REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 23 (2018) 392–397

Available online at www.sciencedirect.com

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Original research article

Clinical and dosimetric factors associated with the development of hematologic toxicity in locally advanced cervical cancer treated with chemotherapy and 3D conformal radiotherapy

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ARTICLE INFO

Article history:
Received 2 November 2017
Received in revised form
10 May 2018
Accepted 23 July 2018
Available online 13 August 2018

Keywords:
Cervical cancer
Hematologic toxicity
Chemoradiotherapy

ABSTRACT

Aim: To identify clinical and dosimetric factors associated with the development of hematologic toxicity (HT) for cervical cancer (CC) treated with chemotherapy and 3D conformal radiotherapy.

Background: Chemoradiotherapy is the standard of care management for CC patients with IB2-IVA clinical stages (CS). This treatment carries toxicities, standing out the one that occurs at the hematologic level.

Subjects and methods: CC patients with IB2-IVA CS treated with chemotherapy and 3D conformal radiotherapy (50 Gy) plus Brachyterapy (7 Gy x3 or 9 Gy x2) at our institution between March 2016 and March 2017. Clinical and dosimetric factors were studied as was their probable association with the development of HT.

Results: 59 patients were analyzed. 89.8% of the subjects developed some grade of HT and 50.2% developed ≥grade 2 toxicity. No statistical relationship was found for the dosimetric factors: V10 > 90% ($p = 0.47$) and V20 > 80% ($p = 0.17$). Regarding clinical factors: neither age >50 years ($p = 0.88$) nor diabetes mellitus (DM) showed statistical relationship with development of ≥grade 2 HT ($p = 0.88$ and $p = 0.61$, respectively). On the contrary, obesity showed a significant association ($p = 0.02$). For other factors analyzed, we found statistical correlation for epidermoid histology and ≥III A CS ($p = 0.01$ and $p = 0.02$, respectively).

Conclusions: We did not find statistical relationship between HT and the clinical factors of age >50 years and DM. Statistical relationship for the dosimetric factors V10 > 90% and V20 > 80% was not found as well. On the contrary, obesity, epidermoid histology and ≥IIIA CS, showed statistical significance for development of HT ≥grade 2.

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https://doi.org/10.1016/j.rpor.2018.07.011

1. Background

In the year 2012 an estimate of 530,000 women were diagnosed with CC. This type of cancer is the fourth most prevalent cancer of the female reproductive system worldwide.[1,2]

The standard treatment for patients with locally advanced CC is CS IB2, IIA2-IVA,[3] according to the annual classification of the International Federation of Gynecology and Obstetrics (FIGO). The treatment consists in chemoradiotherapy according to the National Cancer Institute (NCI) advice, which is based on the results of 5 clinical randomized phase III trials.[4–8]

This kind of treatment carries toxicity, primarily at the gastrointestinal, genitourinary, and hematological systems.[8] It is true that hematologic toxicity rarely poses a threat to patients life, but it does compromise the oncological treatment results by delaying or suspending the chemotherapy sessions.[9,10] It also affects directly the mechanisms of tumoral damage of radiotherapy by anemic states.[10–13]

Up to 60% of the medullar function is developed at the pelvic bones and vertebrae. The bone marrow is extremely radiosensitive, and the blood cells acutely respond by lowering their count in a gradual manner.[14,15]

The conventional treatment technique with radiation therapy uses four radiation fields (anteroposterior, posteroanterior and two laterals), obtaining a box-like dose distribution where therapeutic target volumes and normal tissues at risk of side effects (intestine, rectum, bladder, bone marrow) are included. These are defined by the international consensus on contouring.[17,18]

The bone marrow contouring method is normally realized by delineation of three sites: illiac bones (from the iliac crest to the superior border of the femoral heads), lower pelvis (pubis, ischium, acetabulum, and proximal femur) and lumbosacral spine (from the superior L5 border to the complete sacrum).[16,19]

Another alternative treatment technique is the Intensity-modulated radiation therapy (IMRT). This therapy concentrates the dose in a better way at the target volume with minimal doses to normal pelvic tissues.[20,21] With the use of IMRT, a reduction of 30% of hematologic toxicity is achieved over the leukocyte recount at grade 2 or greater stage and over a 20% in hemoglobin levels.[20] This allows the achievement of adequate restrictions in doses of that technique, in radical and adjuvant scenarios.[22–27]

Other clinical and dosimetric factors have been studied to predict the occurrence of HT during chemotherapy and radiotherapy in cervix uterine cancer. Age, clinical stage, and BMI have been studied as clinical factors but no statistical significant relationship has been established with the development of grade 2 or higher hematological toxicity.[28] However, we have found in literature that factors like hyperglycemic, obesity and age modify the radiotherapy effects in tumoral cells and at normal tissues.[29,30] The prediction factor with greater impact is the DVH values for bone marrow. This is the percentage volume of bone marrow radiated with special care to the bone marrow levels that receive more than 10, 20, and 40 Gy (V10/V20/V40).[17,22,28,31] When more than 90% of the bone marrow volume receives a greater dose of 10 Gy, a risk to develop acute grade 2 or higher hematologic toxicity is 70%. The risk is only 10% when 10 Gy is applied.[22]

The objective of this study is to evaluate clinical and dosimetric factors associated with the development of hematologic toxicity (HT), especially the ones with a grade II or greater of the Radiation Therapy Oncology Group, for patients with locally advanced cervical uteri cancer treated with chemotherapy and 3D conformal radiotherapy.

2. Subjects and methods

Case-controls study nested in a retrospective cohort in cervix uteri cancer patients with IB2-IVA clinical stages treated with chemotherapy and 3D conformal radiotherapy carried out between March 2016 and March 2017 at the High Specialty Hospital number 25 of the Mexican Social Security Institute. Clinical and dosimetric factors were studied and their probable association with the development of HT.

Patients received 45–50.4 Gy to the PTV in 1.8–2 daily fractions with concurrent weekly cisplatin or other agents (carboplatin). No bone marrow constraint was used. Candidates for brachytherapy received 7 Gy or 9 Gy in 3 or 2 sessions, respectively, with high dose rate brachytherapy.

The principal clinical variables studied were age greater than 50 years, diabetes mellitus, and obesity. Histology, clinical stage by FIGO, and diagnose of arterial hypertension were also researched. The dosimetric factors evaluated were V10 > 90% and V20 > 80%. We also crossed results for the concomitant chemotherapy received and the number of cycles. The patients had to have a normal hematic biometry prior to the treatment and also the results of a control hematic biometry within the first 30 days after the last radiotherapy session. Based on the final hematic biometry, the grade of hematic toxicity was classified as the RTOG suggests for anemia, leukopenia, neutropenia, and thrombocytopenia.

An univariate analysis was performed, applying mean, median, mode, and standard deviation depending on the parametric and nonparametric variables. Proportions for the quality variables were also applied. A bivariate analysis was performed for the quality variables, using chi-square and student's *t*-distribution with a 0.05 *p* value significance level.

The purpose of those statistical tests was to establish the variable dependency.

This study is adjusted to the principles of the Helsinki declaration (and to the Tokyo, Venice, Hong Kong, and South Africa Assemblies). The study complied with the rules and legislation of the General Health Law applied to Health Research.

This protocol was submitted to and approved by the local research scientific committee of the Social Security Mexican Institute.

3. Results

59 patients were analyzed between March 2016 and March 2017. The mean age of the studied patients was of 46.3 years. 54% of the patients were older than 50 years and only 28% had a weight classified as normal for the World Health Organization. The most frequent histology was the epidermoid, representing 72%. The most prevalent clinical stages were IIB

Table 1 – Analysis of clinical factors associated with the development of hematologic toxicity in cervical and uterine cancer treated with chemotherapy.

	Total	Toxicity ≥G2		OR (95% C.I.)	p
	(n = 59)	Yes (n = 30)	No (n = 29)		
Age (years)	46.3	46.8 ± 12.7	45.9 ± 13.2		0.806
Age >50 years	27 (45.8%)	14 (46.7%)	13 (44.8%)		
Age <50 years	32 (54.2%)	16 (53.3%)	16 (55.1%)	1.07 (0.39–3.00)	0.887
BMI (kg/m^2)	28.2	26.4 ± 4.3	30.1 ± 5.0		0.004
Normal (healthy weight)	17 (28.8%)	11 (64.7%)	6 (27.2%)		
Obesity	22 (37.2%)	6 (35.2%)	16 (72.7%)	0.20 (0.05–0.80)	0.021
Histology					
Epidermoid	43 (72.8%)	25 (92.5%)	18 (64.2%)		
Adenocarcinoma	12 (20.3%)	2 (7.4%)	10 (35.7%)	6.94 (1.35–35.60)	0.011
FIGO stage					
IB2-IIB	30 (50.8%)	11 (36.6%)	19 (65.5%)		
IIIA or greater	29 (49.1%)	19 (63.3%)	10 (34.4%)	3.28 (1.12–9.54)	0.026
Diabetes mellitus	5 (8.4%)	2 (6.6%)	3 (10.3%)	0.62 (0.09–4.01)	0.612
Arterial hypertension	7 (11.8%)	4 (13.3%)	3 (10.3%)	1.33 (0.27–6.55)	0.722

The results shown are mean with minimum and maximum values.

Table 2 – Analysis of clinical factors associated with the development of hematologic toxicity in cervical and uterine cancer treated with chemoradiotherapy.

	Total	Toxicity ≥G2		OR (95% i.c.)	p
	(n = 59)	Yes (n = 30)	No (n = 29)		
Chemotherapy agents					
CDDP	55 (93.2%)	29 (96.6%)	26 (89.6%)		
Others	4 (6.7%)	1 (3.3%)	3 (10.3%)	3.35 (0.33–34.19)	0.284
Cycles of chemotherapy					
<5 cycles	13 (77.9%)	4 (13.3%)	9 (31.0%)		
≥5	46 (22.0%)	26 (86.6%)	20 (68.9%)	2.93 (0.79–10.89)	0.101
V10 of bony pelvis					
>90%	51 (86.4%)	25 (83.3%)	26 (89.6%)		
≤90%	8 (13.5%)	5 (16.6%)	3 (10.3%)	0.58 (0.12–2.67)	0.478
V20 of bony pelvis					
>80%	54 (91.5%)	26 (86.6%)	28 (96.5%)		
≤80%	5 (8.4%)	4 (13.3%)	1 (3.4%)	0.23 (0.02–2.21)	0.172
Dose (Gy)	49.4	49.5 ± 1.5	49.2 ± 1.7		0.505
Pelvis volume (cm^3)	1079.5	1090 ± 262	1068 ± 116		0.672
V10 (%)	94.6	94.6 ± 5.3	94.5 ± 3.7		0.948
V20 (%)	89.1	88.7 ± 7.5	89.5 ± 4.33		0.632

The results shown are mean with minimum and maximum values.

and IIIB with 42% and 41%. The mean dose of radiotherapy was of 49.4 Gy. 86.4% of the patients had a V10 > 90% and 91.5%, a V20 > 80%. Tables 1 and 2 show the clinical characteristics and the treatment as well as the dosimetry used.

Speaking of the HT results, 89% of the patients developed some grade of HT. 50.8% had an hematologic toxicity equal or greater than grade 2. Of these, 72.9% of the patients had some grade of anemia, cellular type being the most common. Following this, 57.6% of the patients had leukopenia, 27.2% had neutropenia, and 3.4% had thrombocytopenia. The severity of the hematic toxicity is explained with more details in Table 3.

At the bivariate analysis, clinical factors of age >50 years and diabetes mellitus (DM) showed no statistical significance relationship with the development of HT. The obesity variable did show statistical significance ($p = 0.021$). The dosimetric factors V10 > 90% and V20 > 80% did not show statistical significance ($p = 0.478$ and $p = 0.172$, respectively). Other variables, like the histological type, clinical stage, the chemotherapy agent used, and the number of cycles used were analyzed. We found statistical correlation with the development of ≥grade 2 HT in the epidermoid histology and on ≥III A clinical stages ($p = 0.01$ and $p = 0.02$, respectively) as shown in Table 1.

4. Discussion

Our study tried to identify clinical and dosimetric factors related to the development of hematologic toxicity in patients treated with a 3D four fields radiation technique. In our study subjects, up to 89% developed some grade of hematologic toxicity. Making another analysis of toxicity severity developed, we saw that over 50.8% developed toxicity grade 2 or higher, and this group was the most important because of its relationship with less effective chemoradiotherapy treatment.[9,10]

Those results show a minor incidence percentage of hematologic toxicity in comparison to the one presented by

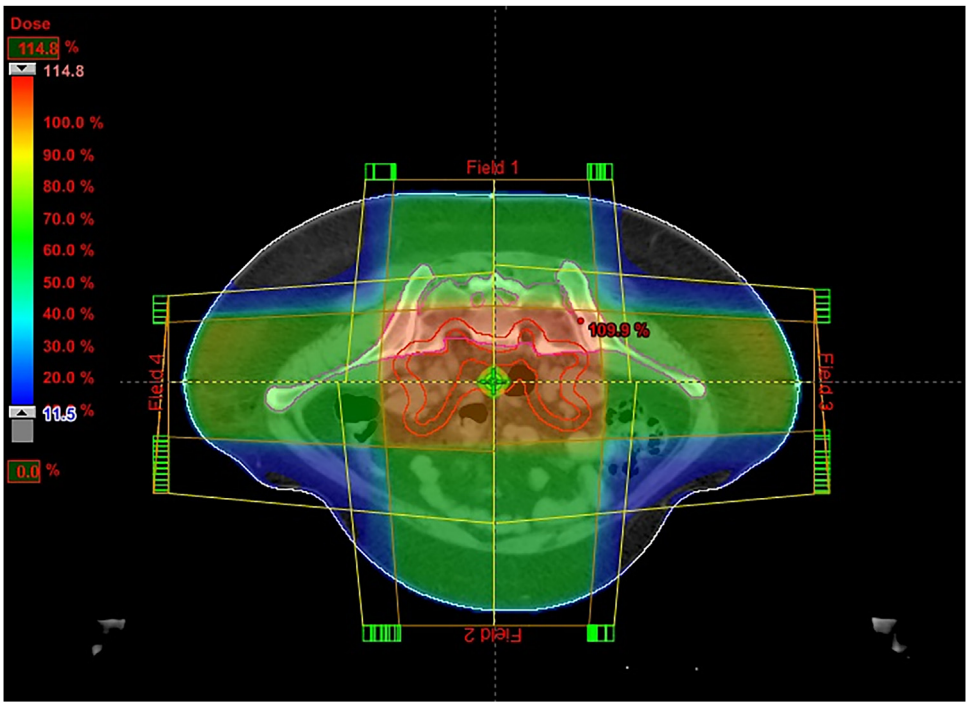

Fig. 1 – Dose distribution in 3D conformal technique.

Table 3 – Severity of the hematologic toxicity.

Cell type		N
Final hemoglobin (g/dL)	10.3 (6.5–13.4)	59 (100%)
Anemia		28 (47%)
Grade 1		12 (20%)
Grade 2		3 (5%)
Grade 3		
Leukocytes final (u/μL)	3692 (1197–24,850)	59 (100%)
Leucopenia		17 (28%)
Grade 1		11 (18%)
Grade 2		6 (6%)
Grade 3		
Neutrophils final (u/μL)	2500 (900–20,600)	59 (100%)
Neutropenia		5 (8%)
Grade 1		9 (15%)
Grade 2		2 (3%)
Grade 3		
Platelets final (u/μL)	211,500 (51,800–520,100)	59 (100%)
Thrombocytopenia		1 (2%)
Grade 1		1 (2%)
Grade 2		0 (0%)
Grade 3		
Hematologic toxicity		53 (89.8)
G2 toxicity or >		30 (50.8%)

The results shown are mean with minimum and maximum values.

Albuquerque et al.[28] They reported incidence in several grades of hematologic toxicity in 100% of their population and grade 2 or higher toxicity in 67.5% The two dosimetric factors that have been related to the hematologic toxicity development are V10 > 90% and V20 > 80%. Mell et al.[16] reported grade 2 or higher HT incidence in 72% ($p = 0.01$) when the dosimetric restriction was exceeded V10 > 90%. Meanwhile, Albuquerque et al.[28] also described an increase in the risk of hematologic toxicity when the V20 > 80% restriction was exceeded.

Nevertheless, in this study we did not find a statistically significant relationship between the dosimetry restrictions, found in IMRT studies, and the development of hematologic toxicity. In contrast with worldwide literature, only 14% met the V10 < 90% restriction and 8.5%, V20 < 80%. This result shows the difficulty to preserve the bone pelvis as an organ at risk with the 3D conformal four fields technique (Fig. 1). The IMRT is a better treatment option for the fulfillment of the dose restriction to the bone pelvis, as well as to the bladder and rectum. This treatment carries less urinary and gastrointestinal toxicities. However, the 3D technique is still, in the first instance, the most commonly used technique for the treatment of this group of patients in our environment.

The clinical factors have been studied in multiple studies but no relationship has been found with the development of hematologic toxicity in this group of patients.[28] This work confirms those findings for age higher than 50 years and DM. However, when comparing obesity to a normal BMI, we found that this is a statistically significant factor for the development of grade 2 or higher hematologic toxicity ($p = 0.21$). This is the first research that shows that finding. Theoretically, this corresponds to data recently published where it is explained that the increased levels of adenosine, adenosine triphosphate and lactate influence the differentiation and functions of immune cells and produce alterations of hematopoiesis through the expansion of suppressor myeloid populations.[32]

When analysing other factors, we could identify that the epidermoid histology was statistically significant compared to other histologies like adenocarcinoma and adenosquamous carcinoma ($p = 0.011$) without theoretical support found in actual literature. Clinical stage equal or higher than IIIA by

FIGO was statistically significant ($p = 0.026$) to the development of hematologic toxicity in this group of patients as well. This is related to higher PTV volumes radiated in higher CS patients and consequently higher bone marrow volumes radiated.

So, we have a group of patients (with obesity, epidermoid histology or CS IIIA-IVA) that is clinically susceptible to HT in grade 2 or higher when a 3D conformal 4 fields technique is used. These patients should be considered as a high-risk group for HT and they should be considered for preventive strategies.

5. Conclusions

In patients treated with 3D four fields radiation technique, statistical relationship between HT and the clinical factors of age >50 years and DM was not found. Statistical relationship with the dosimetric factors V10 > 90% and V20 > 80% was not found either. On the contrary, obesity, epidermoid histology and ≥IIIA CS showed statistical significance for development of HT ≥ grade 2. For this reason, this patient group should be studied for having high risk to develop HT and preventive strategies are encouraged being the consideration of a change of technique to IMRT with bone marrow constraints the first option.

Conflict of interest

None declared.

Financial disclosure

None declared.

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