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Editorial

Neoadjuvant chemotherapy for unresectable liver metastases of colorectal cancer – too good to be true?

At present, surgery is the only curative treatment for liver metastases from colorectal cancer. Five-year survival has been 20%–45% after hepatic resection in the largest series published to date [1]. Extent and location of the metastases determine resectability and presence of extrahepatic disease is a strong prognostic factor for poor outcome [1], although the resection of synchronous lung metastases is possible in selected patients [2, 3]. Liver metastases from other primary tumor sites are generally a reflection of disease dissemination and surgery is not considered a curative treatment option anymore in these cases. The situation is different with colorectal cancer, where the portal venous drainage system favors metastases to the liver without systemic dissemination. In addition, metastatic inefficiency leads to the destruction of a majority of metastatic deposits within blood vessels or lymphatic channels and has been taken as an explanation for the confined metastastic potential of colorectal cancer [4].

Liver involvement is an important problem in colorectal cancer, which is present in 40%–70% of patients with metastatic disease. However, the liver is the sole site of metastases in only about half of the cases [5–7]. Stangl et al. determined the natural history of colorectal liver metastases in a recent prospective series on 1099 patients. Thirty-one percent of the patients underwent liver resection and complete tumor clearance was achieved in 78% of those cases. The five-year survival was 32% after hepatic resection. In contrast, if surgery was not possible the median survival of patients receiving chemotherapy or no treatment was 12 and 7.5 months, respectively [8]. It can be concluded from this and other large series, that unresectable liver metastases from colorectal cancer are nearly always fatal within five years [5]. After liver resection, about 40% of the recurrences seem again confined to the liver [1] and a three-year survival of 33% has been reported in this situation [9]. However, more often relapses occur outside the liver. This underlines the need for better diagnostic tools to screen patients for extrahepatic disease before surgery. Promising options are whole-body positron emission tomography with (fluorine-18)-2-fluoro-2-deoxy-D-glucose [10] or the detection of genetic material of micrometastases by molecular amplification methods [11]. Despite the fact, that adjuvant chemotherapy has been proven very successful in primary colorectal cancer [12], there is only recent evidence of a benefit after liver surgery [13, 14].

Clinical prognostic factors are of limited practical use to select suitable patients for hepatic resection, which have a low risk for extrahepatic disease. Fong et al. identified positive resection margin, size greater than 10 cm, disease-free interval less than 12 months, multiple tumors, and extrahepatic disease as independent predictors of poorer outcome by multivariate analysis [1]. However, a good outcome was possible even in the presence of poor prognostic factors and it is doubtful whether individual patients should be precluded from surgery on the bases of prognostic factors alone. Taking all these uncertainties into consideration, it is fortunate, that the growing expertise in hepatic surgery has helped to bring down the mortality rate of this procedure close to zero [1, 15, 16]. In experienced centers, the choice of hepatic resection is rarely a fatal decision these days.

What can we offer, if liver metastases from colorectal cancer are not resectable in the first place? The standard approach in this situation is systemic chemotherapy, which is based on fluorouracil since more than four decades. Treatment with fluorouracil alone has resulted in response rates of about 10% as demonstrated by the results of two meta-analyses [17, 18]. Among all chemotherapy combinations in clinical use, only biomodulation of fluorouracil with leucovorin or methotrexate has translated into significantly higher response rates (19%–23%) and prolonged survival compared to fluorouracil alone [17–20]. On the background of such modest results, the pessimistic attitude of the medical community towards the treatment of advanced colorectal cancer is understandable [21].

Only recently, new and exciting treatment options have become available for colorectal cancer. Irinotecan and oxaliplatin, two drugs, which are unrelated to fluorouracil, have shown clear activity even after failure of fluorouracil [22, 23]. Oxaliplatin, a 1,2-diaminocyclohexane platinum compound, has demonstrated reproducible synergistic activity with fluorouracil. In non-pretreated patients, oxaliplatin with fluorouracil and leucovorin has resulted in response rates from 34% to 67% [23]. This treatment combination has also been used to test the exciting concept of chronomodulation, which is based on the observation that the differential proliferative activity of normal and tumor cells as well as the metabolic (de)activation of drugs is subjected to circadian rhythms [24]. Higher doses can be given, if drug delivery is adjusted to the circadian rhythm of tissue tolerability. In a randomized study in metastatic colorectal cancer, patients treated with chronomodulated chemotherapy with oxaliplatin, fluorouracil, and leucovorin achieved a significant benefit in terms of response rate (51% *versus* 29%), toxicity, and median time to treat-

ment failure compared to constant-rate infusion of the same drugs. The fact, that a higher dose intensity for both fluorouracil and oxaliplatin could be achieved in the chronotherapy arm is possibly responsible for the better antitumor effect compared to constant-rate infusion [25].

Having this potent chemotherapy regimen at hand, a group of expert chronotherapists and liver surgeons developed a novel neoadjuvant treatment concept for unresectable liver metastases from colorectal cancer. The paper of Giacchetti et al. in this issue reports their experience with a median follow-up of 5.5 years [26]. Treatment with mostly chronomodulated oxaliplatin, fluorouracil, and leucovorin resulted in a response rate of 59% and most of these patients (78%) could be resected with tumor-free resection margins. The estimated five-year survival after neoadjuvant chemotherapy and surgery was 58%. The prognostic importance of resectability is underlined by the results of the multivariate analysis and the fact, that the median survival was 15.5 months in non-operated patients, while it has not been reached yet in the resected group. A median of 5.5 months of chemotherapy was necessary to achieve optimal preoperative tumor reduction. In four cases, pathologically complete responses occurred. Thirty-one percent of all patients screened for surgery could be radically resected. 20% of the resected patients did not relapse, whereas the exact timeframe of this observation is not given. Relapses occurred early, after a median time of 12 months with a range of 9–16 months. In a third of the relapsed patients repeat hepatic resection was possible for recurrences confined to the liver.

The interpretation of a retrospective series such as the one by Giacchetti et al. [26] is a teaching exercise for all sorts of traps and biases, the thourough discussion of which would be all too nit-picking in view of the novelty of the concept of neoadjuvant chemotherapy in colorectal cancer. The bottom line, however, is whether we can trust the initial surgical assessment of resectability. Obviously, if resectable liver metastases would have been erroneously declared inoperable at first assessment, this study could easily turn meaningless. Fortunately, the surgeons involved in the study belong to the leaders in their field and the chance of misjudgement is remote. Still, the initial resectability must have been on the edge in some cases, since 16 patients turned resectable after only minor (25%–49%) responses to chemotherapy and 6 even after less than 25% tumor reduction. There is also the question of selection bias, since only 35% of the patients had $\geqslant 25\%$ liver involvement. The extent of hepatic replacement by tumor is the most important determinant for survival in colorectal cancer metastatic to the liver [8, 27] and relatively low-risk patients might have been preferentially included in this study. However, even these caveats in mind, the five-year survival reported in this paper is very impressive compared to other series on patients with inoperable liver metastases [5, 8, 27]. On the background of the generally sombre outlook for patients with inoperable liver metastases from colorectal cancer, already the message, that better prognosis patients can be selected, is a promising message.

Where can we go from here? Before neoadjuvant chemotherapy can be adopted as standard treatment for unresectable colorectal cancer liver metastases, it would be helpful to have results from prospective series and data from independent centers. The authors of such series should not hesitate to give a detailed listing of the number, size, location and reason for unresectability for each liver metastasis in addition to response to chemotherapy and long-term outcome after resection. We need information, whether chemotherapy can 'cure' individual metastases or increases resectability only by allowing wider resection margins because of tumor shrinkage. If complete and durable pathological responses can be induced in individual metastases, it might be possible to limit the resection to metastatic sites, which persist after chemotherapy. This should further increase the rate of technically resectable patients. A recent case report has demonstrated complete disappearance of liver metastases after hepatic arterial infusion chemotherapy alone without evidence for relapse after more than eight years [28]. The usual call for a large randomized phase III study must probably go unheard for liver resection after neoadjuvant chemotherapy, since it will never be possible to perform a trustworthy trial in view of the inherent methodological problems. It would be difficult and probably unethical to convince a patient in the control arm of such a study to leave potentially resectable metastases after chemotherapy unresected. In addition, surgical expertise is nearly impossible to control for as has shown a recent study assessing the value of extended lymph-node dissection for gastric cancer [29].

How can we optimize neoadjuvant chemotherapy? The optimal dose, schedule, and combination of oxaliplatin, irinotecan, and fluorouracil plus leucovorin, the presently most effective drugs in colorectal cancer, will have to be assessed. Neoadjuvant treatment should also bring the concept of hepatic arterial infusion (HAI) to a reappraisal. One of the important rationales for HAI is the fact, that liver metastases derive their blood supply mainly from the hepatic artery, while normal liver parenchyma is supplied predominantly by the portal vein [30]. HAI with fluoropyrimidines alone has led to much higher (41% *versus* 14%) response rates in the treatment of nonresectable liver metastases compared to intravenous treatment [31]. In addition, the systemic toxicity of chemotherapy can be diminished by HAI and the dose intensity can be improved due to the metabolic function of the liver. Despite these obvious merits, the role of HAI in the treatment of colorectal cancer has remained controversial since a clear survival benefit compared to systemic treatment could not be demonstrated [31]. However, for the purpose of selecting a useful neoadjuvant chemotherapy regimen, response rate rather than survival should be the primary endpoint. Chemoembolization exploits the predominantly arterial blood supply of liver metastases even further, since it combines chemotherapy with the ischemic effect of vascular occlu-

sion, but this approach can be associated with considerable liver toxicity [32]. For drugs with a dose-response relationship and a high potential of systemic toxicity, isolated perfusion of the liver is an option, which allows to give as much drug as can be tolerated by the normal liver parenchyma without systemic exposure [33]. In addition to conventional drugs, biomolecules with cytotoxic potential or with chemosensitizing properties such as vectors containing wild-type *p53* will also be ready for regional administration through the hepatic artery in the near future [34].

With this multitude of neoadjuvant treatment options for liver metastases, resources will have to be allocated wisely. Rather than spending hundreds of patients on a non-conclusive randomized study with an arbitrary experimental arm, well performed phase II trials should be encouraged with detailed description of disease parameters and long-term outcome. Giacchetti et al. can take credit for providing the participation in such studies with the incentive of five-year survival [26].

M. M. Borner
Institute of Medical Oncology
Inselspital
Bern, Switzerland

References

1. Fong Y, Cohen AM, Fortner JG et al. Liver resection for colorectal metastases. J Clin Oncol 1997; 15: 938–46.
2. Smith JW, Fortner JG, Burt M Resection of hepatic and pulmonary metastases from colorectal cancer. Surg Oncol 1992, 1: 399–404
3. Lehnert T, Knaebel HP, Duck M et al. Sequential hepatic and pulmonary resections for metastatic colorectal cancer. Br J Surg 1999; 86. 241–3.
4. Sugarbaker PH. Metastatic inefficiency: The scientific basis for resection of liver metastases from colorectal cancer. J Surg Oncol 1993; 3 (Suppl): 158–60.
5. McMasters KM, Roh MS. Surgical treatment of hepatic metastases. In Lotze MT, Rubin JT (eds): Regional Therapy of Advanced Cancer. Philadelphia: Lippincott-Raven Publishers 1997, 99–117.
6 Foster JH, Lundy J. Liver Metastases. Curr Probl Surg 1981; 18: 157–202.
7. Gilbert HA, Kagan AR. Metastases: Incidence, detection, and evaluation without histologic confirmation. In Weiss L (ed): Fundamental Aspects of Metastasis. Amsterdam: North-Holland 1976; 385–405.
8. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet 1994: 343: 1405–10.
9. Nordlinger B. Vaillant JC, Guiguet M et al. Survival benefit of repeat liver resections for recurrent colorectal metastases: One hundred forty-three cases. J Clin Oncol 1994; 12: 1491–6.
10. Flamen P. Stroobants S, Van Cutsem E et al. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. J Clin Oncol 1999; 17: 894–901.
11. Mori M. Mimori K, Ueo H et al. Clinical significance of molecular detection of carcinoma cells in lymph nodes and peripheral blood by reverse transcription-polymerase chain reaction in patients with gastrointestinal or breast carcinomas. J Clin Oncol 1998; 16: 128–32.
12. Midgley R, Kerr D. Colorectal cancer. Lancet 1999: 353: 391–9
13. Kemeny N. Cohen A, Huang Y et al. Randomized study of hepatic arterial infusion and systemic chemotherapy *versus* systemic chemotherapy alone as adjuvant therapy after resection of hepatic metastases from colorectal cancer. Proc ASCO 1999: 18: 1011.
14. Kemeny MM, Adak S, Lipsitz S et al. Results of the Intergroup (Eastern Cooperative Oncology Group and Southwestern Oncology Group) prospective randomized study of surgery alone *versus* continuous hepatic artery infusion of FUDR and continuous systemic infusion of 5-FU after hepatic resection for colorectal liver metastases. Proc ASCO 1999; 18: 1012.
15. Rees M, Plant G, Bygrave S. Late results justify resection for multiple hepatic metastases from colorectal cancer. Br J Surg 1997; 84· 1136–40.
16. Taylor M, Forster J, Langer B et al. A study of prognostic factors for hepatic resection for colorectal metastases Am J Surg 1997; 173: 467–71.
17. Advanced Colorectal Cancer Meta-Analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. J Clin Oncol 1994; 12. 960–9.
18. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: Evidence in terms of response rate. J Clin Oncol 1992; 10. 896–903
19. Borner MM, Castiglione M, Bacchi M et al. The impact of adding low-dose leucovorin to monthly 5-fluorouracil in advanced colorectal carcinoma: Results of a phase III trial. Ann Oncol 1998; 9. 535–41.
20 Poon MA, O'Connell MJ, Wieand HS et al. Biochemical modulation of fluorouracil with leucovorin· Confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. J Clin Oncol 1991; 9: 1967–72.
21. Blijham GH, Labianca R, Bleiberg H. Should patients with advanced colorectal cancer be treated with chemotherapy? Eur J Cancer 1997; 33: 815–24.
22. Cersosimo RJ. Irinotecan. A new antineoplastic agent for the management of colorectal cancer. Ann Pharmacother 1998; 32: 1324–33.
23. Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: A review of preclinical and clinical studies. Ann Oncol 1998; 9: 1053–71.
24. Lévi F, Giacchetti S. Chronomodulation of chemotherapy against metastatic colorectal cancer. In Bleiberg H, Rougier P, Wilke H-J (eds): Management of Colorectal Cancer. London: Martin Dunitz Ltd 1998; 289–306.
25. Lévi F, Zidani R, Misset JL. Randomised multicentre trial of chronotherapy with oxaliplatin, fluorouracil, and folinic acid in metastatic colorectal cancer. Lancet 1997, 350: 681–6.
26. Giacchetti S, Itzhaki M, Gruia G et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 1999; 10 (6): 663–9 (this issue).
27. Lahr CJ, Soong SJ, Cloud G et al. A multifactorial analysis of prognostic factors in patients with liver metastases from colorectal carcinoma. J Clin Oncol 1983; 1: 720–6.
28. Hanazaki K, Kawamura N, Wakabayashi M et al. Long-term survivor with liver metastases from rectal cancer treated by hepatectomy after hepatic arterial infusion chemotherapy. Hepatogastroenterology 1998; 45: 816–20.
29. Brennan MF. Lymph-node dissection for gastric cancer. N Engl J Med 1999; 340: 956–8.
30. Ridge JA, Bading JR, Gelbard AS et al. Perfusion of colorectal hepatic metastases. Relative distribution of flow from the hepatic artery and portal vein. Cancer 1987: 59: 1547–53.
31. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. Meta-Analysis Group in Cancer. J Natl Cancer Inst 1996; 88: 252–8.

32. Borner M, Castiglione M, Triller J et al. Considerable side effects of chemoembolization for colorectal carcinoma metastatic to the liver. Ann Oncol 1992; 3: 113–5.
33. Rougier P. Are there indications for intraarterial hepatic chemotherapy or isolated liver perfusion? The case of liver metastases from colorectal cancer. Recent Results Cancer Res 1998; 147: 3–12.
34. Anderson SC, Johnson DE, Harris MP et al. *p53* gene therapy in a rat model of hepatocellular carcinoma: Intra-arterial delivery of a recombinant adenovirus. Clin Cancer Res 1998; 4: 1649–59.

Book review

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Molecular biology of B-cell and T-cell development. J. G. Monroe, E. V. Rothenberg (eds). Humana Press Inc., Totowa, NJ, USA, 1998. 601 pp, $125.00.

In recent years, our knowledge concerning the ontogeny of B and T cells has greatly expanded. New information about lymphocyte development has had a significant impact on our understanding of human cancer and on the design of novel therapeutic approaches. Cell surface markers allow us to identify many of the steps in lymphocyte development, and molecular biology provides the techniques for studying the weight of single-gene products along this pathway. All of the new biological data emphasize that lymphomas, which derive from the neoplastic transformation of lymphocytes at different stages of maturation, are necessarily a heterogeneous group of diseases.

The book edited by Monroe and Rothenberg gives us a detailed overview of the ontogeny of B and T cells. Its first 24 chapters cover the development of lymphocytes, explaining the role of different transcription factors, and describing interactions among hematopoietic cells and microenvironmental factors (non-hematopoietic cells, cytokines, extracellular matrix) and systemic factors, such as the endocrine system. The final three chapters provide examples of the clinical application of the new knowledge: stem cell transplantation for hematopoietic neoplasms, possible uses of placental blood and gene therapy for immunologic disorders.

References are plentiful and updated to 1997. My major criticism of the book is that it covers almost exclusively the early phases of B- and T-cell development while excluding any discussion of the features of peripheral lymphocytes.

'Molecular biology of B-cell and T-cell development' can unequivocally be recommended to people involved in the study of lymphocytes and lymphoma research. The topics covered in this volume provide a comprehensive view of the most relevant advances in the field. However, if a clinician is seeking an introduction to the molecular mechanisms underlying lymphomas, this book should not be his or her first choice; for that purpose it is too complex and basic research-oriented.

F. Bertoni
Bellinzona