Reports of Practical Oncology and Radiotherapy 25 (2020) 856–859

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Review

Approach to radiation therapy in the Jehovah's Witness patient: An overview

James M. Jurica[a,b], Jay A. Messer[b,c], Bin S. Teh[a], Brian E. Butler[a], Andrew M. Farach[a,*]

[a] Baylor College of Medicine, Houston, TX, United States
[b] Department of Radiation Oncology, Houston Methodist Hospital, Houston, TX, United States
[c] Department of Radiation Oncology, The University of Texas Medical Branch, Galveston, TX, United States

ARTICLE INFO

Article history:
Received 4 April 2020
Received in revised form 7 July 2020
Accepted 17 August 2020
Available online 25 August 2020

Keywords:
Jehovah witness
Radiation oncology
Anemia
Hematologic toxicity
Bone marrow sparing
BMS-IMRT

ABSTRACT

Jehovah's Witnesses are well-known in the medical community for their inability to accept blood products. Novel methods of treatment are often needed to avoid anemia and hematologic toxicity as inability to receive blood products may increase the risk of treatment related complications. We provide an overview of radiation treatment for Jehovah's Witness patients with an emphasis on bone marrow sparing strategies with intensity modulated radiation therapy (IMRT) to minimize hematologic toxicity.

1. Introduction

The Jehovah's Witnesses (JW) is a Christian religion comprised of approximately 8.6 million members in the United States as of 2019.[1] Founded by Charles Taze Russell in 1872, the JW religion prohibits the consumption or infusion of whole blood or blood products. This doctrine was originally issued by "The Watchtower," the governing body of the JWs, in 1944, and is derived from three biblical passages: Genesis 9:4, Leviticus 17:14, and Acts 15:20.[2] Among the JW, there is some allowance for interpretation of blood products. While packed red blood cells, white cells, platelets, and plasma are universally prohibited, other products such as erythropoietin, albumin, and recombinant factor VIIa are more open to personal interpretation.

Prohibition of blood product use has created the need for novel treatment methods of anemia and hematologic toxicity (HT) in this population. Over the past fifty years, medical and surgical specialties have addressed complications related to treating JWs and advances in these fields have led to better outcomes and higher quality of life in this population.

Despite the robust research tailored toward the treatment of JW in the general medical community, there is a notable absence of related literature in radiation oncology. Radiotherapy is commonly known to cause anemia and HT through inhibition of hematopoiesis, making optimization of treatment to spare bone marrow paramount in this population. Bone Marrow Sparing Intensity-modulated radiation therapy (BMS-IMRT) is a relatively new modality that has been shown in certain cancers to reduce HT in comparison to both conventional 3D-conformal radiation therapy (3D-CRT) and standard IMRT. This technology could prove particularly efficacious in the treatment of JW as transfusion is not a viable option. The breadth of clinical use with BMS-IMRT is rapidly expanding to include both pelvic and non-pelvic malignancies, and Phase II and III trials examining post-treatment factors such progression-free survival (PFS) and quality of life (QOL) are currently underway. In this article, we intend to provide an overview of bone marrow sparing, focusing on BMS-IMRT, and to demonstrate the potential benefit in the treatment of JW patients.

2. Development of anemia/hematologic toxicity and treatment outcomes

Development of anemia and HT in oncology patients is often multifactorial and may result from malignancy or iatrogenic factors. Rates of malignancy induced anemia, (Hgb <12 g/dL) are

* Corresponding author at: Department of Radiation Oncology, Houston Methodist Hospital, 6565 Fannin St., Ste#DB1=077, Houston, TX 77030, United States.
E-mail address: amfarach@houstonmethodist.org (A.M. Farach).

https://doi.org/10.1016/j.rpor.2020.08.014
1507-1367/

estimated to be 60% before treatment across common cancers.[3] Patients undergoing chemotherapy face higher rates of anemia due to the myelosuppressive effects of treatment. It is estimated that up to 90% of patients receiving chemotherapy develop cytopenia.[4] As chemoradiation is commonly utilized as standard of care across various cancers, the hematological impact of radiotherapy in oncology patients warrants consideration.

Development of anemia during radiation treatment is a negative prognostic indicator. Anemia reduces oxygen delivery to the tumor, causing intratumoral hypoxia and conferring resistance to radiation both indirectly and directly. Indirectly, hypoxia induces changes in gene expression and alterations in the proteome that decrease radiosensitivity. Directly, oxygen makes the DNA damage done to tumor cells by radiation permanent by inhibiting cell-mediated repair. As a result, it is estimated that the dose of radiation needed to treat a hypoxic tumor is increased by 2.8–3.0 times.[5] This translates to poorer outcomes for anemic patients, who are shown to have decreased survival rates and higher rates of treatment failure when compared to non-anemic patients. Dunst et al., found a 61% increase in 3-year local failure rate in cervical cancer patients with Hgb <11 g/dL when compared to patients with Hgb >13 g/dL ($p = 0.0001$) and 47% decrease in 3-year overall survival.[6] These findings are consistent across solid tumors and may disparately affect outcomes for JW patients who are unable to receive blood products due to their religious convictions.

The impact of increasing radiation dosage to circulating immune cells has recently been recognized as an important predictor of patient outcomes. The estimated dose of radiation to immune cells (EDRIC) is a quantifiable variable based on radiation dosage to the heart, lungs, and body that predicts overall survival (28.2 months with EDRIC < 5.1 vs. 14.3 months with EDRIC > 7.3) in patients with stage III non-small cell lung cancer (NSCLC).[7] The breadth in clinical use of EDRIC continues to be elucidated, however, minimization of EDRIC in treatment planning for NSCLC may also benefit JW patients and improve overall outcomes.

3. Radiation and bone marrow sparing

While malignancy and chemotherapy induced anemia and HT may be non-modifiable factors from a radiation oncology perspective, advances in treatment models may help radiation oncologists lessen the negative impact on bone marrow caused by treatment. Radiation causes DNA breakage and subsequent destruction of hematopoietic stem cells in a dose dependent manner. Over 40% of active bone marrow is in the pelvis, making patients with pelvic malignancies particularly susceptible to the toxic effects of radiation. Currently, the most commonly used radiation treatment modalities are 3D-CRT and IMRT. 3D-CRT has long been considered the standard of care for radiation treatment of most pelvic malignancies. IMRT is increasingly utilized to spare normal tissues but does so at the expense of increased integral dose which may impact the blood pool. BMS-IMRT relies on the concept that HT is directly associated with both volume of active bone marrow irradiated and the dosage of radiation. Patients receiving V10 ≥ 90% or V20 ≥ 75% to pelvic bone marrow are more likely to develop grade 2 or worse HT, and additionally are more likely to have chemo treatment withheld.[8] BMS-IMRT optimizes treatment planning to decrease radiation to active bone marrow below the aforementioned levels while maintaining adequate tumor coverage and avoiding normal tissue structures. BMS-IMRT does not allow for complete avoidance of bone marrow, instead relying on identification and avoidance of active bone marrow using FDG-PET/CT scans to decrease rates of HT without sacrificing treatment plan quality. An atlas of active bone marrow may also be used for treatment planning in place of customized active bone marrow-sparing treatment planning with similar results.[9]

4. BMS-IMRT in clinical practice

Over the past 10 years, BMS-IMRT has been used to treat various malignancies with promising results. In the treatment of cervical cancer, BMS-IMRT has been shown to significantly reduce V10 and V20 to active bone marrow when compared to 3D-CRT and IMRT. Figs. 1 and 2 below show a comparison between 3D-CRT, IMRT, and BMS-IMRT planned target volumes (PTV) for a single patient with cervical cancer at our institution and the corresponding dose volume histogram, respectively.

Recent studies have demonstrated similar results with BMS-IMRT as those shown in Fig. 2 above.[10–12] Platta et al. found BMS-IMRT reduced V10 by 11.6% and V20 by 9.5% when compared to IMRT.[12]

Dosimetric planning to reduce active bone marrow irradiation is key, and optimization of dosimetric planning is an area of ongoing interest. There is evidence in cervical cancer patients that bone marrow sparing can be maintained without adversely affecting other organs at risk (OAR) by adding dose volume constraints to specific subsites such as the os coxae and lumbosacral spine rather than dose constraining all bone marrow.[13] As dosimetric planning improves, these measures are likely to translate to decreased HT in cervical cancer patients. Most recently, a phase II clinical trial comparing BMS-IMRT with IMRT found significantly lower rates of neutropenia 8.6% vs. 27.1%. with a trend toward decreased HT.[14]

Given these findings, it follows that BMS-IMRT could be particularly efficacious in treatment of cervical cancer in JW and could lead to a higher PFS, and an overall higher QOL. These two parameters are the focus of an ongoing stage III trial (INTERTECC-3) of stage IB-IVA cervical cancer patients treated with concurrent cisplatin and either BMS-IMRT or 3D-CRT.[15]

While most predominant in cervical cancer treatment, the study of BMS-IMRT approaches is rapidly expanding in other tumor sites. In the treatment of advanced lung cancer, BMS-IMRT was found to reduce the dose delivered to thoracic BM by 23.7% in comparison

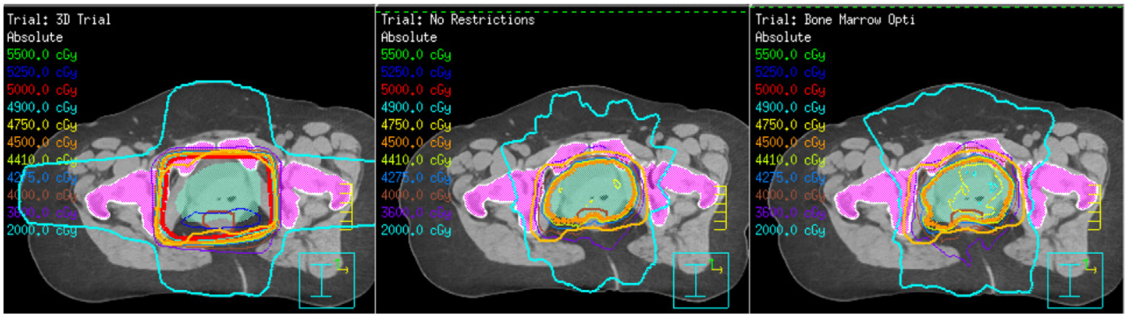

Fig. 1. 3D-CRT (left) IMRT (middle) and BMS-IMRT (right) PTVs for patient with locally advanced cervical cancer.

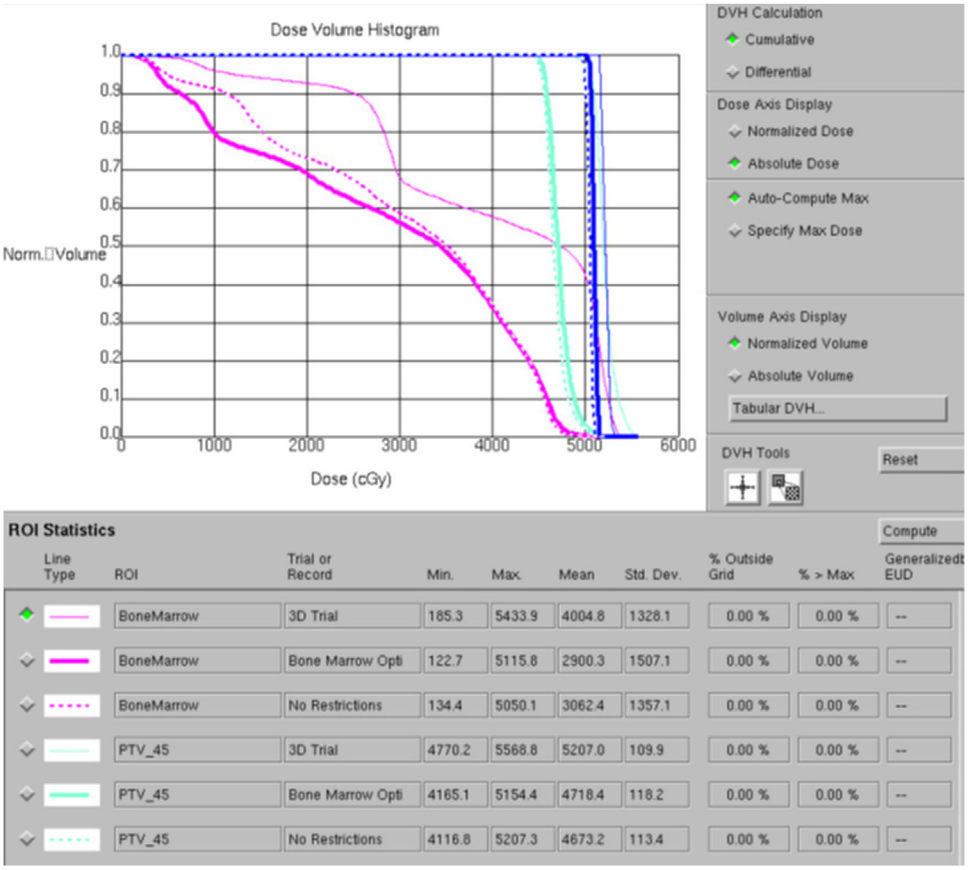

Fig. 2. Corresponding pelvic bone marrow dose volume histogram with 3D-CRT (thin pink line) IMRT (dotted pink line) and BMS-IMRT (thick pink line) treatment plans for patient 1. BMS-IMRT demonstrates significantly lower V10 and V20 than IMRT and 3D-CRT.

to 3D-CRT without adverse changes to PTV or other OARs.[16] A subsequent study quantified the hematologic risk of increased dosage to thoracic bone marrow, finding an odds ratio of 1.041 for development of grade ≥3 HT per Gy increased dosage to thoracic bone marrow.[17] In the treatment of stage II-III rectal cancer, BMS-IMRT demonstrated a 4% decrease in V10 and an 8.3% decrease in V20.[18] A prospective study comparing IMRT with BMS-IMRT for locally advanced rectal cancer found significantly decreased rates of HT in patients treated with BMS-IMRT, although no statistical difference was found in disease-free or overall survival.[19] In treatment of anal cancer, BMS-IMRT was associated with a 10.4% decrease in V10 to pelvic bone marrow and a 17.4% decrease in V20 with similar PTVs and dosage to OAR.[20] BMS-IMRT has also shown benefit in the treatment of gastric cancer, seminomas, and is expanding to include other malignancies. Although there is a relative paucity of data on survival of patients treated with BMS-IMRT for many malignancies, there is likely benefit in decreased rates of HT; this is of substantial importance in the JW population as rates of HT may affect outcomes more significantly than in the general population.

5. Conclusion

As medicine continues to advance, more opportunities to treat JW patients safely and with equal efficacy exist. BMS-IMRT offers patients undergoing radiation therapy decreased risk of HT without compromising treatment plan quality. This technology is a great option in JW patients who may be more vulnerable to the harmful impacts of HT. In this population, utilizing BMS-IMRT should be considered with increased priority and further study is warranted to minimize the disparity of outcomes.

Funding

No funding sources were involved in the creation of this manuscript.

Declarations of interest

None declared.

Acknowledgement

The authors would like to acknowledge to contributions and feedback provided by Jessica Varisco PBMC, coordinator for the blood conservation / bloodless program at Houston Methodist Hospital.

References

1. Jehovah's Witnesses. *How many of Jehovah's witnesses are there worldwide?*; 2020. Accessed 20 March 2020 https://www.jw.org/en/jehovahs-witnesses/faq/how-many-jw/.
2. Jehovah's Witnesses. *Why Don't Jehovah's Witnesses accept blood transfusions?*; 2020. Accessed 20 March 2020 https://www.jw.org/en/jehovahs-witnesses/faq/jehovahs-witnesses-why-no-blood-transfusions/.
3. Birgegård G, Aapro MS, Bokemeyer C, et al. Cancer-related anemia: pathogenesis, prevalence and treatment. *Oncology*. 2005;68(Suppl 1):3–11, http://dx.doi.org/10.1159/000083128.
4. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med*. 2004;116(Suppl 7A):11S–26S, http://dx.doi.org/10.1016/j.amjmed.2003.12.008.
5. Vaupel P. Tumor microenvironmental physiology and its implications for radiation oncology. *Seminars Radiat Oncol*. 2004;14(3):198–201, http://dx.doi.org/10.1016/j.semradonc.2004.04.008.
6. Dunst J, Kuhnt T, Strauss HG, et al. Anemia in cervical cancers: impact on survival, patterns of relapse, and association with hypoxia and angiogenesis. *Int J*

Radiat Oncol Biol Phys. 2003;56(3):778–787, http://dx.doi.org/10.1016/S0360-3016(03)00123-8.
7. Ladbury CJ, Rusthoven CG, Camidge DR, et al. Impact of radiation dose to the host immune system on tumor control and survival for stage III non-small cell lung Cancer Treated with definitive radiation therapy. *Int J Radiat Oncol Biol Phys*. 2019;105(2):346–355, http://dx.doi.org/10.1016/j.ijrobp.2019.05.064.
8. Mell LK, Schomas DA, Salama JK. Association between bone marrow dosimetric parameters and acute hematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;70(5):1431–1437, http://dx.doi.org/10.1016/j.ijrobp.2007.08.074.
9. Li N, Noticewala SS, Williamson CW, et al. Feasibility of atlas-based active bone marrow sparing intensity modulated radiation therapy for cervical cancer. *Radiother Oncol*. 2017;123(2):325–330, http://dx.doi.org/10.1016/j.radonc.2017.02.017.
10. Mell LK, Tiryaki H, Ahn KH, Mundt AJ, Roeske JC, Aydogan B. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1504–1510, http://dx.doi.org/10.1016/j.ijrobp.2008.04.046.
11. Murakami N, Okamoto H, Kasamatsu T, et al. A dosimetric analysis of intensity-modulated radiation therapy with bone marrow sparing for cervical cancer. *Anticancer Res*. 2014;34(9):5091–5098.
12. Platta CS, Bayliss A, McHaffie D, et al. A dosimetric analysis of tomotherapy based intensity modulated radiation therapy with and without bone marrow sparing in gynecologic malignancies. *Technol Cancer Res Treat*. 2013;12(1):19–29, http://dx.doi.org/10.7785/tcrt.2012.500300.
13. Bao Z, Wang D, Chen S, et al. Optimal dose limitation strategy for bone marrow sparing in intensity-modulated radiotherapy of cervical cancer. *Radiat Oncol*. 2019;14:118, http://dx.doi.org/10.1186/s13014-019-1324-y.
14. Mell LK, Sirak I, Wei L, Tarnawski, et al. Phase 2 multicenter clinical trial of bone marrow–sparing intensity modulated radiation therapy with concurrent cisplatin for stage IB-IVA cervical cancer. *Int J Radiat Oncol Biol Phys*. 2016;96(2):S13, http://dx.doi.org/10.1016/j.ijrobp.2016.06.046.
15. Mell LK, Available from: https://clinicaltrials.gov/ct2/show/study/NCT01554397. NLM identifier: NCT01554397. Accessed 20 March 2020 *Phase II/III clinical trial of intensity modulated radiation therapy with concurrent cisplatin for stage I-IVA cervical carcinoma*. San Diego: University of California; 2020.
16. Bazan JG, Barney C, DiCostanzo DJ, et al. Normal tissue complication probability modeling of acute hematologic toxicity in patients treated with concurrent chemoradiation for locally advanced lung cancer. *Int J Radiat Oncol Biol Phys*. 2017;99(2):E440, http://dx.doi.org/10.1016/j.ijrobp.2017.06.1656.
17. Barney CL, Scoville N, Allan E, et al. Radiation dose to the thoracic vertebral bodies is associated with acute hematologic toxicities in patients receiving concurrent chemoradiation for lung Cancer: results of a single-center retrospective analysis. *Int J Radiat Oncol Biol Phys*. 2018;100(3):748–755, http://dx.doi.org/10.1016/j.ijrobp.2017.11.025.
18. Rui M, Hongzhi Q, Ge S, et al. Dosimetric comparison of postoperative intensity-modulated radiotherapy for stage II-III rectal cancer. *Chinese J Radiat Oncol*. 2011;20(5):411–413.
19. Wang Y, Yu D, Zhang B. Clinical study of bone marrow-sparing neoadjuvant chemoradiotherapy for rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2018;102.3:e22, http://dx.doi.org/10.1016/j.ijrobp.2018.07.241.
20. Menkarios C, Azria D, Laliberté B, et al. Optimal organ-sparing intensity-modulated radiation therapy (IMRT) regimen for the treatment of locally advanced anal canal carcinoma: A comparison of conventional and IMRT plans. *Radiat Oncol*. 2007;2:41, http://dx.doi.org/10.1186/1748-717X-2-41.