Preliminary results of mitomycin C local application as post-treatment prevention of vaginal radiation-induced morbidity in women with cervical cancer

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Summary

Purpose: To determine the usefulness of local mitomycin C application in the prophylaxis of vaginal narrowing after irradiation.
Material and methods: 31 patients with advanced cervical cancer qualified for the study. They underwent brachytherapy with iridium-192 isotope and external beam therapy with linear accelerators. In a blind probe method 16 patients were chosen to have an aqueous solution of mitomycin C applied to the vagina.
Results: Radiotherapy caused a shortening of vaginal length in both groups (study and control). In the "mitomycin C group" complete vaginal occlusion was visibly less frequent as were solid fibrotic vault changes.
Conclusions: This mode of morbidity prevention can potentially diminish the occurrence of local vaginal fibrosis and thus may improve patients' quality of life. Further investigations are needed to confirm these results.

Key words: Cervical cancer; Morbidity; Mitomycin C; Radiotherapy; Vaginal fibrosis.

Introduction

There are approximately 3,500-4,000 new cervical cancer patients each year in Poland [1]. In Lodz (the second biggest city in Poland) this diagnosis is found in 250-300 women every year [1]. More than a half (approx. 60%) of these cancers are diagnosed as Stage II and III according to FIGO [2, 3]. Treatment of cancer in those stages is based on iradiation treatment (usually combined brachy- and external beam therapy). Almost a half of this group, ie., about 2,000 women, could be cured with radiation therapy. To improve treatment efficacy many trials have been conducted: special irradiation schedules, contemporary chemotherapy, surgery and hyperthermy combinations [4, 5]. New brachytherapy techniques have been developed such as for example high-dose rate Iridium irradiation, with an application time of several minutes – which is much more comfortable than previous methods over several days of irradiation fraction. The treatment course is now easier for patients.

Individual computed-dose assessment and its three-dimensional planning lead to increased treatment effectiveness and diminish the frequency of sequelae [6].

Efforts by radiotherapists and oncologists tend to minimalize the most serious post-treatment lesions such as vesico-vaginal and recto-vaginal fistulas, serious forms of cystitis, ureteric and bowel fibroses or necroses. Damage occurs in 6.0-17.0% of patients after pelvic irradiation [7, 8]. Gynaecologic oncologists observe in their daily practice a strong influence of radiation treatment on the quality of sexual life and patient behaviour [9]. Only a few reports have mentioned that a majority of cervical cancer patients suffer from significant shortening and narrowing of the vagina [10]. Except for psychological factors, a major adverse effect of radiation is local normal tissue damage. Rigid vaginal contraction and persistent concrescences make it very difficult or simply impossible to resume a normal sexual life [11]. These adverse effects do not permit correct clinical bimanual cancer control of monitoring morbidity and promote various infections caused by retention of discharge.

In recent years some data on chemotherapeutic agent activity against fibroblast proliferation have been published [12]. Some important results involved eye and larynx surgery [13, 14]. There is a similiarity between pathophysiologic and histologic conditions of the mucosa in the eye and larynx after surgery and local features of vaginal mucosa after irradiation treatment. Authors have not realized that the use of mitomycin C may be effective in avoiding proliferation of vaginal mucosa fibroblasts.

The goal of this study was to assess local prophylactic mitomycin application after radiation therapy in cervical cancer patients to avoid permanent, solid and rigid vaginal vault adhesions.

Material and Methods

Investigations were conducted at the Gynaecologic Radiotherapy Department, Copernicus Memorial Hospital in Lodz, the Oncology Clinic of Medical Sciences University, Poznan and at the Radiotherapy Department of the Medical University, Lodz. The study was initiated in May 2003 and finished in June 2004. Bioethics Commission approval for this trial was obtained. A group of 31 patients with squamous cervical cancer in Stage II and III according to FIGO were included in the study. Photon beam 9 MeV was used in the treatment. A total

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dose of 44.0 Gy/t in 22 fractions of 2.0 Gy/t per day was delivered five times a week for five weeks. External beam therapy was combined with brachytherapy of ^{192}Ir isotope, in a high dose rate modality – to total dose of 35.0 Gy/point A in five fractions once a week. In 16 patients (study group) mitomycin as a prophylaxis was locally applied. Seven patients were in Stage II and nine in Stage III. The remaining 15 patients with no application of chemotherapeutic agent (control group) were diagnosed as Stage II (7 women) and Stage III (8 women).

Application of the drug took place two and four weeks after completion of radiotherapy. The application technique was as follows: after insertion of a dry speculum into the vagina the uterine cervix and vaginal vault were very gently wiped with a sapless gauze (it was important not to cause any contact bleeding). Afterwards a sterile wet mitomycin C/water solution-soaked gauze was inserted. The substance concentration was 0.4 mg/ml (an ampoulle content of 40 mg underwent dilution of 100.0 ml in 0.9% natrium chloride at 30°C). The duration of this washing was approximately four minutes and was followed by rinsing the vagina with clean 0.9% natrium chloride solution.

In all patients just after the end of therapy the following were determined: the outcome of treatment (remission – complete, partial or none, progression); vaginal length in comparison to the same parameter measured before treatment; and presence or absence of local, acute radiation sequelae. The next vaginal length measurement was obtained during the routine control visit six months after radiation therapy.

Results

Values of measurements were compared between the groups. Obtained results were compiled statistically using a CSS Statistica programme (Statsoft Inc, Tulsa, OK, US). The Student's t-test was used with $p < 0.005$ being considered statistically significant.

Shortening of the average vaginal length after radiotherapy was recorded in both the study and control groups (respectively, $p < 0.001$; $p < 0.001$). A statistically significant difference in degree of shortening of the vagina between the groups was not found. Due to the small number of patients statistical analysis of local morbidity was not done (Table 1).

Higher occurrence of total vaginal occlusion and presence of solid fibrotic vaginal changes were clearly visible in the control group.

Mitomycin tolerance in the study group was good, and no local or general adverse symptoms related to it was observed.

Table 1. — *Characteristics of study and control groups.*

	Study group (n = 16)	Control group (n = 15)	p
Age	51.65 ± 7.22	53.17 ± 11.4	ns
Complete cancer regression after therapy	16	15	ns
Vaginal length before treatment [cm]	8.18 ± 1.24	8.06 ± 1.39	ns
Vaginal length measured after treatment [cm]	6.50 ± 2.02	5.67 ± 3.04	ns
Complete vaginal occlusion [n]	1	4	–
Vaginal vault and walls synechiae [n]	2	4	–
Vaginal wall rigidity [n]	1	1	–
Other local morbidity	1	1	–

Discussion

Schover *et al.* found that sexual dysfunction occurring after radiotherapy is much more frequent and more intensive than dysfunction developing after radical surgical procedures [15]. For Stage II and III cervical cancer radiotherapy is still the standard modality of treatment. After completion of radiation therapy decreased sexual activity and sexual excitation are commonly observed and may be due to vaginal dryness [10]. Severe pain during attempted sexual intercourse (dyspareunia) is a frequent symptom in these cases. Krumm and Lamberti reported that complaints may be caused by a lack of proper rehabilitation, which should consist of special vaginal dilatator use and hormonal replacement therapy [16]. However according to other authors rigid dilatators may cause serious injuries [17]. Another reason for worsening of quality of life and diminishing sexual satisfaction may be the female genital tract anatomical changes that develop after radiation therapy. The most important anatomical changes are: shortening of the vagina, induration of the walls and even complete occlusion. It has been suggested that post-treatment changes of the vaginal anatomy (previously considered as "normal") may affect sexual satisfaction [15].

Mitomycin C is an antibiotic with alkylating activity. It is active in the late G1 phase and early S phase and in whole, the G2 part of the mitotic cycle. It creates cross bindings between DNA, RNA and protein threads or could disrupt them. It inhibits DNA, RNA and protein synthesis. The agent is administered parenterally in a dose of 10-20 mg/m^2 of body surface as a treatment of some gastrointestinal tract cancers, head and neck malignancies, and cervical cancer recurrences. It is one of the polychemotherapy regimen components. Adverse effects after parenteral use of mitomycin C are widely known, such as after cytostatics, whereas, when locally administered it does not cause toxicity [19, 20]. Only intraocular liquid pressure increases after ophthalmologic use of this medication [21].

In comparison to eye and larynx mucosa the vaginal surface seems to be much more resistant to chemical injuries, even after radiation treatment. It was the basis of our experiment safety with local mitomycin solution application to prevent vaginal wall adhaesions after irradiation and the obtained results are promising. We have not noticed any adverse effects of this substance and the frequency of complete and partial vaginal occlusion was lower. The small number of observed patients did not permit a regular statistical analysis to be performed.

Some practical aspects of our investigation should be mentioned. One of them is application time. Just after radiotherapy intensive reparative and healing processes are initiated in infiltrated cervices, many necrotic substances are profusely discharged, and sometimes blood serum or whole blood is excreted. After one to two weeks these phenomena decrease and reparative activity diminishes. Then vaginal biology becomes more stable and normal. Acute radiation injury disappears, inflammatory changes lessen in intensivity, and the scaring process

begins. It is probably combined with the beginning of connective tissue proliferation. Fibrinoids and mucus are excreted and deposited on the surface of the radiation-injured vaginal surface. Liquid mucus is exuded into too scant capacity (this depends, among others on hormone deficiency). Then connective tissue proliferates, the elements appear on the mucosal surface and in deeper layers in an abnormally large volume. Lack of sufficient mucopolysaccharide production causes vaginal wall adhaesion. If any physical trauma (sexual intercourse, bimanual medical examination, dilatator use, irrigation, etc.) is not performed – the adhaesion becomes stronger, and vaginal occlusion may soon appear, within several weeks. Instrumental or manual "unsticking" of vaginal mucosa and concretion breakage is very unpleasant and painful for the patient, and threatens profuse haemorrhaging. Later, after several months, vaginal occlusion is very durable and any simple mechanical procedures in an attempt to open this organ are inefficient. An open, unnarrowed vagina is a very important part of the female genital tract: periodical medical controls for local recurrence and prevention of vaginal infections are mandatory. For women cured from cancer appropriate vaginal dimensions, soft walls, and lack of adhaesions have an important influence on the quality of life [22].

With adequate specialistic sexual guidance and local and general hormone replacement therapy, satisfying sexual activity may be reinstated in patients recovering from cervical cancer.

Local usage of chemotherapeutic agents to prevent vaginal narrowing and occlusion is performed to improve women's quality of life and to shorten recovery time. It can diminish the risk of sexual problems as well as emotional and social problems.

This investigation suggests the potential benefits of local mitomycin C application but larger studies are needed to confirm the results – perhaps with higher drug concentrations.

Conclusions

1. The preliminary results suggest that mitomycin C application in patients with cervical cancer treated with irradiation can potentially diminish the occurence of local morbidity as well as improve the quality of life.

2. The low number of patients in the observed groups does not permit us to make definitive conclusions.

3. Further investigations on prevention of irradiation-related vaginal fibrosis could be useful and should be continued.

References

[1] Wojciechowska U., Didkowska J., Tarkowska W., Zatoński W.: "Nowotwory złośliwe w Polsce w 2002 roku. Centrum Onkologii im. M. Sklodowskiej-Curie, Warszawa, 2004, 73, 84.

[2] The 24th FIGO Annual Report on the results of treatment in gynaecological cancer. *J. Epid. Biostat.,* 2001, *6*, 11.

[3] The 25th FIGO Annual Report on the results of treatment in gynaecological cancer. *Int. J. Gynecol. Obstet.*, 2003, *83,* 45.

[4] Rose P., Bundy B., Watkins E., Thigpen J. *et al.*: "Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer". *N. Engl. J. Med.*, 1999, *341*, 708.

[5] Vasanthan A., Mitsumori M., Park J.H., Zhi-Fan Z. *et al.*: "Regional hyperthermia combined with radiotherapy for uterine cervical cancers: a multi-institutional prospective randomized trial of the international atomic energy agency". *Int. J. Radiat. Biol. Phys.,* 2005, *61,* 145.

[6] Thomadsen B.R., Shahabi S., Stitt J.A.: "High dose rate brachytherapy in carcinoma of the cervix: Physics and dosimetry considerations". *Int. J. Radiat. Oncol. Biol. Phys.,* 1992, *24,* 349.

[7] Pedersen D., Bentzen S.M., Overgaard J.: "Early and late radiotherapeutic morbidity in 442 consecutive patients with locally advanced carcinoma of the uterine cervix". *Int. J. Radiat. Oncol. Biol. Phys.*, 1994, *29,* 941.

[8] Perez C.A., Brady L.W.: "Principles and Practice of Radiation Oncology". Philadelphia, Lippincott-Raven, 1998, 1795.

[9] Wolff J.P., Goldfarb E., Cachelon R.: "Cervical cancer – psychology and sexuality". *Bull. Cancer,* Paris, 1980, *67*, 116.

[10] Brunner D.W., Lanciano R., Keegan M. Corn B. *et al.*: "Vaginal stenosis and sexual function following intracavitary radiation for the treatment of cervical and endometrial carcinoma". *Int. J. Radiat. Oncol. Biol. Phys,* 1993, *27,* 825.

[11] Grigsby P.W.: "Late injury of cancer therapy on the female reproductive tract". *Int. J. Radiat. Oncol. Biol. Phys.*, 1995, *31,* 1281.

[12] Hu D., Chen P.P., Oda P.: "The effect of mitomycin C after long-term storage on human Tenon's fibroblast proliferation". *J. Galucoma,* 1999, *8*, 302.

[13] Wilkins M., Indor A., Warmabl R.: "Intraoperative Mitomycin C for glaucoma surgery (Cochrane Review)". Cochrane Library, 2005, 1.

[14] Rahbar R., Shapshay S.M., Healy G.B.: "Mitomycin effects on laryngeal and tracheal stenosis, benefits and complications". *Ann. Otol. Rhinol. Laryngol.,* 2001, 1.

[15] Schover L.R., Fife M., Gershonson D.M.: "Sexual dysfunction and treatment for early stage cervical cancer". *Cancer,* 1989, *63,* 204.

[16] Krumm S., Lamberti J.: "Changes in sexual behavior following radiation therapy for cervical cancer". *J. Psychosom Obstet. Gynecol.*, 1993, *14,* 51.

[17] Hoffman M.S., Wakeley K.E., Cardosi R.J.: "Risks of rigid dilatation for radiated vaginal cuff: two related rectovaginal fistulas". *Obstet. Gynecol.*, 2003, *5,* 101, 1125.

[18] De Vita V.T., Hellman S., Rosenberg S.A.: "Cancer. Principles and Practice of Oncology". Philadelphia. Lippincott-Raven, 1997, 412.

[19] Hashemi H., Taheri S.M.R., Fotouhi A., Kheitosh A.: "Evaluation of the prophylactic use of mitomycin C to inhibit haze formation after photoreactive keratectomy in high myopia: a prospective clinical study". *Ophtalmol.,* 2004, *4*, 12.

[20] Rubinfeld R.S., Stein R.M.: "Topical mitomycin C for pterygia. Is single application appropriate?". *Ophtalmol. Sur Las.,* 1997, *28*, 662.

[21] Mietz H., Jacobi P.C., Krieglstein G.K.: "Postoperative application of mitomycin C for trabeculectomies". *Arch. Ophtalmol.,* 2000, *118,* 1341.

[22] Jensen P.T., Groenvald M., Klee M.C., Thranov J. *et al.*: "Longitudinal study of sexual function and vaginal changes after radiotherapy for cervical cancer". *Int. J. Radiat. Oncol. Biol. Phys.,* 2004, *58,* 1321.

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