中，僅發生第一級之噁心及嘔吐。與過去全身放射治療經驗相較，全骨髓放射線治療較不具毒性且可達相近的治療結果。整個治療過程建議於治療前給予止吐劑以降低治療之副作用。
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關鍵詞：導航螺旋刀、多發性骨髓瘤、全骨髓放射線治療