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Results of treatment with concurrent radiotherapy and cisplatin-based chemotherapy for cancer of the uterine cervix – a preliminary assessment

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Aim. To compare the results of radiochemotherapy and radiotherapy in patients with cervical cancer.
Material and methods. Fifty three patients with locally advanced cervical cancer, undergoing combined radiochemotherapy (C) and a control group of 50 patients treated with irradiation only (R) entered the study
Results. All patients in group C treated with concurrent radiochemotherapy showed positive therapeutic effect – no cases of stable disease nor progress. Complete remission (CR) was observed in more than half of the cases (54.72 %) directly after treatment, as compared with group R – 19.64%. However, more than 70% of patients treated with combined therapy demonstrated bone-marrow damages. Only 4 of these patients (7.55%) did not complete cytostatic treatment because of thrombocytopoenia. Low thrombocyte count caused permanent exclusion of the patient from the chemotherapy schedule. Post-irradiation side effects, such as proctitis, urocystis and enterocolitis posed another problem: combined radiochemotherapy increased the percentage of patients with post-irradiation reactions, although the intensity of these reactions was neither increased nor lenghtier.
Conclusion. Our results of combining irradiation with cisplatin-based chemotherapy treatment allow to reccomend this schedule of therapy as a standard for locally advanced cervical cancer treatment.

Wstępna ocena wyników leczenia raka szyjki macicy napromienianiem skojarzonym z chemioterapią opartą na cisplatynie

Cel. Badanie podjęto w celu wykazania różnicy w wynikach leczenia radiochemioterapią i radioterapią, oraz wskazania metody skuteczniejszej w leczeniu raka szyjki macicy.
Materiał i metoda. Badaniem objęto 53 chore na płaskonabłonkowego raka szyjki macicy, poddane radiochemioterapii w okresie od maja 2000 r. do czerwca 2001 r. z powodu nowotworu zaawansowanego miejscowo: stadia kliniczne od IB-2 do IVA – grupa C. Grupę kontrolną stanowiło 50 kobiet z rozpoznanym rakiem szyjki macicy, w stadiach zaawansowania klinicznego od IB-1 do IVA, leczonych wyłącznie radioterapią w 1997 roku – grupa R. Obie grupy były porównywalne pod względem wieku, warunków napromieniania, rodzaju brachyterapii. W grupie C znalazło się więcej chorych z zaawansowanym nowotworem (bulky, oraz przewaga liczebna wyższych stadiów klinicznych). W grupie tej zastosowano wlewy cisplatyny 1 raz w tygodniu w dawce 40 mg/ m^2, lecz nie więcej niż 70 mg na 1 wlew. Z powodu masywnego krwawienia z dróg rodnych 6 chorych napromieniono metodą hiperfrakcji: 2 x 1,2 Gy z przerwą 8 h, aby nie stosować hipofrakcjonacji hemostatycznej.
Wyniki. U wszystkich chorych grupy C zaobserwowano pozytywny efekt terapii, w tym ponad 50% całkowitych remisji. U ponad 70% kobiet stosowano sterydy z powodu leukopenii, a 4 chore nie otrzymały pełnej chemioterapii – 6 kursów cisplatyny, z powodu trombocytopenii, która wydaje się być największym problemem leczenia skojarzonego. Ilość odczynów popromiennych wzrosła, lecz nie wydłużyła się w czasie, ani nie osiągnęła większego natężenia.
Podsumowanie. Wczesne wyniki skojarzonego leczenia radiochemioterapią płaskonabłonkowego raka szyjki macicy są bardzo obiecujące i rekomendują powyższy schemat jako standard terapeutyczny w tym schorzeniu.

Key words: cervical cancer, radiotherapy, chemotherapy, combined radiochemotherapy
Słowa kluczowe: rak szyjki macicy, radioterapia, chemioterapia, skojarzona radiochemioterapia

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Introduction

Cancer of the uterine cervix still remains a frequent cause of death of women in Poland. Unfortunately there has been no evident increase in the five-year survival rate, despite the progress of clinical diagnostic methods, improvement of treatment methods and an increase in the general standard of living [1].

Epidemiological data from the Lower-Silesian Cancer Registry indicate only a slight trend for decreased incidence, i.e. 1-2% per year since 1997. In 1999 cancer of the uterine cervix accounted for 6.8% of total cancer cases among women in Lower Silesia, and it was the third most common tumour after cancer of the breast and the lung. It was also the fourth most common cause of death after cancer of the breast, the lung and the stomach. In 1998 the standarized death rate for cervical cancer was 7.2/100 000 women [2].

The global combined percentage of five-year survival in 1998 was 65.4% for all clinical stages; among them I° – 85%, II° – 66%, III° – 39%, IV° – 11% [3]. In the Lower Silesia this percentage was lower – 55% [2].

The unsatisfactory results of treatment have provoked a search for more efficient therapy schedules, particularly for patients with locally advanced cancer [4-6]. In 25% of these cases the disease had spread and distant metastases could be found. [7, 8]. Recently it has been indicated that the application of chemoradiotherapy, i.e. combined treatment with ionizing irradiation and cytostatic drugs is the optimal solution for the majority of patients with cancer of the uterine cervix. In such a combination the cytostatic drug is both a radio-sensitizer and a systemic supplement for radiation, which is generally local in application [9, 10]. Cisplatin seems to be the most effective drug among the numerous cytostatics tested during the preliminary phase of clinical investigations.

Material

Between May 2000 and June 2001 53 patients with *invasive squamous cell carcinoma of the uterine cervix* (group C of concurrent approach) underwent radiochemotherapy in the Clinic of Oncological Gynaecology at the Department of Oncology of the Medical Academy of Wrocław.

50 patients treated with ionising energy only (i.e. radically irradiated) in the same Clinic in 1997 served as the control R group.

Both groups did not differ as to mean age (48 yrs in group C; 51 yrs in group R). Identical radiotherapy methods based on calculated doses to the radiated area were used for both groups. In both groups stage IVA cervical carcinoma was determined by cystoscopy, and pathomorphologically confirmed as infiltration of the mucosa of bladder (to a maximum diameter of 2.0 cm). In group R the majority (64 %) of patients were in stage I and II of cervical carcinoma (according to FIGO), higher stages (III and IV) dominated in group C (54.7%), (Table I).

Table I. Stage of advancement of cervical carcinoma acc. to FIGO in group R (radiotherapy alone) and group C (concurrent radiochemotherapy)

FIGO stage	No of cases		% in groups	
	R	C	R	C
1 B	11	4	22.00	7.55
2 A	3	2	6.00	3.77
2 B	17	18	34.00	33.96
2 A	1		2.00	
3 B	14	28	28.00	52.83
4 A	4	1	8.00	1.89
All	50	53	100.00	100.00

The groups differed only as to the T character in clinical stage I. Among patients in clinical stage IB, radiochemotherapy (group C) was applied to those with "bulky" tumour (stage IB_2 according to FIGO). In group R (treated with radiation only) there were patients with stage IB_2 with high tumour mass (2 patients) as well as IB_1 – 8 patients with cervical diameter at a lower 4 cm. Six patients of group C were treated (because of intensive vaginal haemorrhage) with hyperfractionational radiation (2 fractions daily, each with 1.2 Gy at 8 hr intervals).

Before starting the concurrent treatment the weight and height of the patients was determined, because the cytostatic doses depended on the body area. The patients underwent careful examination, and those suffering from diseases limiting fluid intake (necessarily increased during cisplatin treatment) were excluded from the study. None of the patients suffered from major circulatory diseases, a number of them reported mild arterial hypertension. During chemotherapy treatment cisplatin was applied in a dose of 40 mg/1 m^2 of body area, the maximum dose not exceeding 70 mg per course. Body surface area varied between 1.4 and 2.0 m^2; maximum weight was 91 kg. Women of body surface >1.75 m^2 received the maximum dose (70 mg).

Methods

Radiotherapy

Megavoltaged teletherapy and brachytherapy with "after-load" was applied. In a period of 5 weeks (from Monday to Friday) the patients were irradiated with a fraction dose (Df) = 1.8-2.0 Gy to the total dose (Dc) = 46.8-50.4 Gy in reference point and, in the case of hyperfractionation, Df = 1.2 Gy (2.4 Gy/24 hrs), Dc = 46.8-50.4 Gy/ in reference point over 4 weeks. Brachytherapy was applied after observing regression of tumor infiltration. In case of stage IB1 in group R, from the onset of treatment brachytherapy was carried out with external beams (beginning the applications from the probe to the cavity of the uterus). For all the remaining patients (both C and R groups) brachytherapy was initiated in the fourth and sixth week of therapy. In all cases the Selectron LDR/MDR (given in 4 fractions Dc = 6200-6400 cGy in reference isodose) was used.

Chemotherapy

Cisplatin-based chemotherapy at a dose of 40 mg/m^2 of body area (up to a maximum dose of 70 mg) was given in one infusion. Administration took place once a week (on Sundays, between periods of radiotherapy). A maximum of 6 such courses were applied.

Chemotherapy was applied only if the following were met: HB equal or higher than 10.0%, leucocyte count – over 3000, granulocyte count – over 1500, thrombocyte count – over 100 000. During therapy we monitored the function of bone-marrow, the liver and the kidneys. Kidney function was monitored acc. to the urea and creatinine level and with the aid of fluid balance during treatments.

In a number of cases chemotherapy was administerd despite a leucocyte count of 2500, providing the granulocyte count was above 1500. In such cases vitamin B_6, Leucogen or steroids were administered. One patient (admitted from a different hospital after genital haemorrhage) was given two units of packed red cells, and treatment was started at 9.7 g% HB. On the second day (after cytostatic medication) one unit of packed red cells was given. In this case, radiotherapy was considered to be the only possible form of treatment – locally advanced, haemorrhaging cervical cancer.

The therapeutic effect was evaluated directly after treatment using the following criteria: CR – total regression of tumor infiltration confirmed by clinical examination; PR – regression of over 50% of original magnitude; SD – no improvement (state same as before treatment); P – progression of neoplastic growth as compared to the state before treatment.

Toxicity of treatment was estimated according to the WHO scale [NEW Common Toxicity Criteria (CTC), Version 2.0, NCIC CTG MA/BMS CA 151-007, Revised March, 1998]

Results

In the group treated exclusively with irradiation (R) the ratio of patients in class CR was only 0.4 that in class PR, and in ca. 1/3 of patients the early clinical assessment showed therapeutic failure, manifested by progression of the disease in 12 women in stage IIIb.

The scheduled radiotherapy dose was applied in all cases. Because of anemia nine patients underwent blood tranfusion and erythocyte transfusion, however leukopoenia requiring steroid treatment was not observed.

Among the patients in the PR class 6 (12%) had acute post-irradiation reactions of 2nd degree acc. the WHO scale (urocystitis, enterocolitis radiogenes).

All patients in group C showed a positive therapeutic effect – in no case did the disease progress. Directly after treatment complete remission of disease (CR) was observed in more than half of the patients (29 pts – 54.72%), and in those remaining (24 pts – 45.28%) partial remission was observed.

Table II. Comparison of treatment results after radiotherapy (group R) and radiotherapy + chemotherapy (group C)

Result of therapy	No of cases		% in groups	
	R	C	R	C
CR	11	29	19.64	54.72
PR	27	24	48.21	45.28
P	12		32.14	
All	50	53	100.00	100.00

However in more than 70% of patients the bone--marrow function was impaired, sometimes affecting all cell lineages. These 38 patients (71.7%) suffered from leukopoenia (including granulocytopoenia). Both in class CR (22 pts) and in class PR (16 pts). In 5 cases (9.43%) thrombocytopoenia (2 – CR, 3 – PR) was observed.

Because of symptoms of hematologic toxicity in 4 patients (7.55%) complete cytostatic tratement was not applied: one woman received only 2, and three women only 5 cisplatin-based courses. In 21 cases (39.62%) encorton treatment was necessary; (13 CR; 8 PR). Neupogen was given to 5 patients (9.43%- 1 CR; 4 PR). Eight patients (15.09%) received packed red cell transfusions and 3 (5.66%) also required thrombocyte supplementation.

The radiotherapy regime was completed in all patients, however in 24 (45.28%) the acute post-radiation reaction (urocystitis, enterocolitis radiogenes) – classified as 2nd degree occurred. This reaction was successfully treated during radiochemotherapy.

Discussion /Summary – conclusions

In recent years many medical centers have undertaken trials of concurrent radiochemotherapy for cancer of the uterine cervix, using such cytostatics as 5-flurouracyl, topotecan, gemcytabine, hydroxyurea either together with cisplatin or as a monotherapy, and their results have indicated a positive therapeutic effect [11-13]. However, one may find other reports questioning the advantages of such treatment [14]. Because such therapeutic schemes are fairly new, there are no publications in Polish literature regarding the immediate results of concurrent chemoradiation for cervical cancer, nor the safety of this treatment. There is also no data concerning the long-term effect of such treatment.

Our results appear to be similar to the results reported by other authors [7, 15, 16]. It is worth emphasizing, that in the group of patients undergoing radio-chemotherapy we observed improvement in every single case, while in four cases we have even observed spectacular results – a 10-12 cm tumour decreased to 3.0-4.5 cm after therapy. Definitely better therapeutic results were observed after radio-chemotherapy, compared to radiotherapy alone, despite a greater ratio of advanced cases.

Concurrent radiochemical therapy was generally well-tolerated by patients, but some undesirable symptoms were observed. Our study confirms hematologic effects of cisplatin-based chemotherapy together with ionizing radiation, reported by others [17].

The complications caused by anemia [18] and leukopoenia are not a serious argument against the use of chemo-radiotherapy as it is possible to provide compensatory treatment. The one serious problem – low platelet count – may bring on exclusion from completeing the 6 courses, however such was the case only for 4 patients (7.5%), and three of them (5.7%) managed as many as 5 courses. Only in 1 case (1.9%) traetment had to be discontinued after 2 courses.

Radiotherapy did not have to be suspended. Only a 10 day-pause (and in a sole case – a 21day pause) was necessary in patients with a low thrombocyte count (one patient after the first week of radiotherapy + 2 courses of cisplatin, two patients after teletherapy, and before brachytherapy).

Given the high efficacy of the treatment, it is worth considering the possibility of giving the calculated dose (i.e. over 70 mg) to patients with body surface area over 1.75 m^2. The maximal dose for our patients would reach some 80 mg. At present it appears that the 70 mg dose has not been exceeded by any other study group.

There were problems concerning post-irradiation reactions within the digestive system and urinary tract. The application of cytostatics increased the number of patients with post-radiational diarrhoea and inflammation of the urinary tract, but the intensity of these reactions were neither increased nor long-lasting.

Such reactions may have been influenced by the application of brachytherapy only after a 30 Gy dose at the reference point, i.e. only after 4 cisplatin infusions. In the case of treatment with ionizing radiation alone (mainly for the patients in stage IB_1) brachytherapy was often initiated in the second week of external beam irradiation. In those cases a local dose increase of PTV occurred already at the onset of teletherapy, but not at its second phase (or after external beam irradiation), as was the case in the concurrent approach.

In summary our results suggest that programmes combining radiotherapy treatment with cisplatin-based chemotherapy can be recommended as an optimal standard for cervical cancer treatment.

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