Cervical cancer: the role of polychemotherapy in the treatment

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Summary. The article presents the role of polychemotherapy in the treatment of patients with cervical cancer. The use of chemoradiation and neoadjuvant chemotherapy is the perspective method of treatment the patients with locally advanced cervical cancer. The randomized trials have evaluated the efficacy of platinum-based combination chemoradiation therapy.

Key words: cervical cancer, polychemotherapy.

Cervical cancer (CC) – one of the most widespread forms of malignant formations of muliebrias. Annually in the world find out about 500 thousand of patients on CC, that is 5 % oncology diseases. The most of cases of CC (79 %) is registered in countries which develop, in which this form of oncologic pathology occupies 1-st place in the structure of oncogynecology morbidity and is 15 % from all cases of cancer in women [3, 12].

According to the national cancer database of Ukraine a 5-th place in the structure of oncologic morbidity of womanish population belong to CC, and among patients with a cancer in age from 30 to 54 years – 2nd grade place. In relation to all malignant formations for women part of patients on CC is 6,0 %. In 2011 it is discovered 5344 primary patients on CC, morbidity on CC in Ukraine was 21,8 on 100 thousands of womanish population, death rate, — 8,9 on 100 thousands of womanish population [16].

It is set of clinical researches, that 30–45 % patients on CC die during the first 5 years through progress of basic disease, reason of death of patients in such cases is development of local recurrence and remote metastases [2, 6, 13]. From data of different authors, frequency of lymphogenic metastases at clinically or morphologically verified CC IA1 makes the stages 1 %, at IA2 of the stage — 5–8 %, at IB1 of the stage — 12,7 %, at IB2 of the stage — 34 %, at the II stage — 23–45 %,

at the III stage arrives at 50–60 % [2, 6]. Frequency of recurrence for patients on CC IB–IIA makes the stages 10–20 %, and at presence of local forms of CC (IIB, III, IVA of the stage of FIGO) – 50–70 % [3, 9, 18].

From data of literature, almost in 35 % patients on CC III–IV the stages during 2 years after surgical and radial treatment arise up recurrence of disease [2, 3, 8, 17]. A prognosis for such patients is unfavorable: to one year after their origin live so long only 10–15 % patients, and at palliative and symptomatic treatment life-span is measured by months.

Increase of morbidity on CC among the women of young age, and also amount of patients, with the started stages of disease, stipulates the necessity of development of new and perfection of already existent methods of treatment of patients with this pathology.

In the problem of treatment of patients on CC an actual aspect is surgical treatment taking into account his radicalism. Implementation of volume of operation in accordance with the degree of prevalence of tumour process is one of important problems, which widely comes into question in literature. It is well-proven many researches, that after neoadjuvant polichemotherapy (NP) possible implementation of radical operation for patients from initially inoperable CC [1, 4, 10, 19, 20].

In relation to surgical treatment of patients on CC, many authors are offered by both ultraradicalo surgical interferences and the limited is «modified radical» operations [9, 14, 12].

Researches of the last years specify on the givings hope results of application of chemotherapy (CHT) in treatment of natively widespread and metastatic forms of CC [1, 4, 5, 11, 19, 22, 29, 33].

A chemotherapy is applied on the different stages by treatments of CC:

Chemotherapy and radial therapy:

- chemoradial therapy (CHRT);
- chemotherapy is before radial therapy.

II. Chemotherapy and surgical treatment:

- neoadjuvant (preoperative) chemotherapy (NCHT);
- adjuvant (postoperative) chemotherapy.

III. A chemotherapy at metastases and recurrense of CC.

Chemoradial treatment

Introduction in clinical practice of chemotherapy in combination with radial therapy is the perspective going near the increase of efficiency of treatment of patients on natively widespread CC. Such approach has a row of theoretical grounds. Anticarcinogenic preparations strengthen the radial damage of tumour cells due to violation of mechanism of reparation of DNA, synchronization of entry of tumour cells, in the phases of cellular cycle, diminishing of amount of tumour cells, which are in the phase of rest and ability of devitalization resistant to the irradiation tumour cells which are in a hypoxia. In addition, cytotoxic preparations have an influence not only on a primary tumour but also on remote metastases.

In 5 fundamental publications it is reported about the considerable improvement of survivability of patients on CC during the leadthrough of chemotherapy in combination with radial therapy (Table. 1).

Table 1

Results of randomise researches of chemoradial therapy at natively widespread of CC

Research, author	FIGO stage	Treatment on groups	n	4-years NRS*	4-years GS**
Intergroup Peters W. et al. (GOG 109/SWOG 8997/RTOG 91-12) 2000 [9]	IA2-IIA	Adjuvant RT*** pelvis +cysplatyn, 70 mg/m2 (in 1-st and 29-th days), phtoruracil, 4mg/m2(96-hours infusion in 1-st and 29-th days Adjuvant RT of pelvis	127 116	80% (p=0,003) 63%	81% (p=0,007) 71%
GOG 123 Keys H. et al. 1999 [32]	IB2	Preoperative RT of pelvis +cysplatyn, 40 mg/m2 (1-6 weeks) Preoperative RT of pelvis	183 186	80% (p<0,001) 64%	86% (p=0,008) 72%
				5-years NRS	5-years GS
RTOG 9001 Morris M. et al. 1999[36]	IB-IVA	RT of pelvis + cysplatyn, 75mg/m2 in 1-st day and phtoruracil 4mg/m2 in to the 5-day's to continuous infusion RT of pelvis and paraaortic lymphatic nodes	193 193	67% (p<0,001) 40%	73% (p<0,004) 58%
				6-years NRS	6-years GS
GOG 85 Whitney C. et al. 1999 [9, 47]	IIB-IVA	RT of pelvis + cysplatyn, 50 mg/m2 (in 1-st and 29-th days), phtoruracil, 4mg/m2(96-hours infusion in 1-st and 29-th days)	177	60% (p<0,001)	65% (p<0,018)

		Adjuvant RT of pelvis + hydroxurine	191	48%	50
				4-years NRS	4-years GS
GOG 120 Rose R. et al. [40]	IIB-IVA	RT of pelvis + cysplatyn, 40 mg/m2 (1-6 weeks), phtoruracil,	176	60% (p<0,001)	60% (p=0,002) та (p=0,004)
		RT of pelvis + cysplatyn, 50 mg/m2 (in 1-st and 29-th days), phtoruracil, 4mg/m2(96-hours infusion in 1-st and 29-th days)	173	60%	58%
		RT of pelvis + hydroxurine (Hydrea) 3g/m2 2 times on week during 6 weeks	177	45%	34%

*NRS – Nonrecurrence survivability

**GS – General survivability

***RT – Radiation therapy

Taking into account information of randomise researches, well-proven efficiency of simultaneous radial therapy with a chemotherapy on the basis of preparations of platinum [10, 19, 45, 46].

Lately come into the notice of research from the use of campto as in the monomode so in combination with other preparations at chemoradial therapy of natively widespread CC.

From data of Sarris G. and sang., at the use of combination of campto in the dose of 30 mg/m2 1 one time per a week + interferon α2α 3 MO hypodermic + amiphostyn 500 mg v/m on a background standard radial therapy for patients on CC IIB-IIIB general efficiency made the stages (25 patients) 95,4 %, complete remission was looked after in the halves of patients (52,4 %).

Save and effective enough is CHPT natively widespread CC with introduction of campto for 40 mg/m2 weekly in the monomode on a background the standard course of the united radial therapy [19].

It is got the givings hope results of application of combination of cisplatin/gemcitabin in treatment of natively widespread forms of CC.

J. Zabra and sang. used gemcitabin in the dose of 100-125 mg/m2 in combination from cisplatinom for 40 mg/m2 in the weekly mode on a background the united radial therapy. Treatment is conducted 29 by a patient on CC IIB-IVA the stages. The results of treatment of 23 patients are appraised: complete remission is

marked in 21 (91%), in 2 – (9 %) partial, in three there was a recurrense through 6,9 and 11 months. Application of combination of cisplati/gemcitabin (70 mg/m2 1 one time per a week and 1250 mg/m2 in 1,8 day of cycle promotes efficiency of treatment in 75%. The expressed toxic displays were not looked after [49].

In researches of P. Pattaranutaporn and sang. patients on CC of the III stage got gemcitabin in the dose of 300 mg/m2 during 5 weeks parallell with radial therapy in a dose 50 Gr. In 89,5 % patients were looked after complete regression, partial, – for a 1 patient. A general index of efficiency was 94,7 %. Index of one-year survivability without progress of disease – 84,2 % [10, 19].

In a present time GOG probes potential efficiency of radiosensibilisation chemotherapy with the use of cisplatina (75mg/m2 each 14 days) and tirapazamina (290 mg/m2 v/v in 1, 15, 29th days) in comparing to weekly application of cisplatina (40 mg/m2) for women from natively widespread CC, which get radial therapy (RT) (protocol of GOG 219). Tirapazamin – it benzotriazen, that presents the new class of selective hypoxic of anticarcinogenic preparations, which strengthens cytotoxic platinum of in vitro and in vivo.

Chemotherapy before radial therapy

В 9 рандомізованих дослідженнях проведення неоад'ювантної хіміотерапії не призвело до покращання безпосередніх та віддалених результатів ПТ. У 8 із 9 досліджень результати застосування НАПТ з наступною ПТ були гіршими, ніж тільки ПТ [4, 10, 19]. Отримані результати обумовлені тим, що проведення ХТ на першому етапі приводить до елімінації чутливих клітинних клонів і появу клітин, які резистентні як до ХТ, так і до наступної ПТ. Саме селекцією в результаті ХТ резистентних до ПТ пухлинних клітин можна пояснити невдачу останньої.

Neoadjuvant (preoperative) chemotherapy (NCHT)

At the end of 80th a few groups of researchers from the different countries of the world presented the results of application of platinum preparation charts of CHT in quality a preoperative chemotherapy for patients on natively widespread CC IB2-IIIB the stages. The leadthrough of NCHT has certain advantages:

- influence of cytostatic on a primary tumour allows to decrease the sizes of tumour;

- influences on lymphogenic micrometastasis;

- allows to translate the inoperable cases of CC in the resectable state;

and disadvantages:

- a delay in medical therapy (in 20–30% patients not answer);
- opening of radio-resistant of cellular clonals;
- opening of cross resistant with radial therapy.

New approach in therapy of CC has application of neoadjuvant chemotherapy.

In 1998 J. Sardi, A. Giarioli and sang. published the results of randomise research in which it is included 295 patients on CC IIB the stages. Patients were randomise on 4 groups: for patients 1- groups applied only RT, 2- groups are an operation + RT, 3 NCHT + RT, 4- groups – NCHT +operation + RT. After 7 of supervisions found out the statistically well-proven difference in 4 group, where 5-years-old survivability was 65 % in comparison from 48 % in 1 group and 41 % – in 2. Introduction of NCHT before an operation allowed to promote the index of resectableness from 56 % to 80 % [41].

P. Benedetti-panici and sang. (2002) in multicentrum randomise research conducted comparison of efficiency of the combined method of treatment of natively widespread squamous CC and generally accepted method of RT at squamous CC IB-III the stages. 5-years-old general survivability was 58,9 % in a group NCHT with including of cisplatinum with a subsequent radical operation and 44,5 % in a group of RT. In the sub-group of patients with the stage of IIB 5-years-old survivability was 58,6 % in the first group and 42 % – in the second. At the III stage 5-years-old survivability made according to 41,6 % and 36,7 %. Multivariable analysis, conducted P. Benedetti-panici and sang. proved that an answer on NCHT can be the additional prognostic factor of survivability, after the clinical stage, size of tumour, defeat of parametriums [21, 22].

A. Duenas-Gonzales and sang. (2003) bring results over of holiatry of natively widespread forms of CC. In researches included 43 patients on CC IB-IIIB the stages which 3 cycles of NCHT of carboplatinum and paclitaxel conducted. Then executed

radical hysterectomy and adjuvant of RT simultaneously with cisplatinom. A clinical answer on CHT was marked in 41 sick (95 %): complete answer – in 4 (9 %) and partial answer in – 37 (86 %). The forecast general survivability was 79 %. Authors mark that an answer on CHT is not the unique factor which determines resectableness of tumour; an important role is played also by the «aggressiveness» of surgeon. In this research authors explain the high percent of resectableness (95 %) that the resectableness was set intraoperatively: some cases are with a partial answer on CHT, which to surgical interference at rectovaginal research made impression inoperable, on resectable indeed appeared [26].

Y. Kornovski, G. Gorchev (2006) compared the results of treatment in two groups of patients on CC IIB-IVA the stages: the patients of the first group got only RT; patients of the second group are 3 courses of NCHT with subsequent surgical treatment and postoperative RT. 2-years nonrecurrence survivability was 47,3 % in the first group and 76,7 % – in the second [31].

K.Y. Morkhov, V.V. Kuznecov, A.I. Lebedev and sang. (2005) presented experience of complex treatment of 42 primary patients on CC T2bN0M0 and T2bN1M0. On the first stage all patients was conducted 2 cycles of chemotherapy (a chart included cisplatin, bleomicin, ciclophosfan), on the second – conducted controlled from distance RT, on the third – executed extended extirpation uterus with additions. After an operation at presence of factors of risk conducted RT. For comparison the results of the combined treatment were studied 50 patients on CC T2bN0M0 and T2bN1M0. On the first stage all patients of this group got preoperative RT, on the second stage executed extended extirpation uterus with additions, on the third stage conducted controlled from distance or united RT. Patients to which after preoperative RT executed surgical interference are included in an analysis only. 5-years general survivability of patients after complex treatment was 88,3 %, after the combined treatment – 66,1 %. During the first five years after treatment of sign of local progress of CC it was discovered in 24 % patients after the combined treatment and in 9,5 % patients after complex, remote metastases – in 14 and in 2,4 % patients accordingly [12, 14, 19].

T. Sugiyama and sang. (1999) estimated efficiency of neoadjuvant of endarterial chemotherapy with a next radical operation and/or RT for patients on CC IIB-IVA the stages. Treatment consisted in bilateral infusion in the internal illiac arteries of cisplatina and peplomicina by two courses. Radical hysterectomy and limphodisection executed all patients on CC IIb–III the stages which answered on NCHT (16 and 25 patients) accordingly. 4–years nonrecurrense survivability for patients on CC IIB the stages was 86%, III stage - 62,3% [43].

From data of N. Umesaki and sang. application of NCHT is before an operation on a chart: campto 60 mg/m2 in 1,8,15 day + mitomicin 10 mg/m2 in the first day for patients on natively widespread CC allowed to execute a radical operation [44].

Thus, in a present time there is not the unique idea at choice optimum chart of treatment of natively widespread CC. The results of treatment, in spite of certain successes, on the whole remain unsatisfactory. Application of surgical interference with combination with radial therapy and chemotherapy results in the improvement of indexes of survivability. However, the existent methods of clinical diagnostics at the natively widespread forms of CC not always represent the real distribution of tumour, that in many cases results in the unjustified waiver of surgical treatment. CC is natively widespread it remains a problem which needs subsequent development of new approaches in diagnostics and treatment.

Adjuvant (postoperative) chemotherapy

A question about the leadthrough of adjuvant chemotherapy remains not decided. Publications which summarize the results of the use of the adjuvant modes of CHT does not allow expressly to define their place in the standard combined therapy of CC. Expedience of setting of CHT in a postoperative period is justified only in the cases of presence of metastases in regional lymphatic nodes with the obligatory including of preparations of platinum.

A chemotherapy at metastases and recurrense of CC

At the decision of question in relation to application of CHT some additional factors must be taken into account. Basic difficulties of CHT metastatic CC can be related both to genetic and kinetic resistens of tumour cells. Among other reasons of

resistant it follows to select the overactivity of P-hlicoprotein «pump», which throws out cytostatic from tumour cells in connection with expression of gene of plural firmness to medications, and also detoxication of medications through expression of gene of hlutation-5-transferase. Except for it, as a result of before conducted radial therapy there is expressed fibros of soft tissue and obliteration of vessels of small pelvis, that violates the transport of citostatic to the tumour and reduces their efficiency. The previous irradiation of small pelvis diminishes reserve of ostmedullar considerably. The pelvic recurrense of CC can become reason of obstructive changes of ureters and, as a result, kidney insufficiency. All is above-mentioned specifies on the necessity of diminishing of dose of citostatic, use of protectors, exception from CHT of nephrotoxic preparations [19].

There are many charts of chemotherapy, presented in literature, for treatment of patients with recurrense and metastases of CC (table. 2).

Table 2

Efficiency of chemotherapy in treatment of patients with recurrense and metastases of CC (from data of literature)

Authors	Cytostatics and their combinations	Efficiency, %
Omura G. et al., GOG 110, 1997 [37]	Cysplatyn Cysplatyn + Iphosphamid Cysplatyn + Dobromodulcytol	< 22 33 < 22
Pignata S. et al., 1999 [39]	Cysplatyn+ Paclitaxel + Iphosphamid	43,5
Rose P.G. et al., 1999 [40]; Walker J.L., et al., 2009 [46]	Paclitaxel + Cysplatyn	43,3
Zanetta G. et al., 1999 [48]	Cysplatyn+ Paclitaxel + Iphosphamid	66,6
Scbilder R.J. et al., 2000 [42]	Hemcytabin	11,0
Lhomme C. et al., 2000 [35]	Vinorelbin	17,0
Vermorken J. et al., EORTC, 2001 [45]	Cysplatyn Cysplatyn + Bleomicyn + Mitomicyn +Vendesyn	42,0
Moiseenko V. et al., ASCO 2001 [13]	Irynotecan Irynotecan + Cysplatyn	17,1 53,0

	Cysplatyn	21,2
Dimopolos M.A. et al., 2002 [25]	Cysplatyn+ Paclitaxel + Iphosphamid	46,0
Ермакова Н.А. 2002 [10]	Xeloda	16,8
Chitapanarux J. et al., 2003 [23]	Irynotecan + Cysplatyn	67,0
Umesaki N., et al., 2003 [44]	Irynotecan + Mitomicyn	49,0
Lorvidhaya V. 2000 [19]	Gemzar + Cysplatyn	68,4
Choi C.H., et al. 2006 [19]	Cysplatyn+ Paclitaxel + Iphosphamid	46,6
Pestasides D. et al., 2009 [38] Kitagawa R. et al., 2012 [15]	Carboplatin + Paclitaxel	66,0
Kamnerdsupaphon P. et al., 2009 [30]	Cysplatyn+ Paclitaxel + Iphosphamid	66,7

In charts often use cisplatin, which is active citostatic in the monomode, and also in combinations with other preparations. The resulted efficiency of treatment of patients with recurrense and metastases of CC testifies to possibility and necessity of leadthrough of such therapy.

The givings hope results of researches of the last years, which is in literature, specify on the value of CHT in treatment of prognostic of unfavorable contingent of patients from natively widespread and metastatic CC and allow to hope on the considerable improvement of indexes of efficiency of treatment [4, 5, 7, 13, 15, 17, 24, 27- 29].

From data of literature [8, 17, 34], the median of survivability of patients with recurrense and metastases of CC makes 7 months. After exenteration 5-years survivability is 30–60 %. As report Bazhenov A.H. and sang. [2] combination of different methods of treatment allows to get the greater amount of objective answers (68 %), while at application only RT or CHT an objective clinical answer was evened 26 % and 20 %. CHT in most cases for certain did not improve nonrecurrense and general survivability of patients on CC. From data of Filatovoy N.S and sang. [17], two year survivability of patients with recurrense and metastases of CC at RT was 29,7 %, at CHT – 33,3 %, at symptomatic treatment – 3 %.

Consequently, the resulted information testify that possibilities of surgical treatment of patients on recurrent and metastatic CC are limited. Setting of radial therapy in most patients is inadvisable, as its possibilities, as one of methods of adjuvant therapy the treatments already outspent on the previous stage. Combined CHT gives the greater percent of direct effects, improves quality of life, but in most cases does not improve nonrecurrense and general survivability for patients with the widespread forms of CC, that, the problem of treatment of patients with the recurrense of CC is distant from a successful decision. Therefore basic efforts of oncogynecologist must be concentrated on the active warning of recurrense and determination of risk of his origin at treatment of primary patients on CC.

Stormy development of clinical pharmacology is the last years instrumental in appearance of new citostatic with on principle other mechanisms of anticarcinogene activity. Possibility of the use of targetn therapy is studied for patients on CC (bevacisumab, erlotinib, and others) [7, 15].

Conclusion

Chemoradial therapy is the standard and effective enough method of treatment of patients with the natively widespread forms of CC. The leadthrough of NCHT with next surgical interference gives hope results at treatment of patients with the natively widespread forms of CC IB-IIA-B stage, but the subsequent study of its efficiency is needed.

Necessary researches of new approaches of treatment of CC (application of new preparations, new modes, increase of closeness of dose, application of other preparations – not citostatic, radiosensibilisator, application of hypertermy, removal of hypoxia of tissue, during RT, vaccines, gene therapy, and others).

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