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Proton therapy in the management of non-Hodgkin lymphoma

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Abstract

Proton therapy (PT) is a highly conformal type of radiation therapy that can target the tumor while sparing dose to surrounding normal tissues. This study reviews a single institution's experience managing patients with non-Hodgkin lymphoma (NHL) treated with PT. Eleven patients with NHL were treated with PT from January 2008 to January 2014 on an institutional review board-approved outcomes tracking protocol, and included patients with indolent orbital lymphoma ($n = 4$), primary mediastinal B-cell lymphoma ($n = 3$), plasmablastic lymphoma ($n = 2$) and natural killer (NK) T-cell lymphoma ($n = 2$). The median follow-up was 38 months. The 2-year rate of local control was 91%, with one patient with NK T-cell lymphoma having recurrence in-field. Toxicities were limited to grade 2 at highest, during follow-up. PT is a feasible and effective treatment for NHL. Early outcomes are favorable. Longer follow-up and more patients are needed to confirm our findings.

Keywords: Lymphoma and Hodgkin disease, radiation, outcomes, proton beam therapy

Introduction

Non-Hodgkin lymphoma (NHL) consists of a heterogeneous group of malignancies with varied clinical presentation and biological behaviors. The estimated number of new cases in 2014 is 70 000, which represents 4% of all cancers diagnosed and 3% of cancer deaths in the United States [1]. The histological subtypes of NHL are typically classified as indolent and aggressive histologies.

Although NHL is predominantly managed with chemotherapy, radiation therapy is used as definitive treatment among patients with early-stage indolent lymphoma and natural killer (NK) T-cell lymphoma. Radiation therapy is also used as consolidative treatment in patients with early-stage and bulky aggressive histologies following chemotherapy. Despite growing evidence of the benefit of radiation therapy for patients with NHL, concerns regarding radiation-associated late toxicities persist and, consequently, radiation therapy is omitted in the management strategy of many patients for whom it may be of benefit.

In an effort to reduce radiation-related toxicity, several important modifications have been made to traditional historic radiation treatment. These include reducing the dose of radiation in both definitive and consolidative radiotherapy [2], smaller field sizes [3] and using modern radiotherapy techniques, such as intensity-modulated radiation therapy [4,5]. Proton therapy is another way to potentially reduce radiation-associated toxicity. There are several studies examining the dosimetric benefits of proton therapy in patients with Hodgkin lymphoma (HL) [6–8]; however, there are limited published data reporting outcomes of patients with NHL treated with proton therapy.

The present study evaluated the disease control, toxicities and radiation dose delivered to various organs at risk (OARs) using proton therapy either definitively or in combination with chemotherapy among a cohort of consecutively treated patients with NHL.

Materials and methods

Between January 2008 and January 2014, 11 patients with NHL were treated with definitive ($n = 6$) or consolidative radiation therapy ($n = 5$). All patients were treated on an institutional review board-approved outcomes tracking protocol with proton therapy. Prospectively collected data in the charts were extracted, including patient and disease characteristics prior to treatment, chemotherapy, proton treatment plan and acute and late side effects and disease control. This cohort included four patients with indolent orbital lymphoma, three patients with primary mediastinal lymphoma, two patients with plasmablastic lymphoma and two patients with NK T-cell lymphoma. Table I outlines patient characteristics, involved sites of disease and treatment details.

Patients were simulated supine with custom immobilization devices including VacLok™ bags (Civco Medical Solu-

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Table I. Patient and tumor characteristics.

Patient no.	Age (years)	Histology	Site	Stage	Chemotherapy	Role of proton treatment	Radiotherapy dose	Follow-up (months)	Status
1	56	Follicular	Orbit	I	None	Definitive	24 Gy (RBE) in 1.5 fx	57	NED
2	53	Follicular	Orbit	IV	None (previously on rituximab)	Definitive	24 Gy (RBE) in 1.5 fx	45	AWD
3	48	MALT	Orbit	I	None	Definitive	30.6 Gy (RBE) in 1.8 fx	68	NED
4	56	MALT	Orbit	I	None	Definitive	30.6 Gy (RBE) in 1.8 fx	72	NED
5	36	DLBCL	Mediastinum	IA (bulky)	R-CHOP × 6c with CR	Consolidative	36 Gy (RBE) in 1.5 fx	38	NED
6	24	DLBCL	Mediastinum	IIB (bulky)	R-CHOP × 6c with CR	Consolidative	30.6 Gy (RBE) in 1.8 fx	10	NED
7	19	DLBCL	Mediastinum	IIA	Initial: R-CHOP × 6c. Second line: R-ICE × 2c followed by R-ESHAP × 2c, high-dose chemotherapy and autologous stem cell transplant ≥ residual biopsy + disease in prevascular space	Consolidative	41.4 Gy (RBE) in 1.8 fx	36	NED
8	42	Plasmablastic	Stomach and left adrenal gland	IV	Hyper-CVAD × 8c	Consolidative	36 Gy (RBE) in 2 fx	25	NED
9	66	Plasmablastic	Base of skull and paranasal sinuses	IV	CHOP × 6c + gitoxin, then intrathecal methotrexate	Consolidative	60 Gy (RBE) in 1.2 fx BID	53	Died of second cancer
10	4	NK T-cell	Oropharynx, hard palate and hypopharynx	IIE	SMILE × 2c pre- and post-proton therapy (4c total)	Definitive	50.4 Gy (RBE) in 1.8 fx	6	NED
11	57	NK T-cell	Infratemporal fossa, orbit and cavernous sinus	IV	CHOP × 3c	Definitive	59.6 Gy (RBE) in 1.2 fx BID plus 2 Gy × 1	7	Local progression, died

MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; CVAD, cyclophosphamide, vincristine, doxorubicin and dexamethasone; NK, natural killer; R-CHOP, rituximab, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine and prednisolone; c, cycles; CR, complete response; R-ICE, rituximab, carboplatin and etoposide; R-ESHAP, rituximab, etoposide, methylprednisolone, cytarabine and cisplatin; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide; RBE, relative biological effectiveness; fx, fractions; BID, twice daily; NED, no evidence of disease; AWD, alive with disease.

tions, Orange City, IA) and Aquaplast facemasks (Qfix, Avondale, PA) for those patients with disease involving the head and neck region. All patients underwent a three-dimensional (3D) computed tomography (CT) scan with intravenous contrast. Patients with mediastinal disease or abdominal disease underwent a 4D CT simulation to account for respiratory motion during planning. Scans were transferred to MIMVista (MIM Software, Cleveland, OH), and fusions with diagnostic scans were generated. Both the pre- and post-chemotherapy staging scans were fused for patients treated with chemotherapy.

A modified involved-field treatment plan was developed for all patients, similar to the involved-site radiation therapy guidelines [9]. In patients with indolent orbital lymphoma, partial orbital radiation was given [10], where the gross tumor volume (GTV) included gross disease seen on CT simulation, the clinical target volume (CTV) included the pre-biopsy volume as defined on the pre-biopsy CT or magnetic resonance imaging (MRI) scan fused to the CT simulation, and the planned target volume (PTV) was the CTV with a 5 mm margin to account for set-up uncertainty. In patients with NK T-cell lymphoma, the GTV included the sites of involved disease seen on the pretreatment positron emission tomography (PET)/CT scan fused to the CT simulation, while the CTV included a 5 mm margin within the soft tissue in addition to the entire lymph node station in which enlarged lymph nodes were found. A PTV margin of 5 mm on the CTV was used. In patients with primary mediastinal B cell lymphoma and lymphoblastic lymphoma, the GTV was the residual disease seen at the time of CT simulation, while the CTV included all mediastinal, hilar and cervical lymph node stations that were involved at the time of diagnosis with expansion to account for 4D motion of the mediastinum of up to 5 mm, and the PTV was a 5–8 mm margin on the CTV.

Target and OAR volumes were transferred into Eclipse (Varian Medical Systems, Salt Lake City, UT) and 3D conformal proton plans were generated. Patients were treated with passive-scatter proton therapy. A smearing factor was included in the proton range compensator design to account for any intrafraction or interfraction motion perpendicular to the beam. Distal and proximal margins were calculated for each proton beam (CTV depth mm $\times$ 1.025 + 1.5 mm) to account for CT-number-to-proton-stopping-power conversion uncertainties (2.5%). A 1.5 mm water-equivalent margin was added to the range to account for proton beam reproducibility (1 mm), water measurement uncertainty during commissioning (0.3 mm) and range compensator fabrication error (0.2 mm). Field apertures were calculated from the PTV with a block margin to account for the proton beam penumbra at the target depth, and range compensators were calculated using an 8–10 mm smearing margin. The minimum target coverage parameter was PTV dose to 95% volume (D95%) greater than 95%. Thoracic OAR dose constraints were lung volume receiving 20 Gy (V20) $<$ 30%, mean lung dose $<$ 14 Gy and mean heart dose $<$ 20 Gy.

Results

The median follow-up for all patients was 38 months, and seven of the nine living patients have more than 2 years of

follow-up. Two events occurred. One patient with NK T-cell lymphoma had progressive disease immediately after completing radiation therapy and died. Another patient with plasmablastic lymphoma was diagnosed with a gastroesophageal junction tumor outside the radiation field during follow-up and died 6 years following treatment. The 3-year overall survival rate for the cohort was 91% and the 3-year local control rate was 91%. Table II summarizes acute and late radiation-associated toxicities for the entire cohort of 11 patients.

Four patients were treated with definitive proton therapy for indolent orbital lymphoma in an effort to reduce the dose to the brain. Two of these patients had mucosa-associated lymphoid tissue (MALT) lymphoma and received 30.6 Gy (relative biological effectiveness, RBE) in 1.8 Gy fractions. The other two patients had low-grade follicular lymphoma and received 24 Gy (RBE) in 1.5 Gy fractions. All four patients tolerated proton therapy well, with grade 1–2 dermatitis ($n = 4$), grade 1–2 headache ($n = 2$) and/or grade 1 fatigue ($n = 2$). There were no instances of grade 3 or greater acute toxicities. There were no local recurrences at the time of last follow-up. Three patients later developed grade 3 cataracts in the treated eye. In these patients, the lens had been either entirely in the PTV ($n = 2$) or partially in the PTV ($n = 1$). One patient developed late grade 1 anhidrosis and another patient developed late grade 1 epiphoria.

Three patients were treated with consolidative proton therapy for primary mediastinal B-cell lymphoma to reduce the radiation dose to the heart, lungs, esophagus and breasts. Their ages ranged from 19 to 36 years. Two of these patients had a complete response to six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy and one patient required second-line chemotherapy with continued PET-positive residual disease before high-dose chemotherapy with autologous stem cell transplant. The dose of proton therapy delivered ranged from 30.6 to 41.4 Gy in 1.5–1.8 Gy fractions. There were no recurrences at the time of last follow-up. Acute toxicities included grade 1 to 2 dermatitis ($n = 3$), grade 1 fatigue ($n = 3$) and other grade 1 gastrointestinal ($n = 2$) and pulmonary toxicities ($n = 2$). At the time of last follow-up there were no grade 2 or greater late toxicities.

Two patients were treated with consolidative proton therapy for plasmablastic lymphoma. This included one located in the head and neck and the other in the stomach and left adrenal gland. There were no recurrences at the time of last follow-up. The patient with the head and neck site developed a GE junction cancer out-of-field a few years following treatment and died approximately 6 years following proton therapy. Acute toxicities were grade 1 nausea ($n = 1$), grade 1 mucositis ($n = 1$) and grade 2 dermatitis ($n = 1$). There were no grade 2 or greater late toxicities.

Finally, two patients received definitive proton therapy for treatment of NK T-cell lymphoma of the head and neck region in an effort to reduce the dose to the parotid glands, oral cavity and brain. One patient had progressive disease and died 5 months later, while the other patient is a 4-year-old boy with involvement extending from the nasopharynx to hypopharynx, who is free of disease at 9 months after completing treatment. Acute toxicities were grade 1–2 dermatitis ($n = 2$), grade 2 mucositis, grade 2 laryngeal edema requiring steroids, grade 3 dysphagia ($n = 1$) and grade 2 anorexia ($n = 1$).

Discussion

This study is the first to report on a cohort of patients with NHL treated with proton therapy [11]. Proton therapy led to local control rates similar to what is expected with photon radiation, but was delivered with the objective of reducing the long-term side effects of radiation. Several published studies have evaluated the use of proton therapy in HL, but there are few data regarding outcomes of patients treated with proton therapy for NHL. Three studies have evaluated the dosimet-

Table II. Acute and late radiation associated toxicities.

	Acute				Late			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Skin	4	6	0	0	9	0	0	0
Fatigue	6	0	0	0	2	0	0	0
Nausea/vomiting	3	0	0	0	0	0	0	0
Esophagitis	3	0	1	0	1	0	0	0
Xerostomia	2	0	0	0	1	0	0	0
Mucositis	2	0	0	0	0	0	0	0
Weight loss	0	1	0	0	0	0	0	0
Cough/dyspnea	2	0	0	0	1	0	0	0
Dyspepsia	1	0	0	0	0	0	0	0
Cataracts	0	0	0	0	0	0	3	0
Epiphora	0	0	0	0	1	0	0	0
Dry eye	0	0	0	0	0	1	0	0
Dermatitis	1	6	0	0	0	0	0	0
Alopecia	2	0	0	0	0	0	0	0
Headache	1	1	0	0	0	0	0	0
Anxiety/depression	1	0	0	0	1	0	0	0
Dysphagia	0	0	1	0	0	0	0	0
Dysarthria	1	0	0	0	1	0	0	0
Anorexia	0	1	0	0	0	0	0	0
Tinnitus	0	0	0	0	1	0	0	0
Otalgia	0	0	0	0	1	0	0	0
Hypothyroidism	0	0	0	0	1	0	0	0

ric impact of using proton therapy in NHL, including studies from Massachusetts General Hospital (MGH; Boston, MA), M. D. Anderson Cancer Center (MDACC; Houston, TX) and University of Florida (UF; Jacksonville, FL) and there is a case report from Loma Linda University Medical Center (LLUMC; Loma Linda, CA). The study from MGH included four patients with diffuse large B-cell NHL involving the mediastinum treated with proton therapy, and showed reduced cardiac, lung, spinal cord and integral doses with excellent disease control and minimal acute toxicities [12]. The study from MDACC discussing proton therapy in mediastinal lymphoma included two patients with NHL and showed similar results [13]. The UF study evaluating the dosimetric benefit of proton therapy compared with 3D conformal radiotherapy in two patients with primary mediastinal B-cell lymphoma demonstrated a clinically meaningful reduction in dose to the heart, lungs and esophagus [14]. Finally, a case report from LLUMC demonstrated that proton therapy can minimize the volume of normal brain tissue receiving low- to moderate-dose radiation in a patient with primary B-cell lymphoma [15]. These dosimetric studies provide a rationale for the use of proton therapy in the treatment of NHL to potentially reduce the risk of late radiation toxicities. This approach is also supported by the work of Chung *et al*. [16], who demonstrated a 50% reduction in secondary cancer development among patients treated at MGH with proton therapy compared with matched patients from the Surveillance, Epidemiology, and End Results (SEER) program registry.

All three patients with primary mediastinal B-cell lymphoma had an excellent response to consolidative proton therapy and no evidence of disease during follow-up. Patients with primary mediastinal B-cell lymphoma generally present at a young age, similar to those with HL involving the mediastinum, and would likely derive the same benefits with proton therapy as patients with HL. In a prospective study, Hoppe *et al*. [17] demonstrated significant and clinically meaningful dose reduction with proton therapy when compared with 3D and intensity-modulated radiation therapy. These patients with NHL represent an important cohort who should be considered for consolidative treatment with proton therapy. Furthermore, many of these patients are being treated with dose-dense chemotherapy regimens in an effort to avoid radiation therapy and its associated toxicities [18]. Therefore, in the few patients receiving radiation therapy as part of their treatment, proton therapy should be strongly considered.

In patients with orbital lymphoma, local disease control outcomes were favorable and consistent with outcomes described in the literature [19–21]. Given that the majority of patients with indolent orbital lymphoma achieve long-term survival, it is important to minimize the potential for late treatment-associated toxicities. The patients in this cohort had similar rates of subacute toxicities (i.e. cataracts, anhidrosis) to patients treated with photon therapy. Proton therapy has the advantage of sparing the dose to the pituitary, ipsilateral temporal lobe and ipsilateral hippocampal head, all of which receive low-dose radiation with similarly fractionated conventional photon therapy.

Other effective strategies for treating orbital lymphoma have been investigated. In 2011, Lowry *et al*. [2] published their results of 361 sites of indolent NHL randomized to 40–45 Gy in 20–23 fractions or 24 Gy in 12 fractions and 640 sites of aggressive NHL randomized to 40–45 Gy in 20–23 fractions or 30 Gy in 15 fractions. There was no difference in overall response rate, progression-free survival or overall survival between the standard- and low-dose arms in either group. Fasola *et al*. [22] analyzed a cohort of 20 patients with NHL with ocular adnexal involvement treated with low-dose radiation consisting of two fractions of 2 Gy. At a median follow-up of 26 months, the overall response rate was 96% and the complete response rate was 85%. The treatment was well tolerated, with mild acute side effects in 30% and no late toxicities. Furthermore, patients treated with this low-dose regimen have the option of re-irradiation in the case of local-regional relapse. With conjuctival MALT lymphoma (provided there is no disease behind the equator of the globe on high-quality orbital MRI), patients can be treated effectively with an anterior orthovoltage field (250–300 kV) [20]. Considering that very low doses for orbital lymphoma are emerging as an effective alternative, the true value of its use in patients with indolent histologies still remains to be seen. However, more aggressive histologies of the orbit require higher doses, which would benefit from proton therapy.

Although this study demonstrates that proton therapy can be safely and effectively delivered to patients with NHL involving other anatomical areas, including the abdomen and head and neck region, NHL includes a broad range of anatomic disease locations and histologic subtypes, making it difficult to generalize the benefits of a particular radiation modality among all cases of NHL. While low-grade indolent lymphoma (predominantly MALT and follicular lymphoma) and NK T-cell lymphoma can be effectively treated with radiation therapy alone, aggressive histologies (diffuse large B-cell lymphoma, plasmablastic and Burkitt lymphoma) require individualized chemotherapy regimens in combination with radiation therapy. Current National Comprehensive Cancer Network (NCCN) guidelines include photons, electrons or protons as appropriate treatment modalities for NHL, depending on clinical judgement. Although ideal, a randomized controlled trial comparing proton and photon therapy based on a primary endpoint of late toxicity is unlikely because of the numerous potential sites of disease, the long time interval between treatment delivery and manifestation of late side effects, and the shrinking role of radiation owing to persistent concerns of radiation-associated toxicities by medical oncologists. In addition to offering lower radiation doses and involved site radiation therapy, proton therapy may allow more patients to receive the most effective and safe treatment.

The major limitations of the present study are its small sample size and the diversity of primary disease sites and histologies among patients with NHL. Despite NCCN endorsement for the use of proton therapy in cases where the dose to the OARs can be reduced significantly compared with photon radiation, many patients evaluated at our center for proton therapy for whom the proton plans were superior to the photon plans could not obtain insurance coverage for the treatment of their NHL with protons. These experiences

illustrate the challenges that researchers face when investigating the role of proton therapy for different diseases.

The present study did not examine all possible clinical scenarios in which proton therapy may benefit patients with NHL; the patients included in this study represent a typical cross-section of disease presentations encountered by radiation oncologists. More long-term follow-up of all surviving patients included in this study is essential for continued monitoring of disease status and late toxicities.

Conclusion

Proton therapy is a feasible and effective treatment for NHL. Early outcomes are favorable. Longer follow-up and additional patients are needed to confirm our findings. Given the variable disease locations, histologies and biologic behaviors of NHL, prospective studies evaluating proton therapy in the treatment of this disease will be complex, and likely require pooled data from multiple institutions to demonstrate adequate local control and lower rates of late toxicities.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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