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ORIGINAL ARTICLE

PREOPERATIVE CHEMOTHERAPY USAGE EXPERIENCE FOR INTRAHEPATIC CHOLANGIOCARCINOMA

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Abstract

Purpose of the study was to evaluate the safety and feasibility of preoperative chemotherapy in intrahepatic cholangiocarcinoma (IHCC).
Patients and methods. A total of 171 liver resections for IHCC were performed between 2007 and 2021, of which 24 were preceded by preoperative therapy (14.0 %). Systemic therapy was conducted in 11 patients (45.8 %). Regional chemotherapy was provided to 13 patients (54.2 %). In two cases, regional chemotherapy was supplemented with systemic therapy.
Results. A significant increase in the proportion of patients with clinical stage IIIb and higher was observed in the group of patients who had received preoperative therapy (83.3 % vs. 35.4 %, $p < 0.0001$). Complications of preoperative therapy occurred in 45.8 % of patients, with grade three and above complications identified in three patients (12.5 %). The incidence of postoperative complications (37.5 % vs. 42.9 %, $p = 0.79$), post-resection liver failure (8.3 % vs. 13.6 %, $p = 0.7$) and postoperative mortality (4.2 % vs. 3.4 %, $p = 0.68$) in the preoperative therapy group were similar to those in the control group. The rate of radical resections was also identical, 83 % in both groups ($p = 0.8$). The relapses rates within the first six months after the surgery were similar: 25 % of patients in both groups ($p = 0.62$). The median OS reached 36 months in the main group and 32 months in the control one ($p = 0.81$).
Conclusion. Since the main group predominantly included patients with more advanced stages of the disease and yet the treatment resulted in comparable immediate and long-term outcomes, it can be concluded that preoperative therapy can be justified in patients with IHCC who have factors predisposing to poor prognosis. Randomized trials are necessary to determine the rationality, as well as the type and regimen of preoperative therapy to be used in patients with IHCC.

Keywords:
cholangiocarcinoma, combination therapy, preoperative chemotherapy, transarterial chemoembolization, hepatic artery infusion chemotherapy, post-resection liver failure, poor prognostic factors

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Compliance with ethical standards: the ethical principles set forth by the Helsinki Declaration of the World Medical Association Declaration of Helsinki (1964, ed. 2013) were observed. The study was approved by the Committee on Biomedical Ethics at the N.N.Blokhin National Research Institute of Oncology. Informed consent was obtained from all participants of the study.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ОПЫТ ПРИМЕНЕНИЯ ПРЕДОПЕРАЦИОННОЙ ХИМИОТЕРАПИИ ПРИ ВНУТРИПЕЧЕНОЧНОЙ ХОЛАНГИОКАРЦИНОМЕ

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Резюме

Цель исследования. Оценить безопасность и целесообразность предоперационной химиотерапии при внутрипеченочной холангиокарциноме (ВПХК).

Пациенты и методы. С 2007 по 2021 года выполнена 171 резекция печени по поводу ВПХК, из них в 24 случаях – после предоперационной терапии (14,0 %). Системная терапия без добавления регионарной проведена 11 пациентам (45,8 %), преобладали гемцитабин-содержащие схемы (n = 9). Регионарная химиотерапия осуществлена 13 пациентам (54,2 %), В двух случаях регионарная химиотерапия дополнена системной.

Результаты. Выявлено значимое увеличение доли пациентов с клинической IIIb стадией и выше в группе больных с предоперационной терапией (83,3 % против 35,4 %, p < 0,0001). Осложнения предоперационной терапии развились у 45,8 % больных, осложнения третьей степени и выше выявлены у трех пациентов (12,5 %). Частота осложнений после хирургического вмешательства (37,5 % против 42,9 %, p = 0,79), пострезекционная печеночная недостаточность (8,3 % против 13,6 %, p = 0,7) и послеоперационная летальность (4,2 % против 3,4 %, p = 0,68) в группе с предоперационной терапией были сопоставимы с аналогичными показателями в группе пациентов без предоперационного лечения. Частота отдельных осложнений в основной группе не отличалась от частоты осложнений в контрольной группе. Уровень радикальных резекций также был одинаковым – 83 % в обеих группах (p = 0,8). Рецидив в первые полгода от даты операции возникал со сходной частотой у 25 % пациентов основной группы и у 28,6 % – контрольной (p = 0,62). Медиана ОВ достигла 36 месяцев в основной группе и 32 месяца – в контрольной (p = 0,81).

Заключение. Преобладание в основной группе пациентов с более продвинутыми стадиями заболевания при сопоставимых непосредственных и отделенных результатах лечения позволяет сказать, что предоперационная терапия оправдана у пациентов с внутрипеченочной холангиокарциномой при наличии факторов неблагоприятного прогноза. Роль предоперационной терапии в общей группе должна быть определена в рандомизированных исследованиях.

Ключевые слова:
холангиокарцинома, комбинированное лечение, предоперационная химиотерапия, химиоэмболизация печеночной артерии, химиоинфузия печеночной артерии, пострезекционная печеночная недостаточность, факторы неблагоприятного прогноза

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «НМИЦ онкологии им Н.Н.Блохина». Информированное согласие получено от всех участников исследования.

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INTRODUCTION

A combination approach comprising liver resection with regional lymph node dissection and subsequent six-month capecitabine administration as monotherapy is currently the generally accepted treatment approach in cholangiocarcinoma, including cases of intrahepatic location [1]. On the other hand, trials are ongoing in an attempt to improve treatment outcomes in patients diagnosed with this disease. Some authors believe that preoperative therapy can be used for this purpose [2]. It is especially relevant in patients with poor prognosis, in whom early disease relapse can be expected after a seemingly radical resection. For this purpose, prognostic factors can be used to determine the risk of early and very early (within the first six months after resection) relapse. The determination of the probability of very early progression can use both postoperative and, which are more relevant, preoperative values obtained during the preoperative examination [3].

On the other hand, apart from the possible benefits, the neoadjuvant approach is associated with several disadvantages. These include the need for morphological verification, which is associated with a certain risk of complications, and delayed therapy initiation due to a complicated course of the disease in some patients manifested as jaundice or cholangitis. Possible on-therapy disease progression, including prior to the occurrence of any signs of unresectability, cannot be discarded. Another disadvantage is the possible occurrence of serious side effects of chemotherapy, which can reduce chances for surgical intervention and even render it impossible. The development of chemotherapy-induced hepatotoxicity is also possible, which is relevant when we plan an extensive liver resection. Therefore, this approach can be used in trials in patients without the signs of unresectability [4].

Purpose of the study was to evaluate the safety and feasibility of preoperative chemotherapy in intrahepatic cholangiocarcinoma (IHCC).

PATIENTS AND METHODS

There were 171 liver resections performed due to IHCC between May 16, 2007 and October 26, 2021. In twenty-four cases (14.0 %), the surgery was preceded by preliminary systemic and/or regional chemotherapy.

In the preoperative chemotherapy group, the median age was 62 years (31–69), with female patients prevailing (66.6 %, *n* = 16). The course of the disease was complicated by mechanical jaundice in six cases (25 %); percutaneous transhepatic cholangiostomy was the preferred method to ensure bile excretion (*n* = 5). In one case, the bilioduodenal stent was placed.

Based on the abdominal CT and/or contrast-enhanced MRI performed prior to the initiation of the therapy, liver damage mostly manifested as a solitary nodule (87.5 %, *n* = 21). The median tumor size (for the nodule count above one, the size of the largest nodule was taken into account) was 8 cm (3.6 to 15 cm). Single lobe involvement was identified in 11 patients, while three had multiple bilobar involvement. Ten other patients had a single nodule which was located centrally, thus extending to both lobes.

Major vascular involvement was identified in 13 patients (54.2 %). In two cases, patients were diagnosed with portal vein stem invasion; in nine patients, the tumor extended onto the right or left branch of the portal vein; and in two other cases, the right branch of the portal vein was compressed. Three patients featured invasion into one of the lobar hepatic arteries, and four patients had hepatic veins involved. The involvement of the inferior vena cava was diagnosed in one patient.

Eight patients (33.3 %) were diagnosed with tumor extension onto the adjacent tissues (other than vessels): onto the diaphragm in three patients (12.5 %) and onto the extrahepatic bile ducts in five patients (20.8 %). In another female patient, an intraluminal tumor component, descending along the left lobar duct from the main nodule in the left lobe of the liver, blocked the common hepatic duct.

Regional lymph node involvement was identified in 11 patients (45.8 %) based on preoperative examination findings.

It should be noted that clinical stages IIIB and higher prevailed (83 %, *n* = 20). The other four patients had clinical stage IIIA, and two of them had a centrally located nodule.

Stage IV was diagnosed in two patients, with a metastasis in the retroperitoneal lymph node identified in one case, and a lung metastasis in the other.

The median marker (CA 19–9) level was 104.7 IU/mL (5.7–12,000 IU/mL).

Systemic therapy without the adjunction of regional therapy was conducted in 11 patients (45.8 %); gemcitabine-based regimens prevailed (*n* = 9). Gemcitabine in combination with oxaliplatin was used in six cases, in combination with cisplatin in two cases, and in combination with capecitabine in one case. The capecitabine/oxaliplatin/cetuximab regimen and doxorubicin monotherapy were used in one case each.

Regional chemotherapy was carried out in 13 patients (54.2 %). In seven cases, a combination of oil transarterial chemoembolization (TACE) and hepatic artery infusion (HAI) chemotherapy with platinum-containing agents and gemcitabine was employed; oxaliplatin was used in most cases (*n* = 6), and in one case, gemcitabine was supplemented with cisplatin. In five cases, patients underwent TACE with doxorubicin, mostly in the form of oil

TACE (*n* = 4), and in one case microspheres were used. In one patient, oil TACE with doxorubicin was supplemented with carboplatin-based HAIC. TACE with mitomycin C was used in one case. In two cases, regional chemotherapy with gemcitabine and oxaliplatin was supplemented with systemic therapy in the form of either capecitabine monotherapy (four courses) or gemcitabine + cisplatin combination therapy (10 courses).

The median number of regional courses was 2 (1 to 5 courses), and the median number for systemic chemotherapy was 6 (1 to 10) courses.

In most cases, patients underwent extensive liver resection (91.7 %, *n* = 22). In the group of patients who underwent extensive liver resection, in three cases (12.5 %), nodules were found in the contralateral lobe; atypical liver resection (*n* = 2) or microwave metastasis ablation (*n* = 1) was carried out additionally. Central liver segments were resected in two patients (8.3 %).

Hepatoduodenal ligament lymph node dissection, along with the common hepatic artery, behind the head of the pancreas, was performed routinely; additionally, retroperitoneal lymphadenectomy was carried out in three cases (12.5 %).

Bile duct resection was carried out in three patients (12.5 %), with Roux hepaticoenterostomy performed on the small intestine loop. In two cases of planned extrahepatic bile ducts resection, no signs of their involvement were found during the surgery. In another case, an intraductal component was resected from the hepaticocholedochal lumen via the limb of the left lobar duct after left-sided hemihepatectomy.

Circular resection of the portal vein (20 mm in length) was required in one case, and thrombectomy from the portal vein was performed in another; the vessel clamp time was 8 minutes in the first case and 5 minutes in the second one. Lateral resection of the inferior vena cava (35 mm in length) was carried out in one patient. The Pringle maneuver was performed as necessary (29.2 %, *n* = 7).

Postoperative chemotherapy was carried out in 14 patients (58.3 %).

The patients were examined every three months within the first two years and every six months afterwards. Follow-up included abdominal CT/MRI, determination of the CA-199 marker level and chest X-ray or computed tomography. The median follow-up duration (from the date of the surgery) was 33 months.

Objective response was assessed by the Recist 1.1 criteria, and complications of chemotherapy and their severity were assessed by the NCCN criteria.

The Clavien–Dindo classification was used to assess the severity of postoperative complications, and the ISGLS criteria to assess the post-resection liver failure.

Statistical analysis was conducted using the SPSS (version 21) and GraphpudPrism 6 software. Progression-free survival and overall survival rates were calculated by the Kaplan–Meier method, and the differences were compared using the Log-Rank test. To compare the qualitative parameters, contingency tables were created, and the statistical significance of any differences was calculated using the chi-square test with Yates' correction for 2 × 2 tables.

The quantitative parameters, given the small number of observations in one of the two groups, were analyzed using the Mann–Whitney test. $p < 0.05$ was considered statistically significant.

RESULTS

In the group that had received systemic preoperative therapy (excluding two patients who received a combination of systemic and regional therapies), adverse events were reported in nine out of eleven patients (82 %). Grade three complications were reported in two patients (18.2 %); in one case, hepatotoxicity with the escalation of liver enzyme activity developed in a patient treated by the capecitabine/oxaliplatin/cetuximab regimen, and in the other, hematological toxicity and polyneuropathy occurred during therapy by the gemcitabine/oxaliplatin regimen. Both cases required the interval between the courses to be prolonged, and the doses of the drugs to be reduced.

No complications associated with endovascular interventions were reported. Postembolization syndrome was reported in 10 out of 11 patients who had received regional therapy without the adjunction of systemic one (90.9 %). In most cases, it manifested as a transient elevation in liver enzymes up to 2–3 times above the norm (90.9 %, *n* = 10). Clinical manifestations, such as pain in the upper half of the abdomen, nausea, diarrhea, were reported in six patients (54.5 %). In two patients (18.2 %), the syndrome was accompanied by hyperthermia. No myelosuppression or other symptoms of systemic exposure were reported in the regional therapy group.

In two cases, regional therapy was combined with systemic; postembolization syndrome was reported in both patients. Grade one hand-foot syndrome was reported in a patient treated with capecitabine, and grade three neutropenia, as well as nausea, hyperthermia and grade two thrombocytopenia were reported in a patient who had received chemotherapy by the gemcitabine/cisplatin regimen; these demanded a 25 % dose reduction.

To sum up, it can be stated that complications from preoperative therapy were quite frequent (45.8 %, *n* = 11), although grade three adverse events were reported only in three patients (12.5 %), with the prolongation of the interval between the courses and/or dose reduction required in these cases.

Partial response after preoperative chemotherapy was reported in 11 patients (45.8 %), including four

Table. Comparative characteristics of the patients in the preoperative therapy group versus control group

Parameter	Preop CT	No Preop CT	*p*
Age, years (median, min–max)	62 (31–69)	58 (27–80)	0.836
Male, abs.	8 (33.3%)	48 (32.7%)	0.87
Mechanical jaundice, abs.	6 (25%)	16 (10.9%)	0.11
Solitary nodule with a single lobe involvement	11 (45.8%)	68 (46.3%)	0.86
Centrally located solitary nodule	10 (41.7%)	40 (27.2%)	0.22
Multiple liver lesions	3 (12.5%)	39 (26.5%)	0.11
Clinical T4	13 (54.1%)	31 (21.1%)	0.001
Clinical N1	11 (45.8%)	35 (23.8%)	0.04
Suspicion of M1	2 (8.3%)	5 (3.4%)	0.57
Stage IIIb (clinical) and higher	20 (83.3%)	51 (34.7%)	< 0.0001
Baseline CA-199, median (min–max), IU/mL	104.7 (5.7–12,000)	29 (0–58,887)	0.8
Extensive resection	22 (91.7%)	109 (74.1%)	0.11
Central liver resection	2 (8.3%)	16 (10.9%)	0.98
Other sparing resections	0	22 (15.0%)	0.09
Liver SI resection	4 (16.7%)	21 (14.3%)	0.39
Resection of extrahepatic bile ducts	3 (12.5%)	12 (8.2%)	0.76
Vascular resection	2 (8.3%)	6 (4.1%)	0.69
Operative time, median (min–max), minutes	280 (120–490)	180 (90–460)	0.001
Loss of blood (min–max), mL	1,200 (150–3,600)	1,100 (50–6,000)	0.168
Blood transfusions	9 (37.5%)	48 (32.7%)	0.82
Complications	9 (37.5%)	63 (42.9%)	0.79
Clavien–Dindo 3 and higher	5 (20.8%)	29 (19.7%)	0.88
Post-resection liver failure	2 (8.3%)	20 (13.6%)	0.70
Grades B and C liver failure (ISGLS)	1 (4.2%)	8 (5.4%)	0.82
Bile leakage, biloma	5 (20.8%)	33 (22.4%)	0.93
Intra-abdominal bleeding, hematoma	1 (4.2%)	8 (5.4%)	0.82
Mortality	1 (4.2%)	5 (3.4%)	0.68
Mortality due to liver failure	0	3 (2.0%)	0.90
R0 resection	20 (83.3%)	122 (83.0%)	0.80
R1 resection	3 (12.5%)	14 (9.5%)	0.93
R2 resection	1 (4.2%)	11 (7.5%)	0.87
Pathomorphological N+	9 (37.5%)	48 (32.7%)	0.82
Pathomorphological T4	14 (58.3%)	31 (21.1%)	0.0003
Postoperative CA19-9, median (min–max), IU/mL	16.5 (1–384)	12.5 (0–4807)	0.960
Very early recurrence, %*	25	28.6	0.62
Median OS, months*	36	31	0.81
Total number of patients	24	147	–

* Except any patients who died within the thirty-day postoperative period.
Abs. – absolute value;
Max – maximum;
Min – minimum;
Preop CT – preoperative chemotherapy.

patients who had received regional therapy; stabilization was reported in 13 patients (54.2 %). The CA-199 marker level (median) after chemotherapy was 24 IU/mL (5–2,143 IU/mL). The median size of the largest nodule after chemotherapy was 7 cm (3.5–14 cm). In a patient with signs of remote lymphogenous metastases, the enlarged retroperitoneal lymph nodes were no longer visualized, and in a patient with pulmonary metastasis, computed tomography performed after the preoperative chemotherapy did not reveal any tumor lesions in the chest. Table summarizes the major characteristics of the patients in the preoperative therapy group versus the group that did not receive preoperative chemotherapy.

The median size of the largest nodule was 8 cm in both groups (p = 0.9). In the main group, signs of adjacent tissue involvement (T4) were identified at a significantly higher rate (54.1 % vs. 21.1 %, p = 0.0001) during the preoperative examination before the initiation of treatment. The same tendency was observed during the pathomorphological investigation of the resected specimen (58.3 % vs. 21.1 %, p = 0.0003). The rate of lymph node involvement, according to the findings of diagnostic radiological examination, was also higher in the main group; however, morphological examination did not reveal any difference in the rate of their involvement (p = 0.82). Patients in the group that had not received the neoadjuvant approach tended to have a higher incidence of multiple liver lesions (p = 0.11); on the other hand, the preoperative therapy group had a somewhat higher incidence of centrally located nodules, although the difference did not reach statistical significance (p = 0.22). It should be noted that there was a statistically significant increase in the proportion of patients with clinical stage IIIb and higher in the preoperative therapy group (83.3 % vs. 35.4 %, p < 0.0001).

No liver sparing resections for non-central nodules were carried out in the main group, and the difference was close to significant (0 % vs. 15 %, p = 0.09).

There was no significant difference in the rate of vascular resection (p = 0.69) or the need for bile duct resection (p = 0.76) between the compared groups. The median operative time in the main group was higher (280 vs. 180 minutes, p = 0.0001). The Pringle maneuver was more frequently used in the control group (p = 0.01) without a significant difference in the loss of blood (p = 0.168) or the need for blood transfusion (p = 0.82).

Postoperative complications were reported in nine patients in the preoperative therapy group (37.5 %), which did not differ from the rate of complications in the control group (42.9 %, p = 0.79).

Bile leakage and/or biloma formation was reported in five patients (20.8 %); in one case, this was accompanied by common bile duct stricture, and in two cases by hepatoenteric anastomosis failure. Wound infection (4.2 %) and hypertensive crisis (4.2 %) were diagnosed in one case each. One patient had several complications caused by multiple small bowel perforations (4.2 %) that led to peritonitis; portal vein thrombosis, small bowel bleeding, sepsis and multiple organ failure were identified subsequently. Post-resection liver failure was diagnosed in two patients, in one of whom it was accompanied by biliodigestive anastomosis failure and bile leakage. Persistent ascites without signs of portal vein thrombosis or signs of liver failure was observed in one patient (4.2 %).

Five patients in the main group had complications of Clavien–Dindo grade three and higher. Bile duct drainage was required in two groups, including the combination with percutaneous transhepatic cholangiostomy in one of them. Two patients were re-operated: one – due to the formation of biloma in the operation area, and the other – due to duodenal perforation. The patient subsequently underwent two emergency following laparotomies due to small bowel perforations that led to peritonitis and small bowel bleeding in the latter group; the patient died from multiple organ failure caused by peritonitis, sepsis and portal vein thrombosis. The mortality rate was 4.2 %. ISGLS grade B post-resection liver failure developed in one patient (4.2 %), which required a 10-day intensive care unit stay.

It should be noted that the incidence of individual complications in the main group did not differ from that in the control one. It is especially prominent that preoperative chemotherapy did not increase the incidence of post-resection liver failure (p = 0.7) and the risk of ISGLS grade B post-resection liver failure (p = 0.82). No mortality from post-resection liver failure was reported in the main group.

As mentioned earlier, pathomorphological investigation identified ingrowth into the adjacent structures in 14 patients (58.3 %). Most clinically relevant were ingrowth in the bile duct confluence (n = 3), the main stem of the portal vein (n = 1) and the inferior vena cava (n = 1), which required resection of the involved structures. Other cases included diaphragm invasion (n = 6), including in combination with ingrowth into the perinephric fat or lesser omentum (n = 3), tumor extension onto hepatoduodenal ligament elements on the affected side (n = 3). Liver capsule extension without the involvement of the adjacent organs was identified in three cases.

The median count of resected lymph nodes in the main group was 6 (2–15). In nine cases, regional lymph node involvement was reported (37.5 %). One patient, in whom CT showed the involvement of the retroperitoneal lymph collector before the preoperative chemotherapy, had changes in the resected lymph nodes that were indicative of metastasis with complete therapeutic pathomorphosis. Mild therapeutic pathomorphosis of the primary tumor was detected in three patients (12.5 %),

moderate pathomorphosis was noted in four patients (31.3 %), in one case with a complete radiological response to lung metastasis. Pronounced pathomorphosis in the primary focus was detected in three patients (12.5 %), in one case in combination with complete pathomorphosis of metastasis in a distant retroperitoneal lymph node. Complete pathomorphosis was achieved in one patient (4.2 %). Thirteen patients showed no signs of therapeutic pathomorphosis (54.2 %), twelve of them from the regional therapy group.

In one patient, the lung metastasis was not resected since it could no longer be visualized using radiological methods at the time of the surgery. In one case, tumor cells were found along the bile duct resection line during extensive hemihepatectomy with bile duct resection. In two other patients, tumor cells were detected directly at the edge of the liver resection line in the portal area. In the other cases (83.3 %, n = 20), the surgeries were radical. In the control group, the rate of radical surgeries was the same (83 %) as in the main one.

Neither before the treatment nor after the surgery, CA19–9 tumor marker levels differed among the groups.

Although the median follow-up was less than three years in the main group (33 months), we made an attempt to study and compare the preliminary long-term outcomes. Patients who died from postoperative complications were excluded from the analysis. Progression in the main group was noted in 16 patients (66.7 %), with the median time to progression being 12 months from the date of the surgery (13 months in the control group). Six-month progression was noted in 25 % of the patients (vs. 28.6 %). The three-year relapse-free survival was 24.7 % vs. 21.2 %. No significant difference in the relapse-free survival rate was observed between the compared groups (p = 0.62). The median OS from the date of the surgery was 36 months, and the three-year OS rate was 45.5 %. The treatment outcomes in the main group did not differ from those in the control one. The median in the comparison group, was 32 months, and the three-year survival rate was 47.9 %, p = 0.81.

As has been mentioned earlier, the preoperative therapy group predominantly consisted of patients with stage IIIB and higher (83.3 %), which was significantly higher than the same parameter in the comparison group. Besides, we used the surgery date rather than the therapy initiation date as the reference point. We believe that the preliminary results obtained are suggestive of a beneficial effect of preoperative therapy on the disease outcome.

DISCUSSION

According to J. N. Primrose, preventive use of capecitabine post radical surgery for biliary cancer, including in IHCC, is a standard approach to the combination treatment in patients with this group of tumors. As demonstrated in a group of 447 patients with cholangiocarcinoma and invasive gallbladder cancer, including 84 patients with IHCC, this approach helped increase the median OS up to 51 months compared to 36 (p = 0.028) in the main observation group, with no significant heterogeneity depending on the nosology (p = 0.47) shown in the subgroup analysis [1].

Most patients progress within five years after surgery for IHCC, and in most cases the disease recurs within the first two years (78.8 %), which is considered early progression [5]. In a quarter of patients, progression develops within the first six months; such patients have a poor prognosis for life [3]. In some patients, this outcome can be predicted based on prognostic factors. A generalized system (very early recurrence calculator) has been suggested; this system uses scores to give quite an accurate prediction of the likelihood of progression within the first six months after the surgery. It uses such preoperative factors as age, race, presence of cirrhosis, size and count of tumor nodules in the liver and presence of metastatic or suspectedly metastatic regional lymph nodes. Once the resection has been performed, the prognostic scheme is based on such factors as age, race, size, and count of tumor nodules in the liver, metastatic involvement of lymph nodes, microvascular invasion and radicalism [3]. Both schemes have an equal reliability in predicting very early – within six months post resection – progression based on the risk level: for the high risk, it approaches 50 % and for the low risk, 10 %. This makes it possible to use the preoperative model as the predictive one and, therefore, implement it to select candidates for preoperative therapy for IHCC. However, like any model, it has its drawbacks: even at a low-risk level, there is a ten-percent likelihood of very early progression, and at a medium risk level, the chance is as high as 30 %, which suggests that expanding indications for the adjunctive therapy may be rational.

There is evidence indicating, that the treatment outcomes can be improved by the use of the neoadjuvant approach in the entire group [2]. The authors have retrospectively analyzed the treatment outcomes in patients with both extra- and intrahepatic forms of cholangiocarcinoma, with the latter ones prevailing (70 %). Neoadjuvant therapy was administered to 279 patients, and adjuvant therapy was administered to 700 patients. The groups were well-balanced by their main characteristics. The investigators reported a relatively long median time from the establishment of the diagnosis to the surgery (172 days vs. 25 days in the adjuvant therapy group, p < 0.001). It is peculiar that the time prior to the initiation of chemotherapy was longer in the preoperative therapy group (the median of 39 days) than that in the non-neoadjuvant group, although one of the benefits of the neoadjuvant

therapy is the possibility of an earlier initiation of specific treatment in the absence of contraindications. Nevertheless, patients who had undergone preoperative therapy had a higher rate of radical resections (71.2 % vs. 61.6 %, $p = 0.02$). In the preoperative therapy group, the median was 40.3 months vs. 32.8 months ($p = 0.011$) in the adjuvant therapy group. Subgroup analysis also demonstrated the beneficial effect of the neoadjuvant approach in the cohort of patients with IHCC ($p = 0.04$).

A combination of gemcitabine and cisplatin is the most commonly used one in advanced biliary cancer. In phase III randomized trial ABC-02 conducted in 410 patients, this regimen helped achieve the median OS of 11.7 months (vs. 8.1 months in the gemcitabine monotherapy group, $p < 0.001$). The same trend was observed for the median progression-free survival (8.0 months vs. 5.0 months, respectively, $p < 0.001$). The superiority of the combination regimen was demonstrated both in intrahepatic and extrahepatic tumor location. In the combination chemotherapy group, the incidence of neutropenia was higher, but there was no significant difference in the incidence of infectious complications [6]. This regimen currently remains a standard first-line therapy in patients with cholangiocarcinoma in whom target therapy or immunotherapy cannot be applied [7].

A weakness of this regimen was the low rate of objective response (19 % in cholangiocellular carcinoma), as well as the fact that less than half of the patients enrolled in the study completed the full course of therapy [6].

This is not critical when short-term preoperative therapy is provided to an operable patient without any poor prognosis factors. It also does not have any dramatic consequences in case of an a priori unresectable cholangiocellular carcinoma, since such patients require chemotherapy or chemoradiation therapy in any case and undergo surgical intervention only if they achieve the operable status. It should be noted that the conversion rate for systemic therapy may reach 36 % [8, 9].

However, in conditionally resectable tumors, even minor progression may render the patient inoperable. To minimize such a possibility, it makes sense to use regimens associated with a higher objective response rate. The gemcitabine, cisplatin and nab-paclitaxel combination helped achieve a partial response in 45 % and control of the disease in 84 % of inoperable patients with biliary cancer ($n = 60$, of which 68 % had IHCC) [10]. Another option is to use regional therapy for the neoadjuvant approach since it is associated with a higher objective response rate and a lower risk of systemic complications. A 2013 meta-analysis of the outcomes of treatment in 542 patients from 16 studies demonstrated that transarterial therapy helped achieve anti-tumor response in 76.8 % of the patients, including the disease stabilization. The median OS from the initiation of therapy was 13.4 months, and the incidence of grade three and higher toxicity was acceptable (18.9 %) [11]. A 2022 meta-analysis summarizing the results of nine studies demonstrated that hepatic artery chemotherapy infusion helped achieve partial response in 27 % to 59.7 % of the cases, stable of the disease achieved in 40 % to 73 % of the patients. The three-year survival rate was 39.5 %. The maximum incidence of grade three and higher toxicity was 22.7 %, but it should be borne in mind that the participants were patients with unresectable tumors who received multi-course treatment until progression or the occurrence of unacceptable toxicity [12].

In our study, the median number of systemic chemotherapy courses was six, and the median number of regional therapy courses was two. It should be noted that chemotherapy was predominantly (83.3 %, $n = 20$) provided to patients with clinical stage IIIB and higher, i.e., radiological investigations revealed adverse factors such as ingrowth into the adjacent structures or lymph node involvement, and in many cases there was a combination of factors. In two patients, the disease was diagnosed at stage four.

Grade three complications during the preoperative therapy occurred in three patients, which accounted for 12.5 %. They required regimen modification. In the group of patients who had undergone regional therapy alone, there were no side effects associated with systemic exposure of the drugs; however, the procedure caused postembolization syndrome in almost all of them.

All of the patients in our study achieved control of the disease. Partial response was noted in 11 patients (45.8 %), including four patients after regional therapy. Thus, stabilization was observed in 13 cases (54.2 %).

It is very important to note that, in the postoperative period, there was no increase in the incidence of complications ($p = 0.79$) or Clavien–Dindo grade III and higher complications ($p = 0.88$) in the group of patients who had received preoperative therapy compared to the control group. The mortality rate in both groups was about 4 % ($p = 0.68$). The incidence of such a severe complication as post-resection liver failure was identical ($p = 0.7$), including ISGLS grades B and C cases ($p = 0.82$). No mortality from post-resection liver failure was reported in the main group. It is also worth noting that the patients in the main group underwent either extensive or central spare liver resections. There were no cases of technically simpler spare liver resections for non-centrally located tumors in this group, although the difference with the comparison group only tends to statistical significance (0 vs. 15.0 %, $p = 0.09$).

Based on the intraoperative, radiological and morphological data, R0 resection was achieved in 20 patients (83.3 %) in the main group, and this value was identical to the control one. Despite the lack of difference in this parameter, we believe this to be a clear success since the

disease was significantly ($p < 0.0001$) more advanced in the preoperative therapy group. We associate the low level of pathomorphosis in the regional therapy group both with the low sensitivity of cholangiocarcinoma to chemotherapy and with fewer courses of therapy in this group.

Moreover, although the main group predominantly consisted of patients with more advanced stages, the long-term outcomes were not worse when preoperative therapy was used.

The median time to progression was 12 months (13 months in the main group, $p = 0.62$), and very early progression was observed in a quarter of patients compared to 28.6 %. The three-year relapse-free survival was 24.7 % (vs. 21.2 %). The median OS was 36 months in the preoperative therapy group compared to 32 months ($p = 0.81$).

It is worth noting, that the analysis of long-term outcomes in both groups was conducted from the surgery date rather than the date of therapy initiation or the date of diagnosis.

CONCLUSION

It can be stated that preoperative therapy may be approved in patients with intrahepatic cholangiocarcinoma who have factors predisposing to poor prognosis based on the literature data and the results of our study.

According to our data, preoperative therapy was associated with an acceptable complication rate (below 50 %), and grade three and higher side effects were noted in 12.5 % of the patients. Preoperative therapy had no negative effect on the postoperative period (the complication rate was 37.5 % vs. 42.9 %, $p = 0.79$), including in terms of increasing the risks of post-resection liver failure ($p = 0.7$) or mortality (0.68).

Moreover, the rates of R0 resection were comparable between the groups (about 83 %, $p = 0.8$), and the rate of very early recurrence was similar: 25 % in the main group and 28.6 % in the control one (p = 0.62). The median overall survival did not demonstrate significant difference either, reaching 36 and 32 months, respectively ($p = 0.81$). Notably though, the main group had a significantly (83.3 % vs. 34.7 %, $p < 0.0001$) higher rate of tumors diagnosed at stages IIIB–IV, and the other four patients had clinical stage IIIA; this means that all of the patients supposedly had tumor extension beyond liver either as direct invasion or in the form of metastases, either regional or remote.

Undoubtedly, our study has some weaknesses: retrospective data collection, a small number of patients in the main group, different approaches to preoperative therapy (systemic or regional) and various regimens used. Another negative factor is that the analysis excluded patients who did not undergo the surgical phase after chemotherapy. Randomized trials are necessary to determine the rationality, as well as the type and regimen of preoperative therapy to be used in patients with IHCC.

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Гранов Д. А., Подлужный Д. В. – научное руководство;
Патютко Ю. И, Гранов Д. А., Поляков А. Н. – итоговые выводы.