RESEARCH ARTICLE

Hematologic Toxicity of Conformal Radiotherapy and Intensity Modulated Radiotherapy in Prostate and Bladder Cancer Patients

Marcin Miszczyk[1]*, Wojciech Majewski[2]

Abstract

Background: The purpose of this study was to compare hematologic adverse effects and hematologic toxicity (HT) of pelvic irradiation in patients treated with conformal radiotherapy (CRT) and intensity modulated radiotherapy (IMRT) for radical treatment of prostate and bladder cancer. **Methods:** A group of 115 patients with prostate or bladder cancer treated with definitive radical radiotherapy was evaluated retrospectively. Blood test were taken before and after treatment comprising of following indices: white blood cells (WBC) hemoglobin (HGB), red blood cell (RBC), lymphocyte (LC), neutrophil (NC) and platelet (PLT) count. Patients were divided into several subgroups and the data was evaluated statistically using absolute and relative values. **Results:** There was a statistically significant difference in WBC (p=0.007), NC (p=0.031) and PLT (p=0.026) count decrease (absolute values) after treatment, between two treatment methods (CRT and IMRT), all in favor of IMRT. The relationship still proves to be significant regarding WBC (p=0,02) and (NC) (p=0,049) after presenting the data as relative percentage loss of starting value. However using Common Terminology Criteria for Adverse Effects (CTCAE), PLT count toxicity was more common in IMRT group (p=0.045). **Conclusion:** IMRT in comparison to CRT in bladder and prostate cancer patients is associated with a lesser absolute and relative decrease of hematologic indices. The hematologic effect of radiation was observed mainly regarding LC. Patients treated with IMRT suffered from significantly lesser decrease in relative and absolute values of WBC and NC. The mean of absolute PLT decrease count was lower in IMRT group; however, toxicity according to CTCAE was slightly more prevalent in IMRT group.

Keywords: Prostatic neoplasms- urinary bladder neoplasms- radiotherapy intensity-modulated- radiotherapy conformal

Introduction

Radiotherapy (RT) is currently a treatment of choice for many prostate and bladder cancer patients (Bellmunt et al., 2014; Parker et al., 2015) utilizing methods such as three-dimensional conformal radiotherapy (CRT) and intensity-modulated radiation therapy (IMRT) as available modalities. IMRT is shown to induce less significant gastro-intestinal and genito-urinary adverse effects (Zelefsky et al., 2000; Hummel et al., 2010; Michalski et al., 2013), however impact of treatment modality choice on hematologic toxicity (Htox) remains uncertain (Erpolat et al., 2014; Hui et al., 2014; Avinash et al., 2015).

Approximately 50-55% of bone marrow's activity is located in the lumbar sacrum, ilium, ischium, pubis and proximal femur of which as much as 25% in pelvis itself. (Hayman et al., 2011; Hui et al, 2014). IMRT reduces the total dose to normal tissues for pelvic organs and reduces the volume of bone marrow exposed to radiation compared to CRT (Erpolat et al., 2014; Hui et al., 2014),

which correlates with lower Htox (Mell et al., 2006; Mell et al., 2008; Mutyala et al., 2008; Albuquerque et al., 2011; Rose et al., 2011), on the expense of increased volume of surrounding tissues exposed to low-dose radiation (Hall and Wuu, 2003).

The aim of the study is to evaluate hematologic adverse effects of CRT and IMRT in prostate and bladder cancer patients.

Disclosure

The authors declare no relevant or material interest related to the research described in this study. For this retrospective research bioethical commission approval was not necessary.

Materials and Methods

The study includes 115 consecutive prostate and bladder cancer patients treated in a single institution, that met the inclusion criteria. All of the patients were

[1]Department of Radiotherapy Planning, [2]Department of Radiotherapy, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland. *For Correspondence: marcinmmiszczyk@gmail.com

irradiated with radical intention by a single radiation oncologist between 2006 and 2012. The patients were aged between 44 and 87 (mean – 68, median – 69, SD – 7,8). A total of 38 were treated with CRT, and the rest with IMRT. Among them 74 suffered from prostate cancer (23 treated with CRT, 51 with IMRT), and 41 from bladder cancer (15 treated with CRT, 26 with IMRT). Only 5 patients in bladder group were females. The study was retrospective, utilizing data taken during standard treatment process. In all cases, hematologic tests were performed before the start of the treatment and at the end of RT.

Inclusion criteria included patients treated with definitive radical CRT or IMRT radiotherapy for prostate or bladder cancers together with prophylactic pelvic lymph nodes irradiation. Exclusion criteria included: lymphadenectomy, not-completed RT, prior oncological treatment with the exception of neoadjuvant hormonotherapy, and lack of appropriate data.

Patients were treated using linear accelerators with 6 or 20 MV photons in fraction doses of 2 Gy (with one exception of 1.8 Gy fraction dose in 1st phase of treatment). In the first phase of the treatment patients received 44-45 Gy to the primary tumor site and pelvic lymph nodes. In the second phase sequential boost was delivered to the primary tumor site and additionally to enlarged lymph nodes in 3 cases. Regarding the total dose delivered to primary tumor site, in prostate group 74 patients received 76 Gy, while in a bladder group 20 patients received 70 Gy, 15 patients 68 Gy, 4 patients 66 Gy and one – 60 Gy. The total dose delivered to pelvic lymph nodes was 44 Gy in 114 cases and 45 Gy (using fraction dose of 1,8 Gy) in one case. In two cases, sequential boost up to 66 Gy and in one case 50 Gy was given to the enlarged lymph nodes. The preference of RT method changed with time, together with application of daily 2D kV-kV IGRT, but remained a choice of a physician. Neoadjuvant hormonotherapy was administered in prostate cancer patients according to the guidelines. None of the patients received chemotherapy prior or during the period of time regarded in this study.

The study compares the changes in results of hematologic tests such as white blood cell count (WBC), neutrophil count (NC), lymphocyte count (LC), red blood cell count (RBC), hemoglobin count (HGB) and platelet count (PLT) over the course of treatment, between groups of patients treated with CRT and IMRT.

Standardized criteria - CTCAE (Common Terminology Criteria for Adverse Effects) v4.0 for four of the parameters (NC, LC, PLT, HGB) were used to assess the Htox (US Department of Health and Human Services, 2009). Thresholds used for grade 1 toxicity were respectively 1,8 for NC (1,000/mm³), 14 in men and 12 in women for HGB (g/dl), 150 for PLT (1,000/mm³) and 1 for LC (1,000/mm³).

Statistical analysis was performed using STATISTICA 12 software, using tools such as Kolmogorov–Smirnov, Mann-Whitney and t-Student tests, and basic statistical tools. P-values of <0.05 were considered to be significant.

Results

IMRT proves to cause lesser decrease of values of hematologic indices (Table 1, 2). There was a statistically significant difference in WBC (p=0.007), NC (p=0.031) and PC (p=0.026) decrease after treatment between the treatment methods in favor of IMRT. The differences in LC (p=0.69), RBC (p=0.67) and HGB (p=0.71) were not statistically significant.

Presented as relative values (percentage loss of the starting value) (Table 2), the differences are significant regarding WBC (p=0.02) and NC (p=0.049). The differences were not statistically significant regarding LC (p=0.4), RBC (p=0.6), HGB (p=0.6) and PLT (p=0.09).

The relationships are no longer significant after

Table 1. Hematologic Values before and after RT (mean)

	Whole study group		Prostate cancer patients		Bladder cancer patients		Patients treated with CRT		Patients treated with IMRT	
	Before	After	Before	After	Before	After	Before	After	Before	After
WBC	7.48	4.89	6.95	4.5	8.44	5.6	8.35	5.26	7.06	4.71
NC	4.48	3.28	4.02	2.9	5.37	4	5.09	3.61	4.2	3.13
LC	2.1	0.77	2.14	0.79	2.04	0.72	2.22	0.76	2.05	0.78
RBC	4.48	4.22	4.51	4.17	4.43	4.3	4.5	4.21	4.47	4.22
HGB	13.56	12.98	13.92	13.06	12.9	12.84	13.49	12.84	13.59	13.05
PLT	231.35	205.89	216	195.14	259.05	225.29	257.05	223.74	218.66	197.08

WBC, NC, LC and PLT are measured in 1,000/mm³, HGB in g/dl and RBC in 1,000,000/mm³.

Table 2. Decrease of Hematologic Values During RT

	Total mean value	Percentage loss of total mean value	Mean - CRT	Mean - IMRT	Percentage loss - CRT	Percentage loss - IMRT
WBC	2.59	33.02%	3.09	2.35	35.95%	31.58%
NC	1.29	23.78%	1.8	1.06	29.42%	21.19%
LC	1.32	62.19%	1.46	1.26	62.03%	62.16%
RBC	0.26	5.54%	0.29	0.25	6.34%	5.15%
HGB	0.58	3.70%	0.64	0.54	4.41%	3.34%
PLT	25.46	8.91%	33.32	21.58	11.22%	7.78%

WBC, NC, LC and PLT are measured in 1,000/mm³, HGB in g/dl and RBC in 1,000,000/mm³

Table 3. Hematologic Toxicity (CTCAE) – Total Number and Percentage of Patients Suffering from Respective Types and Grades of Hematologic Toxicity

Grade of toxicity	NC	LC	PLT	HGB
0	107 (95.5%)	17 (15%)	98 (85%)	32 (28%)
1	4 (4.5%)	22 (19.5%)	17 (15%)	80 (69.5%)
2	1 (1%)	52 (46.5%)	0 (0%)	3 (2.5%)
3	0 (0%)	21 (19%)	0 (0%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

splitting the data into two separate groups based on the location of the tumor, that is, prostate or bladder. (except for WBC, p=0.049).

Regarding the CTCAE scale, grade 2 and higher toxicity was apparent almost exclusively regarding LC (Table 3).

Only 4 out of 112 patients suffered from grade 1 toxicity regarding NC, 2 in IMRT and 2 in CRT group. In CRT group, only one patient suffered from grade 2 toxicity.

Out of 115 patients, 17 suffered from grade 1 toxicity regarding PLT, 15 in IMRT group and 2 in CRT group.

As much as 80 out of 115 patients suffered from grade 1 toxicity regarding HGB, 53 in IMRT and 27 in CRT group. That considered, only 2 patients in IMRT and 1 in CRT group suffered from grade 2 toxicity.

As few as 17 patients (10 in IMRT and 7 in CRT group) were free from adverse effects regarding LC. Twenty two suffered from grade 1 toxicity (11 – IMRT, 11 – CRT), 52 – grade 2 toxicity (42 – IMRT, 10 – CRT) and 21 – grade 3 toxicity (8 – CRT, 13 – IMRT). Overall over 85% patients suffered from at least grade 1 toxicity regarding LC.

The differences between IMRT and CRT groups were statistically insignificant except for PLT (p=0.045).

Discussion

The toxicity as described by CTCAE criteria did not differ substantially between groups and regarding PLT was in favor of CRT (p=0.045). This could be attributed to a substantial difference in the starting values (Table 1) making IMRT group more prone to reaching grade 1 toxicity even with lesser relative decrease of the index. It is important to note that the study compared differences between the results prior to treatment and immediately after, while we expect the hematologic indices to reach their lowest values later (depending on the parameter).

Hematologic toxicity was generally low in both groups (Table 3), however studies suggest that often it can be more prolonged than expected and we can speculate that adding the chemotherapy to radiation which is nowadays common for bladder and starts to be more frequent in high-risk prostate cancer could make a hematologic toxicity a larger problem (Cozzarini et al., 2016).

Many IMRT vs. CRT comparative studies in chemoradiotherapy treatment of other pelvic malignancies (mainly cervical cancer) have shown similar results. IMRT modalities tend to have less pronounced WBC and NC nadir compared to CRT and lesser incidence of grade 2+ leukopenia and neutropenia, which proves to be associated with lesser amount of irradiated bone marrow (Mell et al., 2006; Mell et al., 2008; Albuquerque et al., 2011; Hui et al., 2014). However, there are studies that disprove the difference in terms of hematologic toxicity between these two methods (Erpolat et al., 2014; Avinash et al., 2015).

The results of studies conducted on all-female groups should be interpreted with caution because of differences in hormonal profiles which can influence the hematologic results and create differences unrelated to adverse effects of RT. Therefore a study performed on mainly male population creates important data. The androgen deprivation therapy which was generally implemented in a group of patients with high-risk prostate cancer might have some impact on hematologic parameters behavior, too (Strum et al., 1997; Gruca et al., 2012).

The androgen deprivation therapy wihch is generally implemented in patients with high-risk prostate cancer might have some impact on hematologic parameters too.

The most prevalent adverse effect of RT was decrease in LC in both groups. It was to be expected since lymphocytes are among most radiosensitive cells and lymph nodes were the target volume for radiotherapy. However the hematologic adverse effects of pelvic RT alone still usually remain without clinical consequences.

In conclusion IMRT in comparison to CRT in bladder and prostate cancer patients is associated with a lesser absolute and relative decrease of hematologic indices. The hematologic effect of radiation was observed mainly regarding lymphocyte count. Patients treated with IMRT suffered from significantly lesser decrease in relative and absolute values of white blood cell and neutrophil count. The mean of absolute decrease of platelet count was lower in IMRT group. These findings suggest that lymphocyte count should be of high concern in patients with pelvic RT and in cases where it's important to decrease hematologic toxicity of RT – IMRT should be preferred over CRT.

References

Albuquerque K, Giangreco D, Morrison C, et al (2011). Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow–sparing pelvic IMRT. *Int J Radiat Oncol*, **79**, 1043–7.

Avinash H, Arul Ponni T, Janaki M, Kirthi Koushik A, Kumar SM (2015). A prospective dosimetric and clinical comparison of acute hematological toxicities in three-dimensional conformal radiation therapy and intensity modulated radiation therapy with concurrent chemotherapy in carcinoma cervix. *J Cancer Res Ther*, **11**, 83.

Bellmunt J, Orsola A, Leow JJ, et al (2014). Bladder cancer: ESMO practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, **25**, 40-8.

Cozzarini C, Chiorda BN, Sini C, et al (2016) Hematologic toxicity in patients treated with postprostatectomy whole-pelvis irradiation with different intensity modulated radiation therapy techniques is not negligible and is prolonged: Preliminary results of a longitudinal, observational study. *Int J Radiat Oncol Biol Phys*, **95**, 690–5.

Erpolat OP, Alco G, Caglar HB, et al (2012). 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*, **35**, 62–6.

Gruca D, Bacher P, Tunn U (2012). Safety and tolerability of intermittent androgen deprivation therapy: A literature review. *Int J Urol*, **19**, 614–25.

Hall EJ, Wuu C-S (2003). Radiation-induced second cancers: the impact of 3D CRT and IMRT. *Int J Radiat Oncol Biol Phys*, **56**, 83–8.

Hayman JA, Callahan JW, Herschtal A, et al (2011). Distribution of proliferating bone marrow in adult cancer patients determined using FLT-PET imaging. *Int J Radiat Oncol Biol Phys*, **79**, 847–52.

Hui B, Zhang Y, Shi F, et al (2014). Association between bone marrow dosimetric parameters and acute hematologic toxicity in cervical cancer patients undergoing concurrent chemoradiotherapy. *Int J Gynecol Cancer*, **24**, 1648–52.

Hummel S, Simpson E, Hemingway P, Stevenson M, Rees A (2010). Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. *Health Technol Assess*, **14**, 1–108.

Mell LK, Kochanski JD, Roeske JC, et al (2006). Dosimetric predictors of acute hematologic toxicity in cervical cancer patients treated with concurrent cisplatin and intensity-modulated pelvic radiotherapy. *Int J Radiat Oncol*, **66**, 1356–65.

Mell LK, Schomas DA, Salama JK, et al (2008). 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*, **70**, 1431–7.

Michalski JM, Yan Y, Watkins-Bruner D, et al (2013). Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the radiation therapy oncology group 0126 prostate cancer trial. *Int J Radiat Oncol*, **87**, 932–8.

Mutyala S, Thawani N, Vainshtein JM, et al (2008). Dose constraint recommendations and a predictive nomogram of incidence of hematological toxicity for cervix cancer patients treated with concurrent cisplatin and intensity modulated radiation therapy (IMRT). *Int J Radiat Oncol*, **72**, 359–60.

US Department of Health and Human Services (2009). National cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. National Institutes of Health/ National Cancer Institute, 1-194.

Parker C, Gillessen S, Heidenreich A, Horwich A (2015). Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, **26**, 69–77.

Rose BS, Aydogan B, Liang Y, et al (2011). Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol*, **79**, 800–7.

Strum S, McDermed JE, Scholz MC, Johnson H, Tisman G (1997). Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade. *Br J Urol*, **79**, 933–41.

Zelefsky MJ, Fuks Z, Happersett L, et al (2000). Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Radiother Oncol*, **55**, 241–9.