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COMBINED CHEMOTHERAPY OF CISPLATIN AND OXALIPLATIN WITH FLUORINE DERIVATIVES IN THE TREATMENT OF RECURRENT AND DISSEMINATED CANCER STOMACH

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SUMMARY

Cisplatin is highly effective against disseminated gastric cancer and its study in combination therapy regimens is of interest in terms of increasing the effectiveness of chemotherapy for this insensitive group of tumors. It is relevant to study the activity of Cisplatin in combination with fluorinated drugs.

Our work analyzed the experience of using the currently standard treatment regimen in European countries, including Cisplatin and daily infusions of 5-Fluorouracil.

Data on the effectiveness and toxicity of a new regimen are presented, where infusions of 5-Fluorouracil are replaced by oral Xeloda.

KEY WORDS : *effectiveness, toxicity, stomach cancer, treatment.*

RELEVANCE

The problem of treating malignant tumors of the stomach remains very relevant, since the total number of cases annually remains significant and in the global structure of mortality, gastric cancer (GC) gives way to its leading place only to lung cancer [1, 6]. Over the past three decades, most developed countries have seen a downward trend in incidence, the rate of which varies greatly. The decrease in the incidence of gastric cancer is most rapid in the USA, Australia, Canada, and Western European countries; it is slowest in Russia, Japan, China, Eastern Europe and South America.

In the structure of cancer incidence in Russia, GC consistently ranks second for people of both sexes and has a steady downward trend in all economically developed regions. From 1990 to 2005, a decrease in its share in the morbidity structure was noted: by 5.3% in men and by 5.8% in women [3, 9].

In the structure of morbidity among the male population of Russia in 2005, GC ranks second after lung cancer and amounts to 11.3%. In women, it ranks third after breast, colorectal and rectal cancer (excluding non-melanoma skin tumors) and accounts for 7.5% [4, 9].

In the structure of mortality of the Russian population from malignant diseases in 2005, stomach cancer was 14.3% in men (second place after lung cancer) and 12.5% in women (third place after breast, colon and rectal cancer). In total, 38,429 people died from gastric cancer [2,7].

The tragedy for most patients is the asymptomatic nature of early cancer, the lack of adequate screening programs, late detection, the aggressive course of the disease and, as a consequence, the impossibility of radical treatment. The proportion of patients with stage IV disease in 2005 reached 41.8%. (the proportion of newly diagnosed patients with stage IV gastric cancer ranges from 28.9% to 66.7% in various regions of Russia) [5].

By the time the diagnosis is made, in most patients with stomach cancer the disease is widespread; radical surgery is possible only in 30-35%) of patients, but even in these cases the rate of disease recurrence is quite high. Five-year survival depends on the stage and is 65% for stage I gastric cancer, 20% for stage II, 10% for stage III and less than 1% for stage IV.

PURPOSE OF THE STUDY

To study the effectiveness and tolerability, long-term results of treatment when using a combined regimen Cisplatin + Capecitabine.

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MATERIALS AND METHODS OF RESEARCH

For the study, we chose the treatment regimen:

Cisplatin 80 mg/m2 intravenously on the first day of the course against the background of antiemetic protection with 5-HT3 receptor antagonists and dexamethasone, a load of saline solution up to 2 liters, followed by forced diuresis.

Capecitabine 2000 mg/m2 per day, dividing the daily dose into two doses every 12 hours, 20 minutes after meals, with a sufficient amount of liquid. Patients began taking Xeloda in the evening of the first day of treatment and continued until the morning of the fifteenth day of the course. Repeat the chemotherapy course every 21 days.

The study protocol included 47 patients aged from 29 to 74 years (median 57 years). Of these: 24 men (51.1%) and 23 women (48.9%).

The average follow-up time for patients was 10.1±6.1 months (from 3 to 25 months).
The prevalence of tumor lesions is presented in Table 20.

RESULTS

As can be seen from table 1 , more than half of the patients before treatment had a primary tumor and damage to regional lymph nodes. Of the parenchymal organs, metastatic lesions of the liver were most often observed (45%).

One of the objectives of our study was to study the effectiveness and toxicity of combination regimens including platinum drugs in elderly patients (65 years and older). The prerequisite for this was the insufficient number of scientific studies on the treatment of cancer in elderly patients, false ideas about the poor tolerance of chemotherapy in this category of patients and the conservatism of the majority of oncologists, who consider old age a contraindication for active treatment. Therefore, below we present an analysis of various parameters for the entire age group of patients and comparative characteristics for various age groups.
The characteristics of patients by age group are presented in Fig. 1.

Table 1
Localization of tumor lesions in patients of the group

Cisplatin+	capecitabine
Localization	Number of patients, (%)
Primary tumor	24 (51.1%)
Regional lymph nodes, including retroperitoneal lymph nodes	28 (59.6%) 15 (31.9%)
Peripheral lymph nodes	11 (23.4%)
Big seal	9(19.2%)
Peritoneum	I (23.4%)
Ascites	13 (27.7%)
Liver	21 (44.7%)
Pancreas	1 (2.1%)
Pelvic organs	6 (12.8%)
Lungs	8(17.0%)
Pleurisy	3 (6.4%)
Bones	3 (6.4%)
Soft fabrics	2 (4.3%)
Adrenal glands	1 (2.1%)
Spleen	1 (2.1%)

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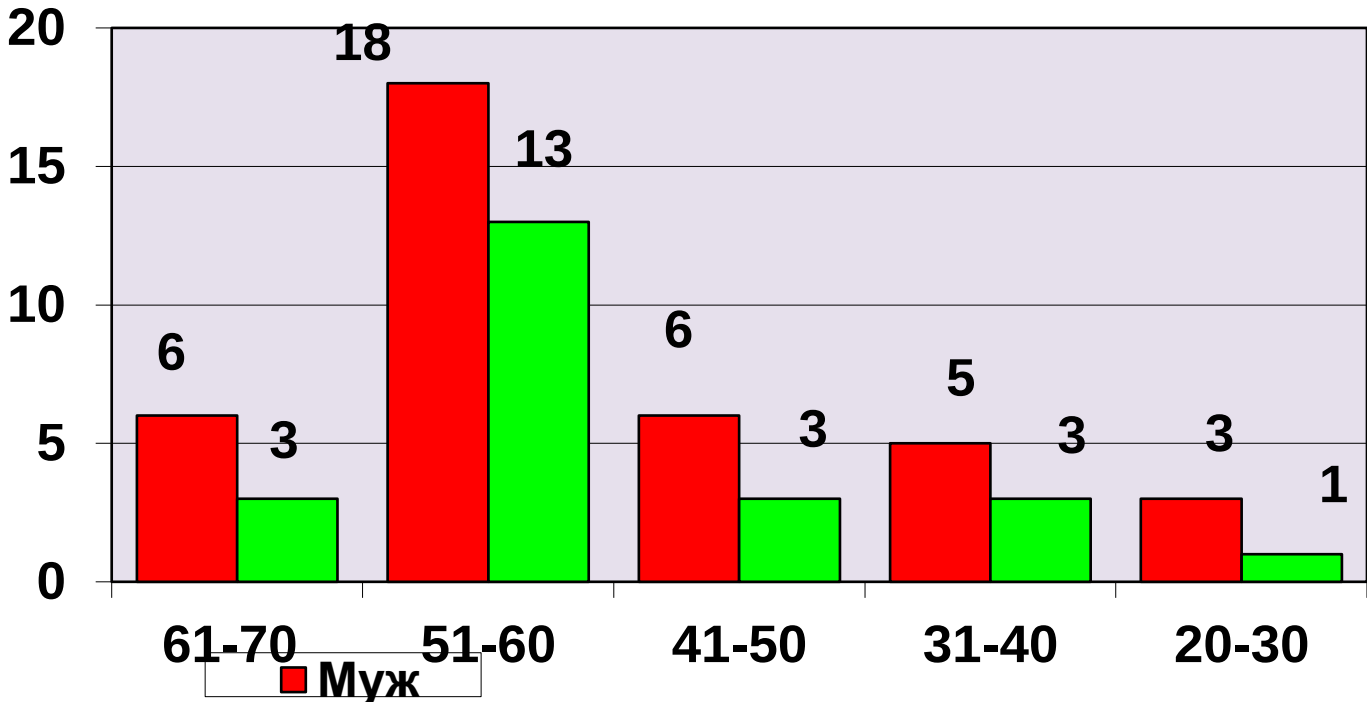
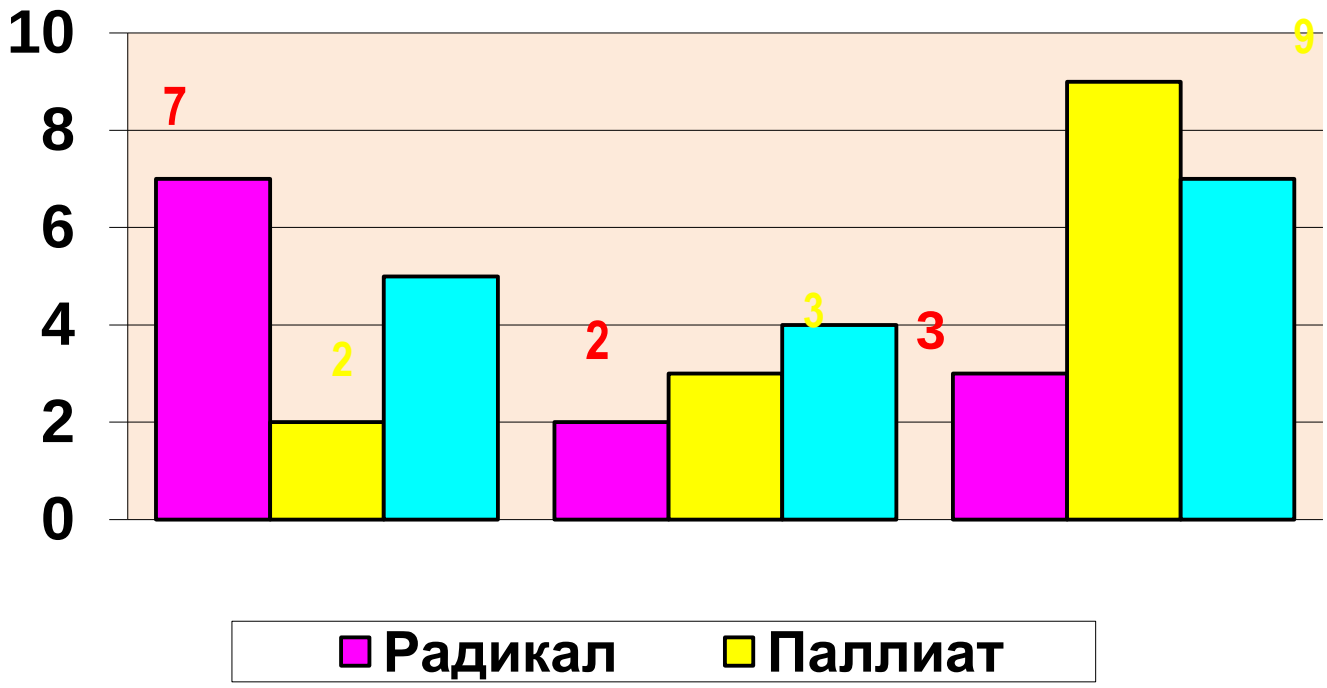
Fig 1.
Characteristics of patients in the Cisplatin+Capecitabine group Distribution of patients by gender and age



As we can see from Figure 1, in the group of elderly patients there was a more unfavorable general status, and extensive tumor lesions were more common.
28 people (59.6%) received previous surgical treatment. Types of surgical care are presented in Figure 2.

Fig 2
The nature of previous surgical treatment of patients in the group Cisplatin+Capecitabine



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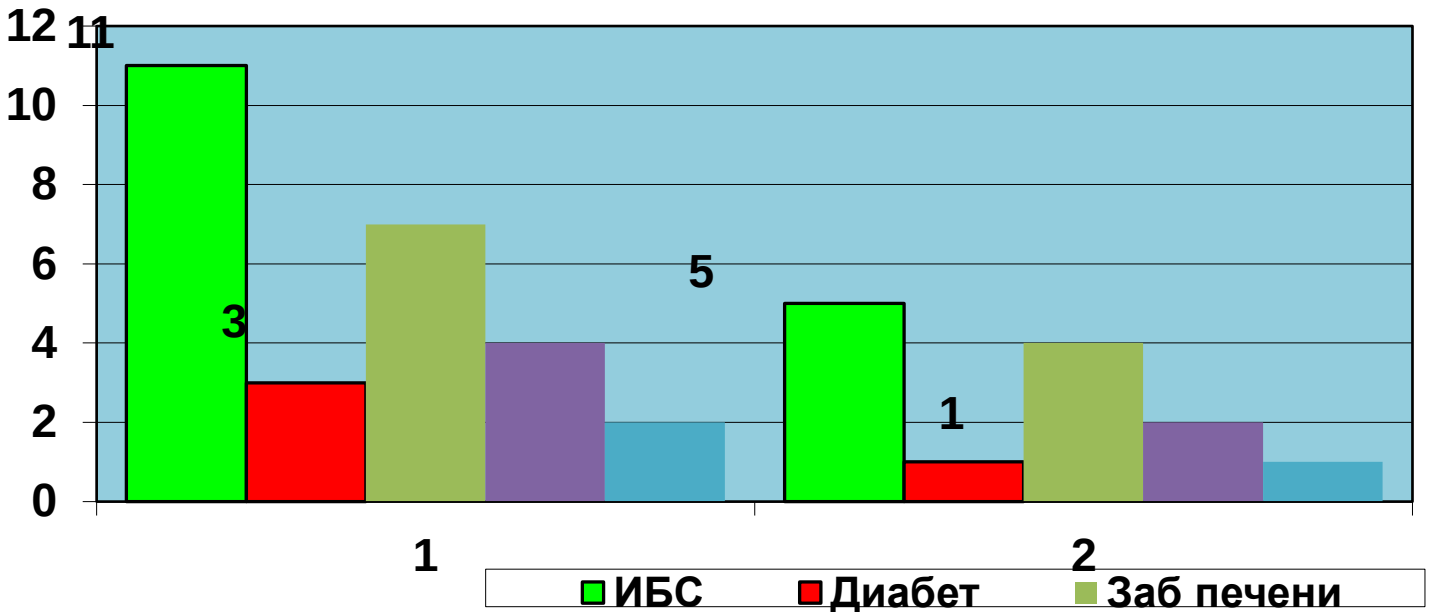
No adjuvant chemotherapy was administered.

We tried to analyze concomitant pathology in more detail, since it is one of the most common reasons for denying specific treatment to elderly patients.
Data on concomitant pathology in patients of different age groups are presented in Figure 3.

Fig 3
Concomitant pathology in patients of different age categories of the Cisplatin + Capecitabine group



n-number of patients in the group
It is important to note that two patients from group A and one patient from group B had a history of myocardial infarction, one (group B) had acute cerebral circulatory failure (the period between the acute condition and inclusion in the protocol was at least 1 year).

Hypertension was recorded in 14 patients (7 patients from each group). 14 patients suffered from coronary heart disease (group A - 6 patients, group B - 8 patients), three of them had circulatory failure 1-2 FC, two had a permanent form of atrial fibrillation.

2 The patient suffered from chronic encephalopathy associated with extensive atherosclerotic lesions of the cerebral vessels.

4 patients had chronic obstructive pulmonary disease (2 patients in each group), 3 had bronchial asthma (1 patient from group A, 2 patients from group B).

2 patients were carriers of viral hepatitis B (1 each in groups A and B),
1 - a carrier of viral hepatitis C (group A), 2 patients had Botkin's disease (group A).
One patient (group B) had a history of infectious meningitis.

Pathology of the genitourinary system was present mainly in the group of "young" patients: 2 cases of chronic cystitis, 1 case of chronic prostatitis, 1 patient had a history of nephrolithiasis and a secondary wrinkled kidney (without functional disorders at the time of inclusion in the protocol). This patient received 2 courses of chemotherapy with stabilization of the process. The level and clearance of creatinine during treatment with Cisplatin were normal. Removed from the protocol due to moving to another place of residence, where he continued chemotherapy. Contact with the patient was carried out by telephone.

In group B, 1 elderly patient had chronic prostatitis.
A total of 210 treatment courses were carried out (average 4.5).
148 (average 4.2) courses in group A, 62 (average 5.2) courses in group B. Data are presented in Table 2.

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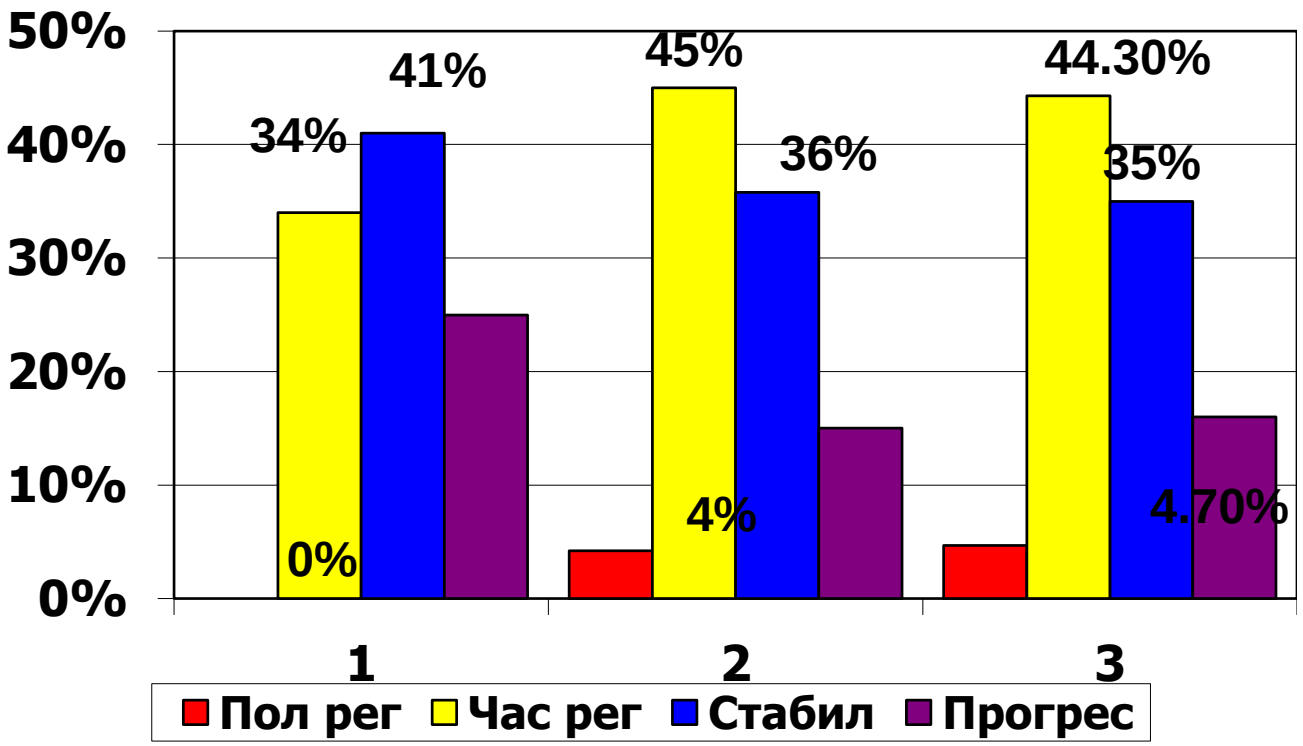
Table 2.
Number of patients by the number of courses administered to one patient using the Cisplatin + Capecitabine regimen

Number courses	Number of patients, (%) entire group	Number of patients, (%) group A (n=35)	Number of patients, (%) group B (n=12)
2	13 (27.7%)	12 (34.3%)	1 (8.3%)
3	2 (4.3%)	2 (5.7%)	-
4	11 (23.4%)	8 (22.9%)	3 (25%)
5	5 (10.6%)	2 (5.7%)	3 (25%)
6	9(19.1%)	6(17.1%)	3 (25%)
7	1 (2.1%)	-	1 (8.3%)
8	6(12.8%)	5 (14.3%)	1 (8.3%)

The largest number of courses was administered to patients under 65 years of age; elderly patients received mainly 4-6 cycles of chemotherapy.

The effectiveness was assessed in 47 patients who received 2 or more courses of treatment. The treatment results are presented in Figure 4.

Fig 4
Evaluation of the effectiveness of treatment in 47 patients using the Cisplatin + Capecitabine regimen



The median duration of effect in the entire group was 3.9 months.
At the end of the study*, the effect of first-line chemotherapy remained in 7 patients (14.9%), 14 patients (29.7%) were alive.
A comparative statistical analysis of the effectiveness of chemotherapy in various age groups is presented in Table 3

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Table 3
Treatment effectiveness in patients of different age groups using the Cisplatin + Capecitabine regimen

Result	Number of patients, (%) group A, months (for median)	Number of patients, (%) group B, months (for median)
Number of patients	35	12
Full regression	1 (2.9%)	1 (8.4%)
Partial regression	14 (40%)	7 (58.3%)
Stabilization	13 (37.1%)	4(33.3%)
Progression	7 (20%)	0*
Overall efficiency	15 (42.9%)	8 (66.7%)
Tumor growth control	28 (80%)	12(100%)*
Median duration of effect	3.3 [1.6-19.9]	4.9 [2.3-17.2]

*** - tendency *towards significance (p*> 0.05) .**

There were no significant differences in the effectiveness of treatment in the two groups.

There is a tendency towards significance ***(p>0.05***) in the difference in the frequency of progression (p= ***0.09***) and in the control of tumor growth ***(p=0.09***).

Control of tumor growth was achieved in 40 (85.1%) patients, which was 80% for the young group (A) and 100% for the elderly group (B), where no progression was recorded at the end of the study.

Considering the low sensitivity of gastric cancer to chemotherapy and the widespread prevalence of the tumor process, such a criterion as control of tumor growth is of great importance, especially for elderly patients and is a positive parameter of our study.

The clinical effect in the form of a decrease in intensity or complete relief of pain, improvement in general well-being, the presence of a certain comfort when swallowing and digesting food, appetite, weight gain, return to "normal" physical activity, and a positive attitude towards their disease was noted by 40% of patients (the same number in both groups).

In 10 (21.3%) patients (group A - 7 (20%), group B - 3 (25%)) during chemotherapy, weight gain averaged 2.4 ± 1.8 kg (from 1 to 6 kg).

CONCLUSIONS

All of the above indicates an increase in the quality of life of disseminated patients and is an important factor that is directly related to a decrease in the manifestations of general intoxication due to a decrease in tumor mass and the implementation of the cytoreductive effect of chemotherapy.

The presence of a clinical effect indicates the low toxicity of treatment, since in this case the antitumor effect prevails over the side effects of chemotherapy.

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