

Concurrent chemotherapy and radiotherapy for cervical cancer

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Summary

Objective: To compare the results obtained following treatment, from a group of patients with locally advanced cervical cancer (Stage IB or higher) treated with concurrent chemotherapy and radiotherapy in relation to a group of patients treated exclusively with radiotherapy.

Material and Method: All patients treated with concurrent chemotherapy and radiotherapy at the Gynaecologic Oncology Unit of the University Hospital Materno Infantil of the Canaries between 1999 and 2000, both inclusive, were included. The first group to be considered was formed by patients who received combined treatment. The second group of patients received radiotherapy exclusively, having been treated in previous years (1997-1998 period). The results were compared in relation to survival in the two following years from treatment (2000-2001) in the group of combined treatment and years 1999-2000 in the group that received only radiotherapy.

To compare the survival of both groups the chi-square test and Odds Ratio were utilised.

Results: The groups compared are homogeneous when looking at the stage of the disease when diagnosed, the histological type of tumour and its degree of cellular differentiation, the CAT results and tumoral markers. Survival of more than two years was observed in the group treated with concurrent chemotherapy and radiotherapy in relation to the group treated exclusively with radiotherapy; chi-square 9.92, $p < 0.01$, OR: 0.1 (0.01-0.6).

Key words: Cervical cancer; Chemotherapy.

Introduction

Cervical carcinoma is the fifth more frequent neoplasia in the general population. In underdeveloped countries it is the neoplasia with the greatest incidence in women, with rates of 26-36 new cases/100,000 citizens/per year. In developed countries the incidence is lower, being estimated at less than 15 new cases per year/100,000 citizens. Spain has one of the lowest incidence rates (5.7 new cases/100.000 citizens/year), though in Las Palmas it is higher (8.7 new cases/100.000 citizens/year) [1].

The extended use of cervical smears has allowed an early diagnosis in many cases, though a significant percentage is still diagnosed in advanced stages.

Traditionally the treatment of cervical cancer could be simplified as follows: in Stages I to IIA, surgery and radiotherapy have offered equivalent expectations, differing in their side-effects; in Stages IIB and onwards radiotherapy has been the treatment used. For bulky Stage IB, there has always been discrepancies. Generally, the treatment of these tumours has consisted of radiotherapy or radiotherapy with surgery [2].

In February 1999 the National Cancer Institute recommended the suitability of concurrent radiotherapy and chemotherapy treatment for locally advanced cervical cancer [3].

Immediately after this, numerous studies compared the concurrent chemotherapy and radiotherapy treatment for

this type of cancer. All of them demonstrated the superiority of a combination of cisplatin with radiotherapy in relation to radiotherapy exclusively or in combination with other chemotherapy drugs in advanced stages of cervical cancer [4-7].

In our Unit we initiated treatment with concurrent chemotherapy and radiotherapy in April 1999.

Objective

The objective of this study was to compare the results obtained following treatment, from a group of patients with locally advanced cervical cancer (Stage IB or superior) treated with concurrent chemotherapy and radiotherapy in relation to a group of patients treated exclusively with radiotherapy.

Material and Method

All patients treated with concurrent chemotherapy and radiotherapy at the Gynaecologic Oncology Unit of the University Hospital Materno Infantil of the Canaries between 1999 and 2000 (both inclusive) were included in this study. The first group consisted of patients who received combined treatment and the second group, that had been treated in previous years (1997-1998), received radiotherapy exclusively.

Concurrent treatment includes: external radiotherapy using a four-field box technique (two anteroposterior fields and two lateral fields). Fractionated doses of 1.2-8 Gy/day were administered, with a total dose of 50-59 Gy after six weeks brachytherapy, which applies high rates of intracavitary doses, (30-

Revised manuscript accepted for publication August 29, 2003

40s Gy). In addition 40 mg of cisplatin weekly needs to be added while the radiotherapy lasts.

These patients were selected with the same stages of the disease, the same type of histological percentage and the same tumour size. The increase in the tumoral markers and the abdomino-pelvic CAT findings were also considered in the selection. The CAT findings were divided into: not affected, pelvic and/or paraaortic gland affection, parametrial infiltration and/or pelvic wall affection.

The homogeneity of the groups was established by the chi-square test.

Thereafter, the results were compared in relation to survival the two following years from treatment (2000-2001) in the group of combined treatment and years 1999-2000 in the group that only received radiotherapy. All the patients included in the study had at least one year of complete follow-up.

To compare the survival of both groups the chi-square test and Odds Ratio were used.

A p value was considered significant for $p < 0.05$ and a CI of 95%.

Results

In the first group 31 patients were studied (concurrent radiotherapy and chemotherapy), and in the second group 35 patients (radiotherapy exclusively).

No significant differences were found when comparing the stages of the disease, chi-square: 6.7, $p < 0.4$ (Table 1).

The most common histological type was scaly carcinoma, with 26 cases in the first group (83.9%) and 31 cases (88.6%) in the second group, while adenocarcinomas were found in five cases (16.1%) in the concurrent treatment group and four cases (11.4%) in the group treated with radical radiotherapy. No significant differences were found in relation to the histological type, or the level of differentiation (chi-square of 41.2, $p < 0.09$) (Table 2).

The mean tumour size was 3.8 cm in the first group with a range of 1.5 to 8 and 4.6 cm in the second group (2-8). No significant differences were found when comparing the total tumoral volume in the groups (chi-square of 12.3, $p < 0.7$).

Average patient age was 44 years in the first group (29-65) and 54 in the second group (27-88). The sample was

Table 1. — Stages of tumor.

	1B1 n (%)	1B2 n (%)	2A n (%)	2B n (%)	3A n (%)	3B n (%)	Total
Radiotherapy+ chemotherapy	6 (19.3)	10 (32.2)	6 (19.3)	7 (22.6)	1 (3.2)	1 (3.2)	31
Radiotherapy	6 (17.1)	8 (22.8)	12 (34.2)	6 (17.1)	2 (5.7)	1 (2.6)	35

Table 2. — Scaly carcinoma - differentiation level.

	G1	G2	G3	Total
Radiotherapy+ chemotherapy	3 (11.5)	10 (38.5)	13 (41.9)	26
Radiotherapy	3 (9.6)	9 (29.0)	19 (61.2)	31

Table 3. — Cat results.

	Not performed	No findings	Positive		
			Pelvo-aortic affection	Parametrial infiltration	Pelvic wall
Radiotherapy+ chemotherapy	3 (9.6)	21 (67.7)	3 (42.8)	2 (28.6)	2 (28.6)
Radiotherapy	2 (5.7)	27 (77.1)	4 (66.6)	1 (16.6)	1 (16.6)

Table 4. — Tumoral markers.

	Increased		Not increased
	SCC	Ca 125	
Radiotherapy+ chemotherapy	11 (73.3)	4 (26.6)	16 (51.6)
Radiotherapy	10 (76.9)	3 (23.0)	17 (48.5)

homogeneous in relation to patient age, with no significant differences found when comparing this parameter (chi-square 6.3, $p < 0.09$).

Both groups were also homogeneous in relation to the CAT findings, with negative results in 67.7% of the women belonging to the first group and 77.1% in the second group. When positive the most frequent part affected was the pelvic-aortic region in both groups (chi square: 54, $p < 0.7$).

The predominant marker was the SCC (serum squamous cell carcinoma) antigen level in both series, with no differences in its frequency of appearance (chi square: 17.8, $p < 0.2$).

Regarding survival, two cases of deaths were registered in the first group (both cases in Stages 1B2) and 14 cases in the second group (4 cases in Stage I B2, 3 cases in Stage IIB, 4 cases in Stage IIIA and 3 cases in Stage IIIB). The survival results in two years were statistically significant (chi square 9.92, $p < 0.01$, OR:0.1 (0.01-0.6)).

Conclusions

Until the publication of the appropriate use of concurrent chemotherapy and radiotherapy for the treatment of locally advanced cervical cancer in February 1999 by the American Cancer Institute, the use of chemotherapy in the treatment of cervical cancer was not a subject that arose interest as the known results were discouraging.

In April 1999 three studies with 343, 403 and 369 patients, respectively, were published with excellent results obtained from the use of concurrent treatment, with an increase in global survival which ranged from 12 to 17% [3-5]. These good results can be explained by the increase of cellular radiosensitivity induced by the drugs used for chemotherapy [3]. During that year two more studies were published involving large numbers of patients (234 and 388, respectively), confirming previous results and even referring to combined treatment in bulky Stage IB [4, 5].

Regarding the drug to be used there seems to be a consensus in stating that cisplatin is the one that offers greater advantages. Its action can be explained in three levels: inhibition of the restorative potential of neoplastic cells, whereas on the other hand it increases the radiosensitivity when hypoxic and it induces a marked reduction of the tumoral volume [7].

The differences found between cisplatin and other drugs such as hydroxyurea, 5-FU or bleomycin are basically a reduction in the risk of death, estimated at 12% (CI 95%: 8-16) [4, 5], a reduction of local recidivation: 13% (13-19), metastasis reduction: 28% (19-30) and its scarce toxicity (associated to platelet deficiency, white blood cell deficiency in percentages which range between 16%-8%, depending on the studies consulted, and GI alterations in the form of diarrhoea as a result of the treatment, which disappear when treatment is suspended) [3, 4, 7].

Regarding the results obtained in our Unit, though too early to talk about survival as a longer observation time is needed, those obtained in the last two years have been very encouraging and significantly better than those obtained in the same period of time using radiotherapy exclusively.

Therefore in agreement with the literature, we also conclude that the treatment of choice for locally advanced cervical carcinoma is a combination of chemotherapy and radiotherapy.

References

- [1] Lloret M., Falcón O., Lara P. C.: "Carcinoma Infiltrante de cérvix: de los aspectos clínicos a la investigación aplicada". 2001, 13.
- [2] Landoni F., Maneo A., Colombo A., Placaa F., Milani R., Perego P.: "Randomised study of radical surgical vs. radiotherapy for stage IB-IIA cervical cancer". *Lancet*, 1997, 350, 535.
- [3] National Cancer Institute. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer". *N. Engl. Med.*, 1999, 340, 1144.
- [4] "Pelvic radiation with Concurrent Chemotherapy Compared with pelvic and paraaortic radiation for High Risk Cervical Cancer". *N. Engl. Med.*, 1999, 340, 1137.
- [5] "Cisplatin Radiation and Adjuvant Hysterectomy Compared with Radiation and Adjuvant Hysterectomy for Bulky Stage IB Cervical Carcinoma". *N. Engl. Med.*, 1999, 340, 1154.
- [6] Green J., Kirwan J., Tierney J. F.: "Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta - analysis". *Lancet*, 2001, 358, 781.
- [7] "A randomised trial of standard versus partially hyperfractionated therapy with or without concurrent 5FU in locally advanced cervical cancer". *Gynecol. Oncol.*, 1998, 69, 137.

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