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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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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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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