

# Randomised trial with Bleomycin, Ifosfamid and Cisplatin as neoadjuvant chemotherapy of the radiotherapy *versus* radiotherapy alone (classic treatment) in patients with cervical cancer in a III B stage

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## 1. SUMMARY

Since 1993 the Portuguese Co-operative Group of Gynaecologic Cancer has pursued a phase III randomised trial using Bleomycin, Ifosfamid and Cisplatin (BIP) as neoadjuvant chemotherapy (group A) of the radiotherapy versus radiotherapy alone (group B) in III B cervical cancer patients. 44 patients have already been introduced in the study - 21 in the group A and 23 in the group B.

The response rate was 88.2% in the group A and 71.42% in the group

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B. The time for progression is between 6 to 16 months in the group A and 5 to 27 months in the other group ( $p=0.124$ ). The overall survival was between 20 to 32 months and 5 to 27 months in the group A and B, respectively ( $p=0.05$ ).

## 2. OBJECTIVES OF THE TRIAL

The Co-operative Group of Gynaecologic Cancer of Portugal proposed a phase III randomised trial with two arms: one group of patients (Group A) is submitted to Bleomycin, Ifosfamid and Cisplatin before radiotherapy; in the other group (Group B) the patients are only submitted to the classic regime of radiotherapy.

This is a randomised trial that pretends to compare the response rate, the overall survival, the time to progression and the dose intensity and the toxicity in the two arms of the trial.

## 3. MATERIALS AND METHODS

44 patients were randomized in the two arms after clinic and histologic confirmation of squamous cells carcinoma of the cervix in a III B stage. All of them were less than 70 years old, had a Performance status of 0 to 2; they had not any former treatment and had done their informed consence. The exclusion criteria were the coexistence of another cancer (except nonmelanoma skin cancer), renal failure (serum creatinine above 1.5 mg/% and/or creatinine clearance  $< 70$  ml/hour), hepatic failure (total and/or fractional bilirubin twice the upper level of normal value and albumin under 30 mg/dl), leukopenia (white blood cells count under  $4,000/\text{mm}^3$ ) and or thrombocitopenia (platelet count under  $100,000/\text{mm}^3$ ), psychiatry or central nervous system disease, chronic obstructive pulmonary disease or ureteric involvement of the cervical cancer

On entering the study the women underwent a review of their clinical history, physical examination and laboratory procedures. CT scan or Nuclear Magnetic Resonance allowed the evaluation of the lombo-aortic nodes involvement. The uni or bilateral involvement of the parametria was clinically evaluated.

All the patients were submitted to a complete clinical and laboratory assessment before each cycle of chemotherapy. During the radiotherapy the clinical evaluation was made every week.

The adverse effects were graded according to the toxicity criteria of National Cancer Institute and the Performance status according to World Health Organisation. The treatment was delayed for a week if the leukocyte and/or platelet count were under  $4,000/\text{mm}^3$  or  $100,000 \text{ mm}/\text{mm}^3$ . No delay in the subsequent courses was allowed for gastro-intestinal, or mild neurologic toxicity and only serum creatinine values above 1.5 mg/dl or clearance creatinine under 70 ml/hour forced a delay of the next cycle. The severe allergic reation were considered a cause for the withdrawal of the patient of the study.

The therapeutic regime were for the group A patients, 3 cycles each 21 days of chemotherapy with Bleomycin - 30 mg each cycle, Ifosfamid - 5

g/m<sup>2</sup> and Cisplatin - 50 mg/m<sup>2</sup>. 15 days after the ending of the chemotherapy the patients were submitted to Radiotherapy similar to the Group B; to the group B patients only Radiotherapy - External Radiotherapy (40 to 60 Gy) and after Brachytherapy (14 to 17 Gy in the A point).

The dose intensity proposed was to the Bleomicin 10 mg/week, to the Ifosfamid 1.67 g/m<sup>2</sup>/week and to the Cisplatin 16.67 mg/m<sup>2</sup>/week

All the eligible cases were included in the analysis unless otherwise is specified.

For the statistical analysis de Student's t test for the parametric variables and the U test of Mann Whitney for the non-parametric variables was used and for the time to progression and overall survival the Log-rank test was made and the Kaplan-Meier procedures were designed in the Statistica for Windows® program.

#### 4. RESULTS

Since November 1993 till November 1996, 44 patients were randomised: 21 in the group A and 23 in the group B.

After the randomisation 4 patients of the group A were excluded from the trial because 3 of them had a severe allergic reactions to Ifosfamid in the first cycle and did not end it and the other didn't fulfill the radiotherapy properly. In the group B, 1 patient had a very quick progression of the disease (pathologic breakbones) during the radiotherapy, 2 patients abandoned the follow up just after the ending the radiotherapy and it wasn't possible to assess the response.

So, it was possible to evaluate 37 patients with the characteristics that are expressed in the next table.

TABLE 1

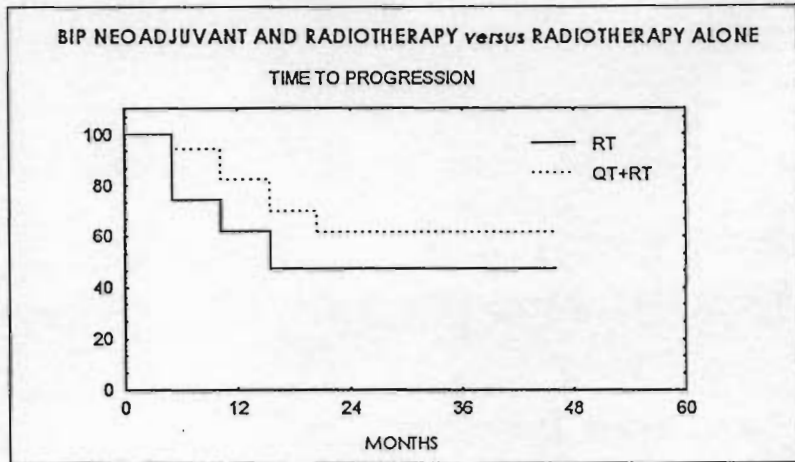
	GROUP A - CT+RT (n=17)	GROUP B - RT (n=20)	P
AGE (Yr)			
median	50.5	54.4	>0.05
range	(29-68)	(33-69)	(n.s.)
PARAMETRIA			
Unilateral involv.	7 (41.2%)	7 (35%)	>0.05
Bilateral involv.	10 (58.8%)	13 (65%)	(n.s.)
L-A NODES			
not involved	15 (88.2%)	16 (80%)	>0.05
involved	2 (11.8%)	4 (20%)	(n.s.)

In the group A the response rate was of 88.2% [11 complete responses (64.7%) and 6 partial reponses (23.5%)]; 1 patients (5.8%) didn't respond and another (5.8%) progressed. In the group B the response rate was of 70% [11 (55%) complete responses and 3 (15%) partial response] and 6 patients (30%) progressed.

In this group, 1 patient (5.8%) didn't present any response to the therapeutics, 3 patients (17.4%) had local recurrence of the illness, 2 (11.6%) patients presented distance metastasis (lung and supra clavicular

nodes). The time for progression was between 6 and 16 months and the medium time for progression reached has not been reached yet (table 2). Only 3 patients died and the overall survival was between 20 and 32 months. The medium overall survival has not been reached yet, too (table 3).

Table 2- BIP neoadjuvant and radiotherapy *versus* Radiotherapy alone - time to progression

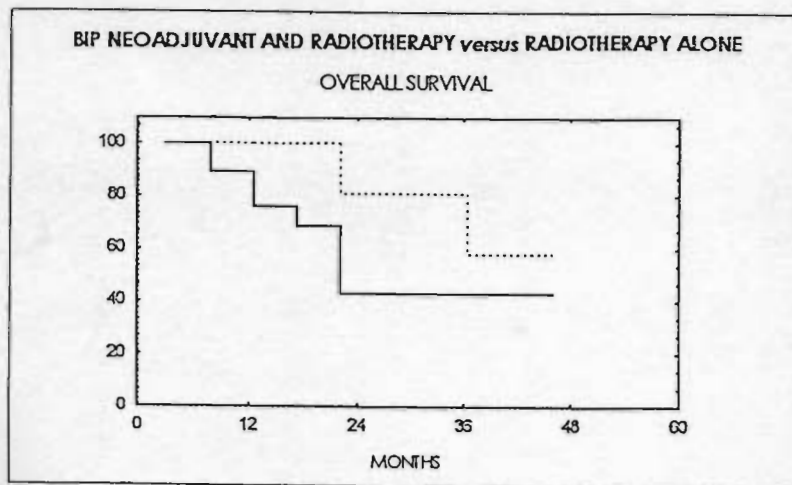


In the group B there were 11 (55%) complete responses, 3 (15%) partial responses, and 6 (30%) patients had progressed before the ending of the first month of follow up. 3 (15%) patients had local recurrence of their cervical cancer and 3 other patients had distance metastasis (lung, supra-clavicular nodes and nervous central system). The time for progression was between 3 and 16 months (Table 2). The medium time for progression was reached at 16 months. The overall survival was between 5 and 22 months and the medium overall survival was reached at 22 months (Table 3).

Although apparently the chemotherapeutic group seems to have better results the application of the Log-rank test doesn't show any statistical significant difference for the time to progression ( $p=0.131$ ), but the difference is significant for the overall survival ( $p=0.02$ ). Some trials [1,2,3,4,5,6,7,10,11] didn't find any significant statistical difference; may be if the AA can evaluate more patients and longer enough, they can make clear the meaning of this difference.

The AA wanted to study the influence of the dose intensity in the results but it wasn't possible, because they only found 3 patients with de Average relative dosis intensity (ARDI) under 0.85, which was the value that they considered as cut-off and all of them were alive at the time of the evaluation. The fact that the chemotherapy precedes any kind of treatment and takes place in the beginning of the illness was enough to justify the good tolerance of the regime; 10 patients ended the third cycle of chemotherapy with ARDI values not under 1,00 and 3 other patients

Table 3- BIP neoadjuvant and radiotherapy *versus* Radiotherapy alone - overall survival



ended the treatment with ARDI values between 0,90 and 0,99. The alopecia was universal and the digestive toxicity was of grade 1 or 2. Only in 3 patients was necessary to postpone the second and the third cycles because of hematologic toxicity.

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