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Drug-Induced Liver Injury and the Likelihood of Hepatocellular Carcinoma During Chemotherapy for Colorectal Cancer (Meta-Analysis)

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Tumor diseases are one of the leading causes of death worldwide. Neoadjuvant and adjuvant chemotherapy can potentially lead to drug-induced liver injury and carcinoma. According to the literature review and meta-analysis, the mean weighted incidence of drug-induced liver injuries for all drugs among patients receiving neoadjuvant chemotherapy for colorectal cancer with liver metastases is 63.2 %. The mean weighted incidence of severe liver injury is 37.2 %. However, we have not found clinical reports of liver carcinoma formation due to chemotherapy. At present, we can say that, despite the theoretical possibility, chemotherapy for colorectal cancer is not accompanied by the development of hepatocellular carcinoma.

Keywords: drug-induced liver injury, chemotherapy, oxaliplatin, irinotecan, colorectal cancer, hepatocellular carcinoma, meta-analysis

Conflict of interest: the authors declare no conflict of interest.

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Лекарственное повреждение печени и вероятность гепатоцеллюлярного рака на фоне химиотерапии колоректального рака (метаанализ)

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Опухолевые заболевания — одна из ведущих причин смерти в мире. Неоадъювантная и адъювантная химиотерапии потенциально могут вести к лекарственному поражению печени и карциноме. По данным обзора литературы и метаанализа, средняя взвешенная частота лекарственных повреждений печени для всех препаратов среди пациентов, получающих неоадъювантную химиотерапию по поводу колоректального рака с метастазами в печень, равна 63,2 %. Средняя взвешенная частота тяжелых поражений печени равна 37,2 %. Однако нами не было обнаружено клинических сообщений о формировании карциномы печени вследствие проведения химиотерапии. В настоящее время мы можем сказать, что, несмотря на теоретическую возможность, прием химиотерапии при колоректальном раке не сопровождается развитием гепатоцеллюлярной карциномы.

Ключевые слова: лекарственные поражения печени, химиотерапия, оксалиплатин, иринотекан, колоректальный рак, гепатоцеллюлярная карцинома, метаанализ

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Introduction

According to estimates from the World Health Organization, in 2019, cancer was one of the leading causes of death in over 100 countries [1]. Literature indicates that in 2020, there were 4.1 million new cases of malignant diseases and approximately 1.9 million deaths from them recorded in Europe alone [1]. The burden of morbidity and mortality from cancer is rapidly increasing

worldwide; this reflects both the overall growth and aging of the population and changes in the prevalence and distribution of major cancer risk factors, some of which are associated with socio-economic development [1]. It is projected that by 2040, there will be up to 28.4 million new cases of malignant diseases globally, which is a 47 % increase compared to 2020 [1]. Under these circumstances, the prevalence of chemotherapy as a treatment method is also expected to rise.

One of the side effects of chemotherapy is drug-induced liver injury [2–4], which can significantly impair the quality of life of patients and may also, presumably, lead to the formation of secondary tumors. For example, there is data on liver damage caused by chemotherapeutic agents such as oxaliplatin, irinotecan, and 5-fluorouracil; however, there are no quality literature reviews or other studies on this issue. Currently, there are also no publications describing cases of liver tumors arising against the backdrop of drug-induced injury from chemotherapeutic agents. There is little reliable data on their carcinogenic activity in the literature. Thus, precise data on the prevalence of liver injuries due to chemotherapy are lacking, although isolated cases of liver damage are mentioned in the literature. The question of the occurrence of secondary tumors due to drug-induced liver injury also remains unresolved.

The aim of this work: to identify and justify possible causes and mechanisms of carcinogenesis induction in the liver and to analyze the frequency of liver injuries during chemotherapy administration.

Materials and methods

To identify possible causes and mechanisms of carcinogenesis induction in the liver, we conducted a literature review on this topic. To determine the prevalence of drug-induced liver injuries (DILI) during chemotherapy, a meta-analysis of the literature was performed. Particular attention was focused on oxaliplatin (chemotherapy regimen Folfox6 and its modifications) and irinotecan (chemotherapy regimen Folfiri and its modifications), for which data on liver damage are available.

Tissue damage to the liver was understood as the following histopathological characteristics:

- signs of chronic liver inflammation (portal inflammation, inflammation without necrosis, partial necrosis, focal necrosis or acidophilia, moderate partial necrosis, severe focal cell damage, severe partial necrosis) [5];
- signs of changes in the hepatic architecture: fibrosis (enlarged fibrotic portal tracts, periportal or portal-portal septa without damaged lobular architecture, fibrosis with architectural distortions but without overt cirrhosis) [5];
- signs of hepatic architecture changes: micronodular, macronodular, mixed cirrhosis, incomplete septal cirrhosis;
- signs of hepatic architecture changes: dysplastic foci;
- signs of sinusoidal injury (sinusoidal obstruction syndrome, SOS);
- capillarization of non-tumorous liver parenchyma and sinusoidal capillarization [6].

The meta-analysis was conducted following the PRISMA guidelines [7]. Since no similar reviews had been previously performed, a comprehensive search of relevant publications was carried out without restrictions on publication date across electronic databases such as MEDLINE, PubMed, Google Scholar, and the Cochrane Central Register of Controlled Trials. The full search query in PubMed in English is as follows: ((“liver”[Mesh Terms] OR liver[Text Word]) AND damage[All Fields]) AND (drugs OR drug-induced OR medicament) AND (damage OR injury) AND ((“Chemotherapy, Cancer, Regional Perfusion”[Mesh]) OR chemotherapy [Text Word]). Full text of the search query in the Cochrane Controlled Trials Register in English: liver AND damage AND (drugs OR drug-induced OR medicament) AND (damage OR injury) AND Chemotherapy And Cancer.

Additionally, a search for publications was conducted in the Russian-language “Elibrary” database using the keywords “liver”, “drug-induced injury”, “chemotherapy”, and “cancer.” No relevant information on the topic under investigation was found in Russian databases.

The following data were extracted from the selected studies: authors, year of publication; study period, country, study design, study quality; type of cancer, chemotherapy protocol or drugs used; total number of patients, number of patients with drug-induced liver injury (DILI), type of liver injury, number of patients with severe forms of DILI (i.e., high-grade sinusoidal obstruction syndrome (SOS Grades 2/3), high-grade perisinusoidal dilation (Grade 3 — complete lobular or centrilobular damage extending to adjacent lobules), significant neutrophilic infiltration, nodular transformation, hepatocellular necrosis, perisinusoidal fibrosis, parenchymal liver fibrosis at stages F2–F4, severe steatosis (> 50 % of hepatocytes affected)); and number of patients with each histological type of severe DILI for each drug.

Inclusion criteria: quantitative analysis of patients with DILI; specification of the chemotherapy regimen or drug used; description of the histological features of liver injury.

Exclusion criteria: data duplication across studies; lack of methodology description; absence of chemotherapy protocol or drug information; absence of quantitative data; studies involving pediatric patients; clinical studies on DILI during chemotherapy in patients with pre-existing chronic liver disease; case reports.

Due to the dichotomous nature of the data in the publications (presence vs. absence of DILI), the overall value was expressed as odds ratio (OR) with 95 % confidence interval (95 % CI). As the factors influencing DILI occurrence were considered identical or similar across individual studies, we assumed homogeneity in outcome frequencies and selected a fixed-effect model for statistical analysis.

Statistical heterogeneity was assessed using the χ^2 test. A p-value < 0.1 and I^2 > 50 % were considered indicative of significant heterogeneity. Risk of bias across studies was visually assessed using funnel plots for each meta-analysis calculation. To estimate the overall frequency of liver injury more precisely, a weighted arithmetic mean was calculated. Statistical analyses were performed using Comprehensive Meta-Analysis (CMA) V3 software [8].

The quality of non-randomized studies was assessed using the Newcastle-Ottawa Scale (NOS) [9, 10]. A score of 7 out of 9 stars was considered indicative of high-quality research. Summary information from each included study was compiled into data tables.

Using the aforementioned search strategy, 533 publications were identified: 441 from MEDLINE, 92 from the Cochrane Central Register of Controlled Trials. Based on the inclusion and exclusion criteria, 8 publications were included in the analysis: 1 from MEDLINE, none from the Cochrane Register, and 7 identified via Google Scholar (Fig.).

Three studies employed prospective design, while five were retrospective. The studies were published between 2006 and 2013 and analyzed cases from 1998 through December 2011. All publications investigated the hepatotoxicity of drugs used in the treatment of colorectal cancer with liver metastases. A total of 1,959 patients were analyzed, of whom 1,162 received chemotherapy

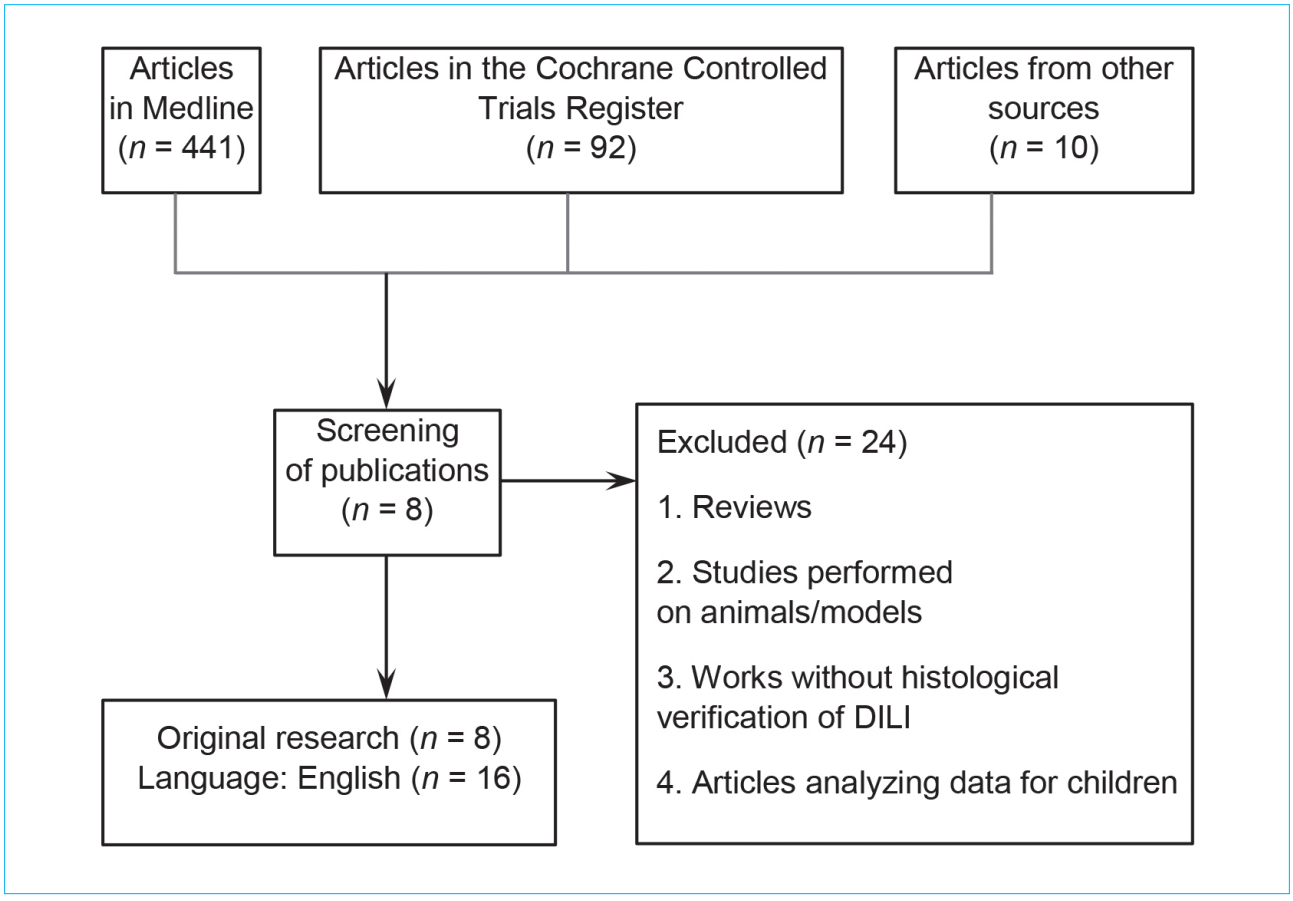

Figure. Article search and selection diagram
Рисунок. Диаграмма поиска и отбора статей

[6, 11–19]. Specifically: 864 patients were treated with oxaliplatin-based regimens, 170 — with irinotecan-based regimens, 44 — with combinations of oxaliplatin and irinotecan, 60 — with oxaliplatin and bevacizumab, and 24 patients received other regimens. A total of 626 patients did not undergo chemotherapy. At least 745 patients were reported to have liver injury of varying severity associated with chemotherapy (approximate figure due to the lack of clear data on the number of patients with liver injury in the study by D. Tamandl et al. [19]). Additionally, 171 chemotherapy patients were excluded from the study by L. Viganò et al. due to short treatment duration, incomplete chemotherapy data, lack of histological verification, or postoperative mortality [16]. All graphical figures and tables with meta-analysis results are available in the Appendix.

Drug-induced liver injuries

Drug-induced liver injury (DILI) refers to liver damage caused by the intake of pharmaceutical drugs, dietary supplements, psychoactive substances, or narcotics [20–22]. On average, DILI develops within 5 to 90 days of initiating the drug [20]. Currently, more than 1,000 agents are known to cause DILI [20]. The most common drugs associated with fatal outcomes due to DILI include analgesics (e.g., paracetamol, diclofenac), antiretroviral agents (e.g., lamivudine), anticonvulsants (e.g., valproic acid), antidiabetic drugs (e.g., troglitazone), antibiotics (e.g., amoxicillin/clavulanate), antineoplastic agents [2, 21, 23], and some monoclonal antibodies (e.g., infliximab), as well as immune checkpoint inhibitors [24]. The clinical spectrum of DILI is highly variable, ranging from transient elevations in liver enzymes to fulminant liver failure resulting in death [23].

Risk factors for DILI include advanced age, female sex, genetic predisposition, drug doses exceeding recommended limits, history of hypersensitivity reactions, concurrent use of multiple hepatotoxic drugs, excessive alcohol consumption, underlying liver disease, and other comorbidities [24].

Two main types of adverse drug reactions are currently recognized. Type A reactions are dose-dependent, predictable, and occur due to the direct toxic effect of the drug. They demonstrate a clear relationship with dose and duration of exposure [20]. Drugs causing type A reactions are toxic at threshold doses (e.g., paracetamol > 10 g/day) [20].

Most cases of DILI fall under type B reactions, which are dose-independent and unpredictable [20]. These reactions result from idiosyncratic mechanisms: either metabolic (due to genetic defects in biochemical or enzymatic pathways) or immunologic hypersensitivity [20, 25].

The liver's central role in xenobiotic metabolism is likely the key reason for its susceptibility to drug-induced damage [26].

After hepatic uptake, drugs undergo Phase I and Phase II enzymatic biotransformation [26]. Phase I metabolism is mediated by cytochrome p450 enzymes. Intermediate bioactive metabolites formed during this phase can damage intracellular organelles (e.g., mitochondria), leading to hepatocellular dysfunction and death [26, 27]. Mitochondrial dysfunction can result in necrosis rather than apoptosis of hepatocytes, thereby intensifying liver inflammation [28, 29].

These potentially toxic intermediates are detoxified in subsequent Phase II conjugation reactions [27]. Depletion or deficiency of conjugating agents may result in accumulation of toxic metabolites, as seen in alcohol-abusing patients taking paracetamol (type A, dose-dependent reaction) [27]. Covalent binding of reactive metabolites to cellular proteins can create immunogenic haptens, triggering immune responses [26].

These described reactions are characteristic of direct, dose-dependent hepatotoxicity. The mechanisms of indirect, idiosyncratic hepatotoxicity remain under active investigation. Genetic polymorphisms, in particular, may contribute to dysfunction of hepatic enzymes and transport proteins, increasing susceptibility to DILI and facilitating dose-independent reactions [22].

In 1993, the Council for International Organizations of Medical Sciences (CIOMS) proposed a classification of DILI based on biochemical parameters, later updated in the 2011 Consensus. According to this classification, three types of DILI are recognized: hepatocellular, cholestatic, and mixed injury [30].

Hepatocellular DILI is defined by alanine aminotransferase (ALT) levels greater than 2 times the upper limit of normal (ULN) or an ALT/alkaline phosphatase (ALP) ratio ≥ 5. This type of injury is generally more severe than the others [20], and clinically resembles viral hepatitis [20, 31]. Histologically, it may present as necrosis, steatosis, or both.

Cholestatic DILI is characterized by ALP elevation > 2 ULN or an ALT/ALP ratio ≤ 2 [20]. Clinically, it mimics extrahepatic obstructive jaundice [31, 32]. Histological patterns include hepatocanalicular (cholangiolytic) cholestasis or bland cholestasis [27, 31].

Mixed DILI is defined by ALT > 2 ULN and an ALT/ALP ratio between 2 and 5 [20]. Histologically, it presents as cholestasis with concomitant parenchymal injury [27].

DILI remains primarily a diagnosis of exclusion. Diagnosis is based on temporal association between drug intake and liver damage, along with the exclusion of alternative causes of liver disease [20, 25]. Symptoms are typically nonspecific and may include fever, nausea, vomiting, jaundice, dark urine, right upper quadrant pain or discomfort [20]. Immunologically mediated DILI features (e.g., fever, rash, facial edema, lymphadenopathy, eosinophilia, lymphocytosis, arthralgia) are seen in about 25 % of cases [26]. Liver enzyme levels have relatively low specificity and sensitivity for diagnosing DILI [25, 30, 32, 34].

Histopathological features of DILI

The most common histological presentation of DILI is acute hepatitis, with or without cholestasis [20]. Hallmarks of acute hepatocellular injury include portal and parenchymal inflammation, hepatocellular damage, and/or necrosis [20]. By definition, fibrosis is absent in acute DILI. Regenerative changes are frequently observed, such as binucleated hepatocytes and thickened hepatic cell plates [20]. Enlarged Kupffer cells are often present within the sinusoids. The term cholestatic hepatitis is used when these features are accompanied by cholestasis [20]. Acute hepatocellular injury may lead to necrosis affecting single hepatocytes (spotty necrosis) or groups of hepatocytes (confluent necrosis) [20]. In some cases, confluent necrosis may be zonal, which can aid in diagnostic interpretation [20]. Extensive confluent necrosis can result in acute liver failure [20]. In late-stage biopsies, the presence of numerous macrophages in the sinusoids is a helpful diagnostic clue indicating resolving hepatitis [35].

When DILI progresses to chronic hepatitis, its histological features become indistinguishable from those of chronic viral hepatitis, with potential progression to fibrosis or even cirrhosis [35]. Signs of acute hepatitis may still be present to varying degrees [35]. Drugs commonly associated with this histological pattern include chemotherapeutic agents such as 5-fluorouracil, tegafur, and tamoxifen [35].

Histopathological features of DILI induced by chemotherapeutic agents

According to the literature, DILI occurs in approximately 50 % of cases involving certain chemotherapeutic agents, particularly taxanes and platinum-based compounds [36]. In a 2012 study, sinusoidal obstruction syndrome (SOS) was reported in 39.8 % of patients undergoing chemotherapy for colorectal liver metastases [6].

Chemotherapy agents can induce hepatocellular injury, cholestasis, or mixed-type liver damage, as well as various forms of sinusoidal injury, including sinusoidal obstruction syndrome [37, 38]. SOS is associated with severe hepatic congestion and potentially fatal centrilobular hepatocyte necrosis [37, 38]. Specifically, in patients receiving neoadjuvant therapy for colorectal cancer, distinctive sinusoidal changes have been described. These include congestive sinusoidal dilatation predominantly in centrilobular zones (observed in 30–65 % of patients), perisinusoidal fibrosis (35–40 %), centrilobular fibrosis (30 %), and atrophy of hepatic cell plates [39]. Such lesions were not observed in the control group of patients who underwent hepatic resection without preoperative chemotherapy [39].

Chemo-radiotherapy regimens involving agents such as busulfan, cytarabine, cyclophosphamide, carmustine, mitomycin, 6-mercaptopurine, azathioprine, dacarbazine, and high-dose radiation are associated with a higher incidence of SOS [40, 41]. The frequency of SOS is also elevated in patients receiving oxaliplatin- or irinotecan-based chemotherapy in combination with 5-fluorouracil as adjuvant treatment prior to hepatic resection of colorectal metastases [40]. Histologically, liver tissue may show steatosis, centrilobular necrosis, and nodular regenerative hyperplasia [40]. Sinusoidal alterations may regress after cessation of chemotherapy; therefore, postponing surgery could be considered in patients with confirmed or suspected sinusoidal injury [40].

Hepatocellular carcinoma carcinogenesis

The development of hepatocellular carcinoma (HCC) is considered to be preceded by cirrhosis and chronic liver diseases (70–90 % of all cases) [42, 43]. Epidemiological data show that hepatocarcinogenesis is closely related to chronic liver damage [43]. One possible explanation for this close correlation is that the development of liver tumors requires the presence of dividing cells, which leads to the stepwise acquisition of genetic damage necessary for cellular transformation [43, 44]. Genetic changes include the activation of oncogenes, genomic instability due to DNA repair defects, chromosomal missegregation, increased expression of growth factors and angiogenesis, activation of telomerase, and others [45]. Alongside this, a certain influence is exerted by the individual genotype of enzymes that metabolize xenobiotics [45].

Another key link in the genetic changes underlying the formation of HCC is active inflammation with oxidative damage [45]. In this context, not only the degree of fibrosis that developed as a result of prolonged inflammation is important for the genesis of HCC, but also the severity

of inflammation [45]. Initially, foci of mild dysplasia are formed, gradually transforming into high-grade dysplasia, 30 % of which evolve into HCC over 5 years [45]. In fact, every patient with chronic liver disease has an increased risk of developing HCC, which depends on the etiology, duration of the disease, and its activity [45].

Possibility of hepatocarcinogenesis due to chemotherapy

Experiments on mice with a deficiency in hepatocytes of TGF-β-activated kinase 1 (TAK1) demonstrated that due to the gene deficiency, spontaneous death of hepatocytes, compensatory proliferation, infiltration of inflammatory cells, and perisinusoidal fibrosis were observed in 1-month-old mice [46]. In more mature mice, multiple tumor nodules developed, characterized by increased expression of fetal liver genes, including α-fetoprotein [46]. Thus, both chronic inflammation of liver tissue, potentially leading to fibrosis and cirrhosis of the liver, and damage to liver sinusoids may potentially be inducers of hepatocarcinogenesis [46].

Meta-analysis of the frequency of DILI during chemotherapy

Out of 1162 patients receiving chemotherapy, 745 had various DILI (64.9 %). According to the analysis, the average weighted frequency of DILI for all drugs among patients receiving chemotherapy is 63.2 %. When assessing the homogeneity of groups in the publications, significant biases were found ($p = 0.0000$). It is not possible to conduct a meta-analysis of the significance of chemotherapy for the formation of liver lesions indicated in the studies due to the fact that most studies lack control groups of patients who did not receive chemotherapy.

Meta-analysis of the frequency of severe DILI during chemotherapy and the significance of chemotherapy intake for the formation of severe liver pathology

We classified severe DILI as high-grade sinusoidal obstruction syndrome (SOS 2/3), high-grade perisinusoidal dilation (Grade 3 — complete involvement of lobes or centrilobular involvement extending to adjacent lobules), significant neutrophilic infiltration, nodular transformation, hepatocellular necrosis, perisinusoidal fibrosis, liver parenchyma fibrosis F2–F4, severe steatosis (affected > 50 % of hepatocytes).

Of the 1162 patients receiving chemotherapy, severe DILI y developed in 310 (26.7 %). Information on severe DILI is available in 6 out of 8 publications, with a total of 310/921 (33.6 %). According to the analysis, the average weighted frequency of severe DILI for all drugs among patients receiving chemotherapy is 37.2 %. When assessing the homogeneity of groups in the publications, significant biases were found ($p = 0.0000$).

At the same time, information on patients with severe liver pathology who did not receive chemotherapy is available in 4 out of these 6 publications. Cases of severe DILI against the background of chemotherapy — 260/772 (33.6 %), cases of severe liver pathology without chemotherapy intake — 20/573 (3.5 %). An analysis of the significance of the factor of chemotherapy intake for the formation of severe liver pathology was performed. When assessing the homogeneity of groups in the publications, significant biases were found ($p = 0.0000$).

Meta-analysis of the frequency of SOS 2/3 due to oxaliplatin intake and the significance of oxaliplatin intake for the formation of SOS 2/3

Among patients receiving oxaliplatin-based chemotherapy, SOS 2/3 occurs in 258/854 (30.2 %). Information is available in 4 publications. According to the data of these publications, among patients receiving oxaliplatin-based chemotherapy, SOS 2/3 occurs in 258/585 (44.1 %). According to the analysis, the average weighted frequency of SOS 2/3 among patients receiving oxaliplatin-based chemotherapy is 45.7 %. When assessing the homogeneity of the groups in the publications, significant biases were found ($p = 0.047$).

At the same time, information on patients who did not receive oxaliplatin-based chemotherapy and had SOS 2/3 is available in 2 of these 4 publications. According to the data of the above publications, there were 208/476 (47.7 %) cases of SOS 2/3 against the background of chemotherapy based on oxaliplatin, and 0/508 (0 %) cases of SOS 2/3 without the fact of taking chemotherapy. An analysis of the significance of the factor of taking chemotherapy based on oxaliplatin for the formation of SOS 2/3 was performed.

Meta-analysis of the incidence of high-grade perisinusoidal dilation due to oxaliplatin administration and the significance of oxaliplatin administration for the development of perisinusoidal dilation

Among patients receiving oxaliplatin-based chemotherapy, high (3rd) grade perisinusoidal dilation occurs in 120/854 (14.0 %) cases. Information is available in 3 publications. According to these publications, high (3rd) grade dilation occurs in 120/403 (29.8 %). According to the analysis, the

average weighted incidence of high perisinusoidal dilation among patients receiving oxaliplatin-based chemotherapy is 31.0 %. When assessing the homogeneity of groups in publications, significant biases were found ($p = 0.047$).

At the same time, information on patients who did not take oxaliplatin-based chemotherapy and had high-grade perisinusoidal dilation is available in 3 of 4 of these publications. According to the data of these publications, cases of high-grade perisinusoidal dilation against the background of oxaliplatin-based chemotherapy are 120/403 (29.8 %), cases of severe liver injuries without the fact of taking chemotherapy are 3/168 (1.8 %). An analysis of the significance of the factor of taking oxaliplatin-based chemotherapy for the formation of high-grade perisinusoidal dilation was performed. When assessing the homogeneity of the groups in the publications, significant biases were found ($p = 0.000$).

Meta-analysis of the incidence of perisinusoidal fibrosis due to oxaliplatin administration and the significance of oxaliplatin administration for the development of perisinusoidal fibrosis

Among patients receiving oxaliplatin-based chemotherapy, perisinusoidal fibrosis occurs in 38/854 (4.4 %) cases. Information is available in 3 publications. Among the patients described in these publications, perisinusoidal fibrosis occurs in 38/463 (8.2 %) cases. According to the analysis, the average weighted incidence of perisinusoidal fibrosis among patients receiving oxaliplatin-based chemotherapy is 10.0 %. When assessing the homogeneity of the groups in the publications, significant biases were found ($p = 0.000$).

At the same time, information on patients who did not receive oxaliplatin-based chemotherapy and had perisinusoidal fibrosis is available in 2 of 4 publications. Cases of perisinusoidal fibrosis against the background of oxaliplatin-based chemotherapy were 33/356 (9.2 %), cases of perisinusoidal fibrosis without the fact of taking chemotherapy were 0/146 (0.0 %). An analysis of the significance of the factor of taking oxaliplatin-based chemotherapy for the formation of perisinusoidal fibrosis was performed ($p = 0.006$).

Meta-analysis of the incidence of parenchymal fibrosis (F2–F4) due to oxaliplatin administration and the significance of oxaliplatin administration for the formation of parenchymal fibrosis

Among patients receiving oxaliplatin-based chemotherapy, parenchymal fibrosis (F2–F4) occurs in 37/854 (4.3 %) cases. Information is available in 2 publications. Among the patients described in these publications, parenchymal fibrosis (F2–F4) occurs in 37/129 (28.7 %) cases. According to the analysis, the average weighted incidence of parenchymal fibrosis (F2–F4) among patients receiving oxaliplatin-based chemotherapy for the formation of parenchymal fibrosis is 29.6 % ($p = 0.000$).

At the same time, information on patients who did not take oxaliplatin-based chemotherapy and had parenchymal fibrosis (F2–F4) is available in both publications. Cases of perisinusoidal fibrosis against the background of oxaliplatin-based chemotherapy are 37/129 (28.7 %), cases of parenchymal fibrosis (F2–F4) without the fact of taking chemotherapy are 7/146 (4.8 %). An analysis of the significance of the factor of taking oxaliplatin-based chemotherapy for the formation of perisinusoidal fibrosis was performed. When assessing the homogeneity of the groups in the publications, it was found that there are no significant biases ($p = 0.135$)

Meta-analysis of the incidence of severe liver steatosis due to oxaliplatin intake and the significance of oxaliplatin intake for the development of steatosis

Among patients receiving oxaliplatin-based chemotherapy, severe liver steatosis (damage to more than 50 % of hepatocytes) occurs in 28/854 (3.2 %) cases. Information is available in 3 publications. Among the patients described in these publications, severe liver steatosis occurs in 28/389 (7.2 %) cases. According to the analysis, the average weighted incidence of severe liver steatosis among patients receiving oxaliplatin-based chemotherapy is 8.7 %. When assessing the homogeneity of the groups in the publications, significant biases were found ($p = 0.000$).

At the same time, information on patients who did not receive oxaliplatin-based chemotherapy and had severe steatosis is available in all three publications. Cases of severe steatosis against the background of oxaliplatin-based chemotherapy were 28/389 (3.2 %), cases of severe steatosis without the fact of taking chemotherapy were 6/178 (3.4 %). An analysis of the significance of the factor of taking oxaliplatin-based chemotherapy for the formation of perisinusoidal fibrosis was performed.

Discussion

According to our literature review, such signs of liver tissue changes as fibrosis and vascular damage can become predictors of carcinogenesis and lead to the formation of primary liver tumors [47].

We also conducted a meta-analysis of the prevalence of drug-induced liver injury and the effect of taking the chemotherapeutic drug oxaliplatin on the development of liver pathology. The average weighted incidence of DILI for all drugs among patients receiving neoadjuvant chemotherapy for colorectal cancer with liver metastases was 63.2 %.

After taking chemotherapeutic drugs (oxaliplatin, irinotecan and others), patients may experience the following severe DILI: high-grade sinusoidal obstruction syndrome (SOS 2/3), high-grade perisinusoidal dilation, significant neutrophilic infiltration, nodular transformation, hepatocellular necrosis, perisinusoidal fibrosis, liver parenchymal fibrosis F2–F4, severe steatosis. The average weighted frequency of severe DILI for all drugs among patients receiving chemotherapy was 37.2 %.

According to the meta-analysis, taking oxaliplatin-based chemotherapy for colorectal cancer with liver metastases is significantly associated with the development of SOS 2/3, Grade 3 perisinusoidal dilation, perisinusoidal fibrosis, parenchymal fibrosis (F2–F4), severe steatosis.

According to the study results, oxaliplatin-based chemotherapy leads to the formation of SOS 2/3 in 45.7 % of cases, perisinusoidal dilatation of Grade 3 — in 31.0 % of cases, parenchymal fibrosis (F2–F4) — in 29.6 % of cases, perisinusoidal fibrosis — in 10.0 % of cases, severe steatosis — in 8.7 % of cases.

Study limitations

Thus, detection of liver cancer during chemotherapy is theoretically possible. However, no information was found to confirm this thesis, i.e., it was not possible to obtain clinical data on the formation of primary liver adenocarcinoma due to chemotherapy, in particular, based on oxaliplatin. Confirmation of this assumption is possible only with the publication of a report on clinical cases of hepatocellular carcinoma development in patients who underwent chemotherapy for colorectal cancer with metastases.

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