The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 02-06-2013
Accepted: 03-07-2013

Vol. 2 No. 8 2013
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Pathomorphosis of Cervical Cancer Stage IIB With the Applying of Preoperative Therapy

Anna Ye. Kryzhanivska [1*], Elvira O. Kindrativ [2], Ivan O. Mikhailyuk [2]

1. Department of Oncology Ivano-Frankivsk National Medical University Ivano-Frankivsk, Ukraine. [Email: anna.nivska@gmail.com]
2. Department of Pathomorphology, Ivano-Frankivsk National Medical University Ivano-Frankivsk, Ukraine.

The article contains the results of study treatment the pathomorphosis squamous cell cervical cancer stage IIb using preoperative therapy. The study included 127 patients with cervical cancer stage IIB , of which 53 received preoperative course of external beam radiotherapy to 2 Gray to a total dose of 30 Gray with potentiation of cisplatin 40 mg/m2 weekly and 74 who applied neoadjuvant systemic chemotherapy according to the scheme FR (cisplatin 100 mg/m2, 5-fluorouracil 1000 mg/m2 from 1st to 4th day) 2-3 courses every 3 weeks, surgical intervention in the volume of panhisterectomy type III. The degree of therapeutic pathomorphosis of parenchymatous-stromal components was evaluated on a scale according to G.A. Lavnikova (1976). Methods of preoperative therapy that we used, led to the development of pronounced therapeutic pathomorphosis, especially in patients who received radiation therapy. Morphological and morphometric study of surgical specimens showed that therapeutic pathomorphosis after application of preoperative chemotherapy allows to achieve tumor devitalization. Consequently, the use of preoperative chemotherapy and radiation therapy are objective conditions for the realization of maximum possible effect of anti blastomic action, that corresponding the operating principles of ablation procedures.

Keyword: Pathomorphosis, Cervical Cancer, Preoperative, Not Adjuvant Therapy.

1. Introduction

Cervical cancer (CC) takes one of the leading places in the structure of the incidence of malignant neoplasms of women in Ukraine. Thus, according to the National Cancer Registry of Ukraine in 201, it was identified 5344 patients with primary cervical cancer, the incidence of cervical cancer in Ukraine amounted to 21.8 per 100 thousand female population, the mortality rate - 8.9 per 100 thousand of female population. It was established that most of the patients are women, with the first stage (35.9%) and the second stage of the disease (40.3%), 16.9% of patients with stage III and only 5% - the patients with stage IV of the process [3].

The indicators of 5-year survival among patients with stage IIB of the cervical cancer that received radiotherapy (RT) as independent method of treatment ranged from 42 to 64.2%, while in the combined treatment 55.2 to 76.9% [6, 10]. The choice of method of treatment of patients with cervical cancer stage IIB is a subject of perennial debate between gynecologists, oncologists, radiation therapists and surgeons. The disadvantages of the first phase of the PA is pronounced fibrotic changes, hardening of the blood vessels and thus complications of admission of drugs in the area of radiation [4, 5].

Despite the improvement of radiation technology, radiation security, implementation of different options of fractionation of doses, the use of radio modifiers currently no healing required. A significant incidence of relapses in parametrical and regional lymph nodes is a consequence of the relative radio resistance of metastatic cancer cells that are found in regional lymph nodes and have a

lower mitotic activity in smaller number of DNA. Regrowth of the primary tumor provides increased mitotic activity of cells in clone populations of cells that remain and develop in conditions of immune failure of regional lymph nodes and tissues of the body as a whole [1, 6, 8].

The search for new and improvement of known methods of treatment of patients with cervical cancer have led many researchers to the conclusion to a wider use of chemotherapy (CT) in the treatment of this pathology. This treatment, although insufficient in itself, may be a significant addition to surgery and / or radiation. Unsatisfactory results of treatment of patients with locally advanced cervical cancer forms, due to the inability of their surgeries, encourage the development of new and improvement of existing methods of neoadjuvant therapy [7].

With neoadjuvant chemotherapy it increases the chances of tumor resect ability and reducing the risk of intraoperative dissemination of tumor cells. Neoadjuvant chemotherapy locally advanced cervical cancer stage IIB will help to:

- Improve the operability of this category of patients to 85%;
- Remove potentially resistant metastatic focuses;
- Reduce the relapse rate by 18% and the incidence of metastases in regional lymph nodes by 17%.

High expectations that the described set of factors will provide conditions for a significant increase in disease-free survival [8, 9].

Histological examination of the removed tumor after preoperative chemotherapy is conducted to assess the degree of therapeutic pathomorphosis and sensitivity of tumors to chemotherapy, which can be used along with other factors to determine the prognosis and the need of additional postoperative treatment [1, 5]. A study of factors that include information about the ability of tumor response to chemotherapy impacts is an important step in the selection of individual treatment strategy.

Therefore, so far not fully elaborated treatment strategy of patients with stage IIB cervical cancer, and in the standards of diagnosis and treatment there are various treatment options for this disease, and the optimal choice usually depends on the subjective opinions of the doctor. In light of these circumstances there is a need for finding and developing new approaches to select the most optimal method of treatment or combination of methods that would ensure the best survival.

The purpose of the study The study of therapeutic pathomorphosis of cervical cancer stage IIb with the application of preoperative therapy.

2. Material and methods

The study included 127 patients with stage IIB cervical cancer, of which 53 received preoperative course of distance radiation therapy with 2 Gray to a total dose with 30 Gray and with the potentiation of cisplatin 40 mg/m2 weekly, also 74 patients, which applied neoadjuvant systemic chemotherapy by the scheme FR (cisplatin 100 mg / m2, 5-fluorouracil 1000 mg/m2 on 1st to 4th day) 2-3 courses every 3 weeks, surgical intervention in the volume of panhisterektomy type III. For the morphological study we have used the surgical specimens of cervical cancer stage IIb. Collecting the slices of cervical cancer was performed from the superficial, central and deep areas of the tumor. The material was fixed in 10% neutral formalin. After this treatment the material was performed by the standard method: the dehydration was carried out in a series of alcohols of increasing concentrations, than the enlightenment in xylene and concluding material in paraffin blocks. From each paraffin block we made the serial sections of 5-6 microns thick. Histological sections were stained with hematoxylin and eosin, three-chromium by Masson and by Van Hizon and OCHH by Zerbino, in modification of Lukasevych. A histological preparation was studied by light microscopy (microscope Axiostar + the firm Carl Zeiss). The degree of therapeutic pathomorphosis of parenchymatous-stromal components was evaluated on a scale of G.A. Lavnikova (1976) [2] the first stage - the ratio between parenchyma and stroma is intact; existing degenerative changes in tumor cells, the second stage - marked by focal disappearance of

parenchyma by necrosis and sclerosis, but most of the tumors retained, III-rd one - most of the tumor parenchyma is necrotic and replaced by connective tissue, the fourth stage - tumor cells are absent.

Volume content of the tumor parenchyma without signs of damage, component and stromal necrosis was assessed in 20 random fields of view, using morphometric 25-nodal net [Avtandylov].

For an objective evaluation of therapeutic pathomorphosis according to G.A. Lavnikova it is used quantitative index - the index of injury (II), which was calculated by the formula II = Ik - Il / Ik x 100, Ik - average volume of viable tumor parenchyma (without treatment), Il - average volume of viable tumor parenchyma (after treatment), II - index damage in percent (from 100 to 0).

The results are analyzed with the use of statistical methods.

3. Results and Discussion

With all the methods of preoperative therapy of the squamous cervical cancer was established the histological tumor tissue devitalization with the development of specific structural changes. Comparison of the dynamics of pathomorphosis of cervical cancer indicates the development of similar structural changes of tumor parenchyma. It is observed the degenerative and necrotic changes in resorption of tumor parenchyma and its replacement by connective tissue, decreased mitotic activity and pathological mitosis, increasing infiltration of the stroma, mainly the lymphoid cell line. In studied samples was noted the development of cervical cancer pathomorphosis of I - IV stages (Table 1). At high incidence of PCT pathomorphosis observed in 71 patients, accounting for 95.9%. High frequency (96.2%) of radiation pathomorphosis confirms radio sensitivity of cervical cancer stage IIb.

Table 1: Pathomorphosis of cervical cancer with different methods of no adjuvant therapy

The degree of pathomorphosis	Preoperative PA (n = 53)		Preoperative chemotherapy (n = 74)	
	Abs.	%±m	Abs.	%±m
I	2	3,8±2,6	3	4,1±2,3
II	20	37,7±6,7*	46	62,2±5,6*
III	11	20,8±5,6	13	17,6±4,4
IV	20	37,7±6,7*	12	16,2±4,3*

Note: * p <0.01 (difference in reliability indices).

Usage of preoperative RT causes extensive characteristic necrotic foci that merge together with the localization in the surface areas at the mucosa and sub mucosal layers. Multiple small disseminated foci with a tendency to merge are typical for central areas of the tumor. At the level of the muscular layer we have the foci of lethal injury of the cancer parenchyma, quantity of which decreases in the deeper areas of the tumor. Mosaic degenerative and necrotic changes, proves probably an uneven sensitivity of the oncocytes to the effects of ionizing radiation and the presence of residual tumor stable complexes. In comparison with the previous group by using non adjuvant chemotherapy, the lethal devitalization of cancer parenchyma significantly dominates the degenerative changes. In central and deep zones the areas of necrosis; they merge together, forming large focal necrotic centers.

Antyblastomic effect is most pronounced when using the preoperative chemotherapy (Table 2). In the preoperative treatment of patients with cervical cancer stage IIb the use of non-adjuvant systemic chemotherapy provides an opportunity to achieve reduction of viable tumor parenchyma of 2.6-fold compared with controls (20,45 ± 2,61 and 52,65 ± 3,17% respectively). The use of the preoperative chemotherapy causes devitalization of tumor parenchyma both in surface and in the central and deep areas. When using the preoperative radiotherapy the content of tumor parenchyma is reduced by 2.3 times compared

with those of control group (22,8 ± 2,63% and 52,65 ± 3,17% respectively).

Table 2: Morphometric changes in cervical cancer tissue with different methods of non-adjuvant therapy (% ± m)

The study groups	Tumor parenchyma,% ± m	Stroma,% ± m	Necrosis,% ± m
Before treatment	52,65±3,17	18,3±1,9	6,53±1,4
Radiotherapy	22,8±2,63*	25,47±1,52*	18,5±2,43*
Radiation chemotherapy	20,45±2,61*	27,42±2,85*	19,34±2,33*

Note: * p <0.05 (difference in reliability indices).

The analysis of morphometric changes in cervical cancer tissue showed an increase in stromal component. Volumetric content of stroma is likely increases in 1.4 and 1.5 times compared with the control group, respectively, when using RT and RCHT. The area of necrosis increased by 2.8 times in patients who received RT and after systemic chemotherapy the necrotic area increased by 2.9 times. The injury index is 61.2%. When using the preoperative CHT the index of injury was 56.7%. Thus, the use of preoperative systemic chemotherapy causes probable devitalization of tumor parenchyma.

Morphological and morphometric study of surgical specimens showed that therapeutic pathomorphosis after application of preoperative chemotherapy allows to achieve a tumor devitalization, coinciding with clinical response. Consequently, the use of preoperative chemotherapy is objective conditions for the realization of maximum possible effect of antyblastomic action corresponding to operating principles of ablation procedures.

4. Conclusions

The used methods of preoperative therapy led to the development of a pronounced therapeutic pathomorphosis. High frequency (96.2%) of the development of radiation pathomorphosis confirms the radio sensitivity of cervical cancer stage IIb. The use of preoperative PT causes devitalization of tumor parenchyma predominantly in surface areas and a focal character. High frequency (95.9%) of therapeutic pathomorphosis confirms the sensitivity of cervical cancer stage IIb to the use of non-adjuvant systemic chemotherapy. The use of preoperative chemotherapy causes devitalization of tumor parenchyma both in surface and in the central and deep areas.

The obtained results of therapeutic pathomorphosis of cervical cancer stage IIb indicate the feasibility of non-adjuvant chemotherapy, which allows for ablation surgery.

5. References

1. Galil G.A. Therapeutic pathomorphosis for different types of preoperative therapy for cancer of the cervix / G.A. Galil-oglu, N.L. Chazova, L.A. Alipchenko and others / / Bulletin of the Ministry of Health of Russia RNTSRR. - 2003. - № 3. - S. 62-63.
2. Lavnikova G.A. Some regularities of radiation pathomorphism of human tumors and their practical use / / Bulletin. Academy of Medical Sciences of the USSR. - 1976. - № 6. - P.13-19.
3. Cancer in Ukraine, 2009-2010 / Z.P. Fedorenko, A. Haysenko, L.A. Gulak and others. / / Bulletin of the National Cancer Registry. - 2011. - № 12. - S. 57-58.
4. Semykoz N.G. Radiation pathomorphosis of organs and tissues of the pelvis in the treatment of cancer of the uterus cervix and body / N.G. Semykoz, V.G. Shlopov / / A.D: UkrNTEK, 2000. - 146 p.
5. Chazova N.L. Morphological characteristics of cervical cancer (therapeutic pathomorphism) / NL Chazova, AM Berschanskaya / / Bulletin of the Ministry of Health of Russia RNTSRR. - 2006. - № 6. - S. 41-50.
6. Hirakawa M. Predictive factor of distant recurrence in locally advanced squamous cell carcinoma of the cervix treated with concurrent chemoradiotherapy./ Hirakawa M., Nagai Y., Inamine M. et al. // Gynecol. Oncol. 2008; 108 (1): 126-9.
7. Moioli M. Chemotherapy with cisplatin and paclitaxel in locally advanced cervical cancer: has this regimen still a role as neoadjuvant setting? / Moioli M, Papadia A, Mammoliti S. // Minerva Ginecol. 2012 Apr;64(2):95-107.

8. Rose PG: Concurrent chemoradiation for locally advanced carcinoma of the cervix: where are we in 2006? Ann. Oncol. / Rose PG // 17 (Suppl. 10): 224-229, 2006
9. Sehouli J. A randomized phase III adjuvant study in high-risk cervical cancer: simultaneous radiochemotherapy with cisplatin (S-RC) versus systemic paclitaxel and carboplatin followed by percutaneous radiation (PC-R): a NOGGO-AGO Intergroup Study. / Sehouli J, Runnebaum IB, Fotopoulou C. // Ann Oncol. 2012 Feb 21.
10. Vale C. Chemoradiotherapy for Cervical Cancer Meta-Analysis. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. /Vale C., Tierney J., Stewart L. et al. // J. Clin. Oncol. 26: 5802-5812, 2008