

Preoperative chemotherapy in the colorectal cancer patients with synchronous metastases to the liver A vote for YES

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The increasing effectiveness of chemotherapy (cht) has led to a rise in interest in preoperative neoadjuvant treatment preceding resection of colorectal metastases. Preoperative chemotherapy is often undertaken as a method of natural evaluation of the progress of metastases before starting metastasectomy, in particular in patients with synchronous liver metastases. This method also has the potential of reducing potentially unresectable metastases and allowing for their safe resection. Optimal selection of patients, the choice of treatment regimen, and timing as well as the most beneficial method of integrating chemotherapy with the surgery has not been defined.

NOWOTWORY J Oncol 2018; 68, 5–6: 282–285

Key words: colorectal cancer, synchronous metastases, neoadjuvant chemotherapy

Introduction

With regards to the frequency of incidence, colorectal cancer ranks third, whilst the liver remains the most frequent location of metastases, affecting about 50% patients [1]. Currently the only potential possibility of cure is the resection of metastases, undertaken first of all in patients with isolated lesions in the liver. However, even after their complete resection and combining modern systemic treatment regimes, only in 20% of cases is the treatment radical, whereas in other cases the disease progresses. At the moment of diagnosing colorectal cancer, 20–25% have stage IV of the disease, including 15–20% patients with synchronous metastases, most frequently located in the liver [2].

Available literature presents at least a few definitions of synchronous metastases: most often they are defined as metastases which were diagnosed at the same time as the primary focus or in a short post-operative period. Irrespective of the treatment, the presence of synchronous liver metastases is an adverse prognostic factor resulting from an adverse cancer biology, and, in comparison with metachronous metastases, can be characterised with a shorter survival period and a larger rate of recurrence. These lesions are most frequently located in the liver which, among others,

may result from the fact that some micro-metastases have not been diagnosed earlier [3]. The rate of five and ten-year survivals after potentially radical metastases resection varies from 37% to 58% and from 20% to 25% respectively [4]. A much worse prognoses in patients with synchronous metastases in the liver can be caused by the delayed diagnosis of a primary tumour or more aggressive tumour biology.

Although the correct treatment of colorectal cancer patients with synchronous liver metastases poses a significant problem, there are no definite treatment guidelines. The majority of publications concerning this issue contain observational studies carried out on a relatively small group of patients or present systematic literature overviews. Significant heterogeneity and the small size of the studied group makes it difficult to create a clinical study which would provide an answer to the question about which of the chemotherapy forms (pre- or postoperative) is more efficient.

Preoperative (neoadjuvant) chemotherapy of synchronous liver metastases

The basic treatment standard for patients with synchronous liver metastases is surgical intervention, yet, at the moment of diagnosing, the majority of patients do not

qualify for surgery on account of the advanced stage of the metastases. Recent improvements in treatment results is both the outcome of better surgical techniques and more effective chemotherapy [5]. Current guidelines concerning metastases resection allow for the removal of all lesions with an appropriate margin (R0) and for conserving a functional part of the liver with a volume of at least 30%; at the same time, preoperative systemic treatment has been increasingly used [6]. The arguments for such strategy comprise first of all the elimination of all possible micro-metastases and a potential chance of cytoreduction making R0 resection possible. At the same time, preoperative chemotherapy allows for identifying those patients who do not respond to systemic treatment or in whose case progression occurs; subsequently intrusive and unnecessary surgery can be avoided. Moreover, during pre-operative chemotherapy lasting a few months, usually some chT, some so-called silent foci are revealed, which leads to a change in the treatment plan. The majority of authors also emphasise the possibility of evaluating the response to chemotherapy, which may have prognostic significance and be helpful in planning further treatment [7].

Combining surgery with chemotherapy has become a generally accepted therapeutic option, whilst the actual sequence of treatment is still widely debated. Randomised clinical trials carried out by the EORTC (European Organization for Research and Treatment of Cancer) have showed that peri-operative chemotherapy significantly prolongs disease-free survival and insignificantly increases overall survival [8].

During the preparation for the "Debates", my opponent and I adopted an assumption that the primary colorectal tumour had been removed in the first stage of the treatment in order to avoid cancer-related symptoms as the most probable source of the next metastases. The classical course of treatment in the majority of cases comprises neoadjuvant chemotherapy (3–6 months), which should be strictly controlled by imaging diagnostics. The objective of such a procedure is to decrease the metastases and increase the chance for R0 surgery. Such a course of action allows for the identification of those foci which do not respond to chemotherapy. The authors of the relatively "old" study from the Memorial Sloan-Kettering Cancer Center analysed the documentation of 330 patients with synchronous liver metastases [9]. Out of 106 patients with similar clinical characteristics, in whom the primary tumour was resected first, one half of the patients received neoadjuvant chemotherapy, whilst the rest underwent the resection of metastases within the period of 4 to 14 weeks of the removal of the primary focus; most of them received adjuvant chemotherapy afterwards. The rate of 5-year overall survival in the group receiving neoadjuvant treatment and adjuvant treatment was not statistically significant, totalling 43% and 35% re-

spectively ($p = 0.35$). A significant observation resulting from the discussed study was that the response to neoadjuvant surgery was a factor affecting the improvement of survival. The subgroup of patients in whom no progression occurred after neoadjuvant chemotherapy benefited significantly from the treatment with respect to OS in comparison with patients on adjuvant treatment (85% vs 35%, $p = 0.03$). The authors emphasised that in the high risk group, with a possible presence of occult metastases, the haste in deciding on a fast surgical intervention is not indicated because during the neoadjuvant chemotherapy some new metastases a fast progression of the ones already existing may be diagnosed or, thus allowing to avoid unnecessary surgery.

A retrospective Korean study evaluated the treatment results of patients with synchronous liver metastases, 53 patients received preoperative chemotherapy, whereas 96 were operated on first and then underwent chemotherapy [10]. The rate of the 3-year disease-free survival (DFS) in the group with preoperative chemotherapy and with surgery first was 31.7 and 20.4% respectively ($p = 0.015\%$), whilst there was no significant difference with regards to overall survival. In the second stage of the analysis, 32 pairs of patients with similar characteristics were selected from both groups; the DFS rate was significantly higher in the patients receiving preoperative chemotherapy (34.2% vs 16.8%, $p = 0.019$), whilst, likewise, no significant differences were found with regards to OS (74% vs 62.2%, $p = 0.244$). The authors of the study emphasise that in the case of multiple liver metastases, the identification of the patients responding to chemotherapy is as important as obtaining complete remission (CR). They believe that in such cases pre-operative chemotherapy is necessary, especially in cases where it is doubtful whether R0 resection is possible.

Another proposed treatment option for synchronous metastases was a three-stage procedure proposed by Mentha et al., addressed first of all to patients without any risk of potential significant conditions resulting from the primary focus and defined as "reversed" liver first resection [11]. The first stage of the treatment was chemotherapy (2–6 courses), then the resection of metastases from the liver and — after a few weeks — the resection of the primary focus. The response to systemic treatment was obtained in 80% patients and in more than a half the symptoms related to the primary tumour receded during chemotherapy. The rate of R0 resectability was 80%, whilst the OS rate in the first, second, third and fourth year was 85%, 79%, 71% and 56% respectively. Unfortunately, with regards to the small number of patients participating in this study, its value is quite limited.

In recent years, an increasing number of reports concerning the simultaneous resection of primary focus and liver metastases have been published; the objective of such treatment was to minimise the risk of progression and to

avoid two surgeries [12]. It must be taken into consideration, however, that an appropriate patient qualification is necessary for such procedures, and only well selected patients should be candidates for such treatment. It is possible to use both preoperative and post-operative chemotherapy, yet there are no direct studies comparing these two strategies.

A lot of information may be gained from a retrospective analysis carried out on the basis of a prospectively gathered database concerning the treatment strategies of patients with synchronous liver metastases [13]. The decisions concerning treatment have always been taken in multi-disciplinary team (MDT) discussions. The most significant characteristics determining the choice of the treatment were the location and the stage of the primary focus and metastases, and in the case of neoadjuvant chemotherapy — also the treatment response. Surgical options taken into consideration comprised the classical strategy (primary focus first and then the metastases), synchronous resection or the *liver first* option. More than 90% of patients received chemotherapy, out of which 73% — preoperative. The survival period of patients who received chemotherapy at any treatment stage, was 10 months longer than in the case of those who were not systemically treated. The median survival period for the classical and synchronic strategy was 40.3 and 12.5 months ($p = 0.021$); whilst for the reverse strategy no median was obtained. It must be stressed that the classical procedure was most frequently used, and only in a few patients was the decision taken to resect metastases at the first stage of surgical intervention. The authors of the study stressed that irrespectively of the selected surgical option, the treatment results seem to be promising and the results of the analysis that has been carried out point out that the presence of more than five metastases, an age of 60 years or above, and R2 resection, are all adverse prognostic factors.

It must be remembered that irrespectively of the choice of the treatment regimen, the duration of neoadjuvant chemotherapy should be limited and a radiological evaluation of the response should be performed every 6 weeks and surgery carried out as soon as the metastases turn out to be resectable. Some reports concerning the liver toxicity of preoperative chemotherapy (oxaliplatin, irinotecan) manifesting mostly as steatosis, nodular regenerative hypertrophy or cirrhosis, raise some concern [14].

These reports concern however not only preoperative treatment, but also adjuvant. Currently, it is believed that the best candidates for preoperative chemotherapy are patients with poorer prognostic factors and with threshold metastases [15].

Summary

Colorectal cancer patients with synchronous liver metastases make up a relatively narrow and heterogenous group that randomised clinical trials which could provide an answer to the question whether pre-operative or post-op-

erative chemotherapy is more efficient, may not only be impossible but also unethical. The choice of the appropriate treatment option is determined by many variables which could significantly affect treatment decisions. That is why, the solution to this problem lies, in my opinion, in the creation of multidisciplinary teams taking individual therapeutic decisions, as already happens in other countries.

To generalise, without taking into consideration an individual approach to the patient, it can be observed that more benefits lie in neoadjuvant than adjuvant therapy, as the preoperative chemotherapy allows for:

1. the elimination of micro-metastases and the reduction of cancer foci, thus increasing the chances of R0 resection;
2. the possibilities of evaluating the treatment response, which might have prognostic significance and be helpful in treatment planning;
3. the identification of patients who do not respond to chemotherapy or those where progression occurs, which allows for the avoidance of surgery;
4. the delay of metastases resection by 3–6 months (for the period of the duration of chemotherapy), which makes it possible to reveal clinically silent foci.

At the same time, the concern that preoperative chemotherapy might result in the fact that resectable lesions may become nonresectable is not justified. It must be stressed that preliminary chemotherapy improves the selection of patients for the resection of liver metastases.

Conflict of interest: none declared

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Received & Accepted: 10 Sept 2018

Based on a presentation at the VI Annual Conference of the *Nowotwory Journal of Oncology*, 'Oncological Debates', held in Warszawa, 6–7th April 2018

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