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Pre- or postoperative chemotherapy in patients with colorectal cancer with synchronous, resectable liver metastases?

Rafał Stec

At the moment, there is no clear scientific data on the use of preoperative chemotherapy in patients with colorectal, synchronous, resectable liver metastases. Below arguments are presented against the use of preoperative chemotherapy in the above clinical situation, based on an analysis of three issues: the toxicity of preoperative chemotherapy and associated perioperative complications, the efficacy of pre- and postoperative chemotherapy, doubts related to the use of preoperative chemotherapy. To summarise, most scientific data is against preoperative chemotherapy as it causes significant adverse effects (hepatotoxicity and consequent postoperative complications) without a significant improvement in survival rates. Therefore, postoperative chemotherapy in this group of patients seems to be the more optimal treatment.

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At the moment, there is no clear scientific data for the use of preoperative chemotherapy in patients with colorectal, synchronous, resectable liver metastases. Below arguments are presented against the use of preoperative chemotherapy in the above clinical situation based on an analysis of three issues:

a) the toxicity of preoperative chemotherapy and associated perioperative complications,
b) the efficacy of pre- and postoperative chemotherapy,
c) doubts related to the use of preoperative chemotherapy.

The toxicity of preoperative chemotherapy and related perioperative complications are important elements that should directly influence therapeutic decisions.

A retrospective study published in 2006 evaluated the hepatotoxicity of preoperative chemotherapy in patients at the University of Texas MD Anderson Cancer Center, who underwent liver resection due to metastatic lesions of colorectal cancer between 1992 and 2005. The analysis covered a total of 406 patients; 248 received preoperative chemotherapy (204 were originally resectable and 44 were originally non-resectable), while the comparative group consisted of 158 patients who underwent surgery without prior chemotherapy. Treatment according to schemes based on irinotecan was associated with an increase in hepatic toxicity in the form of *steatohepatitis*, 8,4% in the entire population; 20.2% vs 4.4% in the group without chemotherapy; p = 0.001; OR = 5.4; 95% CI 2.2–13.5), while the use of oxaliplatin with *sinusoidal dilation* (damage to liver venous sinus, 5.4% in the entire population; 18,9% vs 1.9% in the group without chemotherapy; p = 0.001; OR = 8.3; 95% CI 2.9–23.6), abnormalities in the liver venous sinuses. Patients with *steatohepatitis* (mainly those treated according to irinotecan chemotherapy schemes) revealed a higher risk of 90-day postoperative mortality compared to patients without *steatohepatitis* (14.7% vs 1.6%, respectively): p = 0.001; OR = 10.5; 95% CI, 2.0 to 36.4) [1].

In the systematic review (Lehamn et al. 2012), to which a total of 81 publications were classified (20 concerning the regression of metastatic lesions, 14 related to neoadjuvant chemotherapy in patients with potentially resectable metastases, 17 with hepatotoxicity of preoperative chemotherapy and 30 with complications after liver resection due

Department of Oncology, Medical University of Warsaw, Poland

to metastatic lesions), on the one hand, the lack of benefits in terms of survival improvement from preoperative chemotherapy in patients with resectable metastatic lesions was demonstrated, and on the other, a significant increase in hepatotoxicity of chemotherapy and the related risk of postoperative complications [2].

Another systematic review and meta-analysis (Robinson et al. 2012), comprising a total of 28 clinical trials, confirmed specific hepatic toxicity of oxaliplatin-based chemotherapy in the form of damage to venous liver sinuses of grade II or higher (RR = 4.36; 95% CI 1.36–13.97) and irinotecan--based chemotherapy as steatohepatitis (RR = 3.45; 95% CI 1.12–13.97). In their conclusions, the authors stressed a significant increase in the risk of liver damage associated with preoperative chemotherapy, which may have an adverse effect on hepatic functional reserve in patients with metastases of colorectal cancer to the liver that were removed through a resection of a significant volume of liver [3].

The above observations were confirmed in the retrospective analysis (Martis et al. 2016), to which finally 140 patients were classified (70 received neoadjuvant chemotherapy based on irinotecan, oxaliplatin and 5-fluorouracil with or without a biological agent and 70 without prior chemotherapy), who underwent resection of metastatic lesions from the liver. Multivariate analysis showed that venous sinus damage following chemotherapy was an independent cause of liver function disorders (p = 0.02) and liver-specific postoperative complications (p = 0.016) [4].

Another study indicating significant hepatic toxicity of preoperative chemotherapy is a systematic review (Zhao et al. 2017) in which 788 patients were included. The authors of the multivariate analysis confirmed that severe dilatation of venous sinuses (oxaliplatin treatment) was associated with an increase in the main prevalence (Clavien-Dindo classification of surgical complications, grades III-V [grade III — necessary surgical, radiological or endoscopic intervention, grade IV — life-threatening complications, grade V — patient's death]; OR = 1.73, 95% CI 1.02 to 2.95; p = 0.043), while steatohepatitis (treatment with irinotecan) correlated with an increase in postoperative complications such as ascites, postoperative liver failure, biliary "leakage", intra-abdominal abscesses, abdominal haemorrhaging, postoperative mortality (OR = 2.08, 95% 1.18 to 3.66; p = 0.012) [5].

In addition to toxicity, the second most important parameter of the planned therapy is the efficacy of pre- and postoperative chemotherapy, which should be assessed in the light of objective scientific evidence.

In the summary analysis of two randomised clinical trials (Mitry et al. 2008), in which 278 patients were included (138 in the group treated with adjuvant chemotherapy after surgical treatment and 140 in the group treated with exclusive surgical treatment), the impact of the use of adjuvant chemotherapy after the resection of metastatic lesions from the liver on survival rates was assessed. In the analysis of the whole population, patients with metastases ≤ 1 year in the group undergoing combined treatment accounted for 43.5%, and in the group with exclusive surgery for 42.9%. The median time of progression-free survival (PFS) was 27.9 months in the group with combined treatment and 18.8 months in the group with only surgical treatment (HR = 1.32; 95% CI, 1.00–1.76; p = 0.058), while the median time of overall survival was 62.2 months compared to 47.3 months respectively (HR = 1.32; 95% CI, 0.95–1.82; p = 0.095). Adjuvant chemotherapy has proven to be an independent lengthening factor for both PFS and OS, but with threshold significance. It is worth emphasising that the use of suboptimal chemotherapy containing 5-fluorouracil and folinic acid, but without oxaliplatin, is recommended. The addition of a third drug (oxaliplatin) might be associated with statistical significance [6].

An important publication (Gallagher et al. 2009), despite its retrospective nature (a retrospective analysis of 111 patients from the Memorial Sloan-Kettering Cancer Center [MSKCC] surgical register, whose data were collected prospectively), is an assessment of the efficacy (response to treatment) of neoadjuvant chemotherapy in OS in patients with colorectal cancer with synchronous, resectable metastases to the liver. A multidimensional OS model for liver resection contained the following independent, negative factors: presence of positive surgical margins (HR = 2.41, 95% CI, 1.06–5.47; p = 0.035), presence of metastases in initially removed lymph nodes (HR = 2.43, 95% CI, 1.08–5.51); p = 0.033) and post--resection level of CEA marker ≥ 5 ng/dL (HR = 2.51, 95% CI, 1.32–4.78; p = 0.005); however no correlation was found between OS and the response to neoadjuvant chemotherapy. The exclusion of this dependence may suggest the lack of benefits of its application before the surgical procedure and indicates the use of chemotherapy after surgical treatment [7].

Similar conclusions were reached by Nanji et al. (2013) in the retrospective analysis, in which 320 patients with resectable liver metastases were included (39.1% were patients with synchronous metastases). Multivariate analysis identified 4 factors that independently influence the OS: size of metastases > 6 cm (HR = 2.2, 95% CI, 1.3–3.5; p = 0.002), the presence of metastases in initially removed lymph nodes, trait N1 (HR = 2.0, 95% CI, 1.0–3.8; p = 0.045) and trait N2 (HR = 2.4, 95% CI, 1.2–4.9); p = 0.017), the presence of synchronous metastases (HR = 2.1, 95% CI, 1.3–3.5; p = 0.003) and chemotherapy after resection of metastatic lesions from the liver (HR = 0.42, 95% CI, 0.23–0.75; p = 0.004) [8].

Another published retrospective analysis (Faron M et al. 2014) presented the results of chemotherapy according to the FOLFOX program in the period preceding surgery or after the metastatic lesions resection from the liver. The analysis covered 179 patients, of whom over half were patients with the presence of synchronous metastases to

the liver (58%). In multivariate analysis, postoperative chemotherapy according to the FOLFOX programme proved to be an independent predictive factor for prolongation of both overall survival time (OS — overall survival; HR = 0.55 [95% CI, 0.35–0.87] p = 0.01] and disease free survival (DFS); HR = 0.54 [95% CI, 0.36–0.82] p = 0.0017). The use of preoperative chemotherapy according to the FOLFOX program did not result in a significant increase in vital parameters such as OS and DFS; OS (HR = 0.96 [95% CI, 0.57–1.6] p = 0.87) and DFS (HR = 1.05 [0.66–1.66] p = 0.83), respectively [9].

In a large, multi-centre, retrospective analysis of patients from the European Register (Bonney et al. 2015), whose data were collected prospectively, the efficacy of neoadjuvant chemotherapy in patients with colorectal cancer with synchronous resectable liver metastases was evaluated. Out of over eleven thousand patients, 1301 patients were analysed, divided into two groups: one receiving preoperative chemotherapy (693 patients) and one in which the patients were operated on without previous chemotherapy (608 patients). In multivariate analysis, the independent factors affecting OS deterioration were: trait N(+) > 1, the number of metastases above 3, the serum concentration of CEA above 5 ng/ml and the absence of adjuvant chemotherapy, while for DFS: trait N(+) > 1, serum concentration of CEA above 5 ng/ml and the absence of adjuvant chemotherapy. Summarising the obtained results, the authors have drawn a clear conclusion that preoperative chemotherapy does not have a positive effect on survival parameters in this group of patients [10].

The benefit of adjuvant chemotherapy was obtained by a retrospective analysis of patients (227 patients) from one of the centres (Nishioka et al. 2017), whose were also collected in a prospective manner. The patients were divided into 3 groups: with the presence of synchronous metastases of colorectal cancer to the liver, with "early" metachronous metastases to the liver (≤ 1 year) and patients with "late" metachronous metastases to the liver (> 1 year). The 5-year time of relapse free survival (RFS) in patients with or without adjuvant chemotherapy was 32.8 / 11.2% in patients with synchronous metastases, S-CLM (p = 0.002), 43.7 / 15.2%, respectively, in patients with early metachronous metastases that occurred ≤ 1 year, EM-CLM (p = 0.002), 44.1 / 29.6% in patients with metachronous metastases that occurred > 1 year, LM-CLM (p = 0.163). In turn, 5-year overall survival (OS) rates in patients with or without adjuvant chemotherapy was 77.9 / 45.5% in patients with synchronous metastases, S-CLM (p = 0.021), 81.5 / 39.5%, respectively, in patients with metachronous metastases that appeared ≤ 1 year, EM-CLM (p = 0.015), 76.1 / 65.4% patients with metachronous metastases that appeared > 1 year, LM-CLM (p = 0.411). The presented data show an improvement in the survival parameters of patients with synchronous and early metachronous metastases of colorectal cancer to the liver, but after chemotherapy adjuvant to the surgical procedure [11].

Improvement of survival parameters following adjuvant chemotherapy after preoperative chemotherapy and resection of mainly synchronous metastatic lesions from the liver (the majority of patients) was also observed in another retrospective analysis (Wang et al. 2017). The group of patients in whom postoperative treatment was applied, compared to the group of patients who were only followed up, obtained a significantly longer time to failure of treatment, as well as a longer overall survival time — median values, 10.2 months vs 3.3 months (p = 0.002) and 40.7 months vs 28.1 months (p = 0.005), respectively. These results confirm the value of postoperative chemotherapy as the leading systemic treatment method in patients after the resection of metastatic lesions from the liver [12].

In connection with the planning of chemotherapy treatment in patients with colorectal cancer, a number of doubts arise which cannot be ignored when planning treatment, especially as they may significantly affect the prognosis of patients. These are:

— delay in surgical treatment due to chemotherapy, which may result in the impossibility of technical removal of metastases after systemic treatment due to liver progression of metastatic lesions,
— primary chemoresistance and associated extrahepatic progression, excluding the resection of metastatic lesions from the liver,
— toxicity after chemotherapy, which makes it impossible to undergo surgery (especially the "aggravation" of significant coexisting diseases, "patient inoperable" due to general reasons),
— total regression of lesions in the liver after chemotherapy (also lesions not visible in preoperative imaging), making it impossible to identify their location and the excision of scars by the surgeon.

Summarising, at present there is no clear scientific evidence for the use of preoperative chemotherapy in patients with colorectal cancer with synchronous metastases to the liver, while postoperative chemotherapy seems to be more optimal in this group of patients.

Response

The effectiveness of neoadjuvant chemotherapy was summarised (Nigri et al. 2015) in a systematic review (meta-analysis could not be performed due to potential statistical errors caused by a variety of chemotherapy regimens used in pre- or postoperative treatment) in which the effectiveness of the therapy was compared in two groups of patients: those treated exclusively surgically with or without adjuvant chemotherapy (1785 patients) and those treated with chemotherapy before the surgery (1607 patients). The overall survival percentage in the group of patients treated surgically ranged from 20.7% to 56%, while in the group with neoadjuvant chemotherapy — from 38.9% to

Table I. Summary of studies assessing the efficacy of preoperative chemotherapy vs postoperative chemotherapy

Author/year	Number of patients	Type of study	Study groups
Mitry et al. 2008	278	Aggregate analysis of two randomised clinical trials	A group of patients treated in a combined manner (surgery + adjuvant chemotherapy) compared to the group undergoing surgical treatment only
Gallagher et al. 2009	111	Retrospective analysis	A group of patients treated with neoadjuvant chemotherapy
Nanji et al. 2013	320	Retrospective analysis	A group of patients with resectable hepatic metastases
Faron M et al. 2014	179	Retrospective analysis	A group of patients in whom chemotherapy was applied in the period preceding the surgical procedure or after the procedure of metastatic lesions resection from the liver
Bonney et al. 2015	1301	Retrospective analysis	A group of patients treated with neoadjuvant chemotherapy
Nigri et al. 2015	3392	Systematic review	A group of patients treated surgically only with or without adjuvant chemotherapy and a group treated with chemotherapy before surgery
Nishioka et al. 2017	227	Retrospective analysis	A group of patients treated with adjuvant chemotherapy
Wang et al. 2017	163	Retrospective analysis	A group of patients treated with adjuvant chemotherapy after preoperative chemotherapy and resection of metastatic lesions from the liver vs a group of patients that were only kept under observation

74%, without statistically significant differences in 7 out of 8 subjects included in the study review. The systematic review did not confirm the use of neoadjuvant chemotherapy in patients with colorectal cancer with resectable liver metastases [13].

ESMO recommendations (European Society for Medical Oncology), as well as the NCCN (National Comprehensive Cancer Network) prefer, in the case of resectable synchronous metastases to the liver, especially in the case of favourable prognostic factors, to perform surgery first (primary tumour resection and metastasectomy performed simultaneously or in stages), and then to use adjuvant chemotherapy [14, 15].

There is still the problem of a potentially resectable cancer. In the era of modern, contemporary diagnostics: a PET-CT, liver MRI or modern ultrasound, one can strictly select patients with metastases of colorectal cancer to the liver and classify them into two groups: resectable (and adjuvant chemotherapy) and unresectable, but then we use induction, and not neoadjuvant chemotherapy.

With modern diagnostics, which is necessary before making a decision on metastasectomy, we can reduce the risk of "unnecessary" operations and correctly qualify patients to the appropriate groups. This is confirmed by the lack of clear criteria defining metastases as "potentially" resectable.

Most of the scientific data is against preoperative chemotherapy, which has significant adverse effects (hepatotoxicity and consequently postoperative complications) without significant improvement in survival rates.

A list of studies evaluating the efficiency of preoperative chemotherapy against postoperative chemotherapy is given in Table I.

Conflict of interest: none declared

Rafał Stec, MD, PhD
Medical University of Warsaw
Department of Oncology
ul. Stępińska 19/25
00–739 Warszawa, Poland
e-mail: drrafals@wp.pl

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