ORIGINAL ARTICLES

Effects of whole brain radiation on blood counts

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ABSTRACT

Background: Whole brain radiation therapy is commonly used in the treatment of patients with CNS metastatic disease. Radiation to other areas of the body is associated with decrease in bone marrow proliferation. It is unclear what the effects of WBRT have on blood counts.

Methods: Retrospective chart review of patients with brain metastases treated with WBRT with recorded hematologic values before and after treatment. Univariate analysis was performed to identify statistical differences in outcome via paired t-testing.

Results: Forty-nine patients were analyzed. Median age was 61 and 36 subjects were female. Analysis revealed significantly a median decrease of 0.87 g/dL in hemoglobin values ($p < .01$) and 34 in platelet counts ($p < .01$) after treatment, but no significant decrease in WBC values ($p > .05$).

Conclusion: WBRT leads to a decrease in Hgb and platelets but does not appear to affect WBC counts. Physicians and patients should be aware of this side effect of WBRT.

Key Words: Whole brain radiotherapy, Anemia, Metastatic brain cancer

1. INTRODUCTION

Central nervous system (CNS) metastatic disease is a common site of metastatic spread for many cancers.[1] Several treatment options exist, including whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgical resection.[2–4] Each treatment has its own specific risks and advantages. Guidelines[2] suggest that WBRT be used for > 4 CNS metastatic lesions and in patients with poor performance status. WBRT has several known side effects including chronic neurocognitive effects[4,5] and a decrease in quality of life.[6] The modality involves passage of radiation through the skull, which contains some component of the body's proliferating bone marrow.[7] However, the effect of WBRT on hematologic values is not clear. Biologically, radiation is known to damage more than just DNA in targeted cells, but also induces complex cellular changes and local, non-irradiated cells due to signaling secondary to inflammatory processes.[8] Furthermore, it has been challenging to predict these inflammatory responses with different radiation modalities with varying tumor types at a genetic expression level.[8,9] Past studies have demonstrated direct hematologic toxicity[10] as well as damage to hematopoietic stem cells[11]

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in the radiation field, and in vivo studies have shown that ionizing radiation have decreased bone marrow cellularity.[8] In a 1995 meta-analysis of radiation side effects, ionizing radiation to hematopoietic environments in conventional radiation sites, with focus on the pelvis and mantle, showed significantly decreased proliferative effects, with varying degrees of recovery between different studies.[11]

Table 1. Patients' characteristics

Characteristics	
Age (median)	61 years
Sex	
Female	45
Male	15
Primary tumor	
Lung	25
Breast	14
Uterine	4
Lymph	2
Esophageal	1
Skin	1
Unknown	2
Total number	49

2. PATIENTS AND STUDY DESIGN

The study was approved by the institutional review board at Cooper University Hospital. We retrospectively reviewed electronic health records for 477 patients treated at Cooper University Hospital facilities with whole brain radiation. Patients eligible for this analysis were required to have received WBRT, had available blood counts within a month of starting and within 2 months of completing WBRT, and did not receive any chemotherapy, targeted therapy between the blood count evaluations. Furthermore, colony stimulating factor was not given concurrently with radiation. A total of 477 patients were evaluated, with 49 patients deemed eligible for further analysis. Most of the patients were excluded for not having lab values or not receiving WBRT (treated with radiosurgery and not WBRT). The most common radiation dose for evaluable patients was 30 Gy in 10 fractions (range 15.0 to 45.0 Gy). 36 patients were female, and the most common primary tumors included lung (N = 25), breast (N = 14) (see Table 1). Patients were stratified by pre-treatment hemoglobin, comparing patients who had 12 or higher g/dL (N = 37) and patients with less than 12 g/dL (N = 23). Stratifications were performed using the median values of platelet counts ($253 \times 10^3/mm^3$) and WBC ($7.3 \times 10^3/mm^3$). Mortality data was taken from tumor registry.

Statistical analysis was performed using IBM SPSS version 20 (SPSS Inc. Chicago, IL). The measurements selected for this study were platelet counts, white blood cell counts, and hemoglobin values from no more than 1 month before therapy and no more than 2 months after the WBRT course. Patient blood values were compared using paired t-testing, with all values treated as continuous variables. Mortality values between groups were compared using independent t-tests. All reported p values are two-sided, and significance was determined at $p < .05$.

3. RESULTS

The evaluated eligible 49 person cohort had a mean age at treatment was 61.1 (SD = 11.55, range 29-88) years. Median time from the lab to starting WBRT was 8 days (range 0-27). The median time from the end of WBRT to the repeat lab was 31 days (range 0-61 days), and 65% of patients were treated with 30 Gy in 10 fractions (see Table 2).

Table 2. Treatment Characteristics

Characteristics	
Radiation dose (cGy)	
Median	30
Range	15-45
Treatment time (d)	
Median	30
Range	15-45
First lab to WBRT (d)	
Median	8
Range	0-79
WBRT to repeat lab (d)	
Median	31
Range	0-61

3.1 Overall patient population

The median Hgb value before WBRT was 12.2 g/dL (7.6 g/dL to 15.5 g/dL) and 10.8 g/dL (6.4 g/dL to 14.1 g/dL) after WBRT, the median per patient decrease in Hgb was 0.87 g/dL (-3 g/dL to 5.5 g/dL). This difference was statistically significant ($p < .01$). 63.2% of patients had a decrease in Hgb (median decrease = 1.6 g/dL) and 32.7% had an increase (median increase = 1.05 g/dL). 4.1% of patients did not have a change in Hb.

The median WBC value before WBRT was $7.30 \times 10^3/mm^3$ ($0.6 \times 10^3/mm^3$ to $31.6 \times 10^3/mm^3$) and $6.6 \times 10^3/mm^3$ ($1.3 \times 10^3/mm^3$ to $38.2 \times 10^3/mm^3$) after WBRT, the median per patient decrease in WBC was $0.7 \times 10^3/mm^3$ ($-37.6 \times 10^3/mm^3$ to $13.7 \times 10^3/mm^3$). This difference was not statistically significant ($p > .05$).

The median platelets value before WBRT was $256 \times 10^3/mm^3$ ($51 \times 10^3/mm^3$ to $649 \times 10^3/mm^3$) and $208 \times 10^3/mm^3$ ($15 \times 10^3/mm^3$ to $550 \times 10^3/mm^3$) after WBRT, the median per patient decrease in platelets was

$34 \times 10^3/mm^3$ (-284 $\times$ $10^3/mm^3$ to 208 $\times$ $10^3/mm^3$). This difference was statistically significant ($p < .01$). 65.3% of patients had a decrease in platelets (median decrease = 95 $\times$ $10^3/mm^3$) and 32.7% had an increase (median increase = 64.5 $\times$ $10^3/mm^3$). 2% of patients did not have a change in platelet count.

3.2 Hemoglobin stratification

We looked at differences in blood count decrease based on pre-WBRT levels, and compared patients with Hgb > 12 g/dL and those with Hgb less than 12 g/dL to compare drops at different starting levels. Of the 30 cases where Hgb was at or above 12 g/dL before WBRT, median decrease after WBRT was 1.5 g/dL (-1.2 g/dL to 5.5 g/dL) ($p < .01$). For these patients, median survival was 235 days (SD = 234.3 days, Range = 14-849 days).

Of the 19 cases where Hgb was < 12 g/dL before WBRT, median decrease after WBRT was 0.1 g/dL (-3.0 g/dL to 5.5 g/dL). This difference was not statistically significant ($p > .05$). For this group, median survival was 84 days (SD = 227.4 days, Range = 9-697 days). When comparing these two groups, an independent t-test comparison showed no significant difference in survival between patients with different pre-test hemoglobin levels ($p > .05$) and no difference in magnitude of decrease ($p > .05$).

3.3 WBC stratification

Patients with starting WBC at or above the median starting value (7.30 $\times$ $10^3/mm^3$, N = 25) were compared to those with starting values below it (N = 23). In patients with higher WBC platelets, median decrease was 2.7 $\times$ $10^3/mm^3$ (-12.2 $\times$ $10^3/mm^3$ to 13.7 $\times$ $10^3/mm^3$) compared to the median change in patients with lower starting WBC, having a median increase of 0.3 $\times$ $10^3/mm^3$ (-3.9 $\times$ $10^3/mm^3$ to 37.6 $\times$ $10^3/mm^3$). This difference was found to be statistically different, with there being a more significant decline in WBC for patients with higher starting values ($p < .01$). There was no significant difference in survival times after WBRT between the stratified groups ($p > .05$) and no significant difference in the magnitude of WBC change after WBRT.

Table 3. Blood counts before and after WBRT

	Pre-WBRT (median)	Post-WBRT (median)
Hgb	12.2 g/dL	10.75 g/dL
Platelet	253 × $10^3/mm^3$	207 × $10^3/mm^3$
WBC	7.3 × $10^3/mm^3$	6.6 × $10^3/mm^3$

3.4 Platelet stratification

Patients with starting platelets at or above the median starting value (253 $\times$ $10^3/mm^3$, N = 25) were compared to those with starting values below it (N = 24). In patients with higher starting platelets, median decrease was 91 $\times$ $10^3/mm^3$ (-101 $\times$ $10^3/mm^3$ to 208 $\times$ $10^3/mm^3$) compared to the median change in patients with lower starting platelets, having a median decrease of 24.5 $\times$ $10^3/mm^3$ (-284 $\times$ $10^3/mm^3$ to 205 $\times$ $10^3/mm^3$). This difference was found to be statistically different, with there being a more significant decline in platelet counts for patients with higher starting values ($p < .01$). There was no significant difference in survival times after WBRT between the stratified groups ($p > .05$) and no significant difference in the magnitude of platelet count change after WBRT.

3.5 Overall survival

Median survival of eligible patients who completed WBRT was 162 days (SD = 231.7 days, range = 9-849 days). Patients with starting Hgb > 12 had OS of 235 days as compared to a OS of 84 days for Hgb < 12 ($p > .05$).

Patients with Hgb decrease (63.2%) had a median OS of 162 days while patients without a decrease had a median OS of 163.5 days. This did not reach statistical significance. We also examined subset of Hgb decrease and did not find any value which correlated with worsening OS.

4. DISCUSSION

In the treatment of CNS metastatic disease, several treatment options exist, including WBRT. While there are several advantages of WBRT including reduced chances of subsequent CNS failure there are also several noted disadvantages including chronic neurocognitive effects, with notable effects on memory.[4,5] In addition to this we have found a decrease in blood counts as another toxicity of WBRT. Radiation to other body sites has well noted decrease in blood counts and thus is not surprising that WBRT would also result in a reduction in blood counts. There is less active bone marrow in adult skulls than in the sternum and pelvis, but this study has demonstrated significant hematopoietic effects from WBRT.

The importance of blood counts is demonstrated in radiotherapies in other regions. In studies looking at radiotherapy in neck and gynecological regions, patients with uncorrected anemia were found to have decreased survival and quality of life comparatively to those with higher, non-anemic levels of hemoglobin.[12,13] Also noted was a link between tumor hypoxia from anemia and locoregional failure.[14] We found a trend towards decreased survival in patient with lower initial Hgb levels but this did not reach statistical significance, this may have been from low patient numbers in the analysis.

A recent meta-analysis found that patients treated with WBRT had a worse survival as compared to patients treated with SRS alone.[7] Our results offer a possible explanation,

the decrease in blood counts noted in this study could result in medical oncology groups delaying subsequent systemic therapy to allow for blood counts to recover. It is also possible that the decrease in survival is a direct consequence of the decreased blood counts due to the decrease in Hgb and oxygen carrying capacity (which in effect brings arterial oxygen content to below normal).

The overall population in this study was found to have significant decrease in hemoglobin ($p < .01$) and more specifically, patients in this population who began with Hgb > 12 g/dL had a median drop of 1.5 g/dL ($p < .01$).

This study has several short-comings. The study is retrospective and has a heterogeneous population in terms of age, amount of CNS disease and primary malignancy. Several important variables including performance status, comorbid conditions, and control of primary tumor were not available. Also, while we excluded patients with recent systemic therapy we did not account for previous therapies (chemotherapy greater than 30 days before blood counts, surgery, *etc.*). While recent chemotherapy patients were not included in this analysis, we feel that these patients would be affected similarly if not to a greater degree. Our sample size is fairly low secondary to our exclusion criteria and that for patients not receiving systemic therapy there is seldom a need to check blood counts one month post WBRT. Larger sample size could decrease the chances of our findings being due to chance. Larger numbers may have also allowed us to find various trends in subset analysis.

This study is important in showing the degree of hematologic suppression seen from WBRT. It is important that patients and physicians recognize this potential toxicity of WBRT.

Conflicts of Interest Disclosure

The authors declare that there is no conflict of interest statement.

References

[1] Schouten LJ, Rutten J, Huveneers HA, et al. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. Cancer. 2002; 94: 2698-705. PMid:12173339. https://doi.org/10.1002/cncr.10541

[2] Videtic GM, Gaspar LE, Aref AM, et al. Expert Panel on Radiation Oncology-Brain Metastases, American College of Radiology appropriateness criteria on multiple brain metastases. Int J Radiat Oncol Biol Phys. 2009 Nov 15; 75(4): 961-5. PMid:19857783. https://doi.org/10.1016/j.ijrobp.2009.07.1720

[3] Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006 Jun 7; 295(21): 2483-91. PMid:16757720. https://doi.org/10.1001/jama.295.21.2483

[4] Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009 Nov; 10(11): 1037-44. https://doi.org/10.1016/S1470-2045(09)70263-3

[5] Li J, Bentzen S, Li J, et al. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. Int J Radiat Oncol Biol Phys. 2008; 71: 64-70. PMid:18406884. https://doi.org/10.1016/j.ijrobp.2007.09.059

[6] Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: Quality-of-life results. J Clin Oncol. 2012; 31: 65-72. PMid:23213105. https://doi.org/10.1200/JCO.2011.41.0639

[7] Sahgal A, Aoyama H, Kocher M, et al. Phase 3 Trials of Stereotactic Radiosurgery With or Without Whole-Brain Radiation Therapy for 1 to 4 Brain Metastases: Individual Patient Data Meta-Analysis. Int J Radiation Oncol Biol Phys. 2015; 91(4): 710e717.

[8] Mavragani IV, Laskaratou DA, Frey B, et al. Key mechanisms involved in ionizing radiation-induced systemic effects. A current review. Toxicology Research. 2016; 5(1): 12-33. https://doi.org/10.1039/C5TX00222B

[9] Georgakilas AG, Pavlopoulou A, Louka M, et al. Emerging molecular networks common in ionizing radiation, immune and inflammatory responses by employing bioinformatics approaches. Cancer Lett. 2015; 368(2): 164-72. PMid:25841996. https://doi.org/10.1016/j.canlet.2015.03.021

[10] Hayman JA, Callahan JW, Herschtal A, et al. Distribution of proliferating bone marrow in adult cancer patients determined using FLT-PET imaging. Int J Radiation Oncol Biol Phys. 2011 Mar 1; 79(3): 847-52. PMid:20472367. https://doi.org/10.1016/j.ijrobp.2009.11.040

[11] Erpolat OP, Alco G, Caglar HB, et al. Comparison of hematologic toxicity between 3DCRT and IMRT planning in cervical cancer patients after concurrent chemoradiotherapy: a national multi-center study. Eur J Gynaecol Oncol. 2014; 36(1): 62-6.

[12] Mauch P, Constine L Greenberger J, et al. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. Int J Radiat Oncol Biol Phys. 1995 Mar 30; 31(5): 1319-39. https://doi.org/10.1016/0360-3016(94)00430-S

[13] Hu K, Harrison LB. Impact of anemia in patients with head and neck cancer treated with radiation therapy. Curr Treat Options Oncol. 2005 Jan; 6(1): 31-45. PMid:15610713. https://doi.org/10.1007/s11864-005-0011-4

[14] Varlotto J, Stevenson MA. Anemia, tumor hypoxemia, and the cancer patient. Int J Radiat Oncol Biol Phys. 2005 Sep 1; 63(1): 25-36. PMid:16111569. https://doi.org/10.1016/j.ijrobp.2005.04.049