Objectives of chemotherapy for unresectable liver metastases: Best response or resection?

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Introduction

Preoperative neoadjuvant combination chemotherapy regimens, namely FOLFOX (5-fluorouracil, folinic acid [leucovorin], oxaliplatin) and FOLFIRI (5-fluorouracil, folinic acid [leucovorin], irinotecan [Camptosar]), are now recognised to facilitate the downsizing of colorectal liver metastases and render initially unresectable metastases resectable [1–5]. The addition of targeted therapies [6–11] or a third cytotoxic drug to these standard combination therapy regimens [12–15] might render the treatments even more efficacious in this clinical setting. In addition, advances in surgical techniques have led to changes in the criteria for resectability. Today, the requirement for the liver remnant to be equivalent to 30% of the original liver volume is considered the most critical factor [16]. Even the presence of extrahepatic disease no longer automatically excludes surgery, provided that it is also resectable [17].

The combined effect of more active chemotherapy and better surgical techniques has had three consequences. First, the percentage of patients eligible for potentially curative liver resection is increasing [18]. Secondly, stage IV classification appears today as an oversimplification, because stage IV patients are too heterogeneous; while the American Joint Committee on Cancer (AJCC) classification is appropriate for stages I, II and III, a new staging system for stage IV is needed taking into account the potential different therapeutic strategies [19].

Thirdly, finding the most appropriate end-point for those patients whose liver metastases may become resectable is a real challenge in clinical trial design. Overall survival, although the most objective end-point, is a very long-term end-point for neoadjuvant treatment of stage IV disease and can be influenced by many other factors; therefore it does not seem appropriate as a primary end-point in this type of study. Resectability could become a new end-point for assessing the efficacy of neoadjuvant treatment, both in clinical trials and in practice. However, the indications for resection may also be biased, depending not only on the patient and the metastases, but also on the skill and aggressiveness of the surgeon.

All these points make the trials in this setting terribly difficult, and even clinical practice suffers from this difficulty in identifying a clear objective for neoadjuvant treatment. In order better to understand what we should pursue in clinical practice as well as in future clinical trials we need to return to the basic drive for prescribing chemotherapy in the advanced stages of this disease.

Objectives of chemotherapy: what we really want from the treatment of stage IV disease

Whenever we prescribe chemotherapy for the advanced stages of colorectal cancer, we do not pursue the average demonstrated benefit of that treatment, but we hope that the specific patient we are dealing with will benefit much more than the average patient. That is to say that we pursue complete responses, resectability of unresectable liver metastases and potential cures. We fully acknowledge that these end-points are very ambitious and that only a minority of patients will achieve them. However, this is the real drive for prescribing (and accepting) chemotherapy.

In this connection, the answer to the question ‘best response or resection’ is neither of these: in fact, best response and resection by themselves mean very little. As we will see, obtaining an objective response or tumour shrinkage to the point where we can surgically resect the tumour are not ambitious enough end-points to pursue (in the light of the cost and morbidity of the combined approaches) and may be misleading, particularly in clinical trial design.

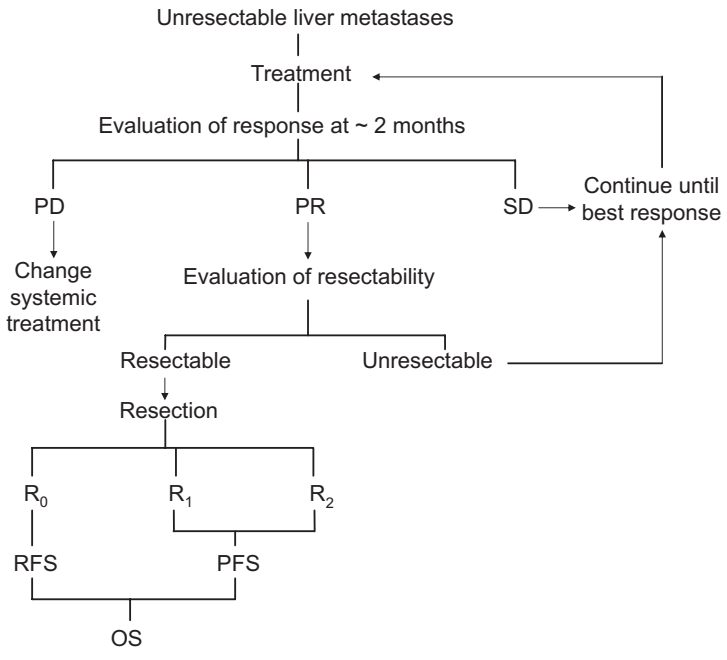

Fig. 1. Phases, end-points and strategies of neoadjuvant treatment of unresectable liver metastases. PD, progressive disease; PR, partial response; SD, stable disease; RFS, relapse-free survival; PFS, progression-free survival; OS, overall survival.

The relevance of resecting liver metastases with or without neoadjuvant chemotherapy

While resection of easily resectable liver metastases has long been accepted as part of the standard management of stage IV disease, resection of initially unresectable liver metastases has become one of the most popular topics of discussion in only the last 2–3 years. The appeal of the topic lies in the fact that resection may be considered as an end-point in itself, that the final result (radical resection) is highly relevant for the patients, and that it involves multidisciplinary management of the patients, universally considered essential.

Apart from the obvious emotional impact of being in a 'no evidence of disease' (NED) state after resection, the relevance of resecting liver metastases comes from the observation that the longest survival times in patients with stage IV colorectal cancer can be achieved only when the disease can still be radically resected. Remarkably, patients undergoing liver metastasis resection have a 5-year survival rate of up to 35%, with a median survival ranging from 33 to 46 months, at the cost of a peri-operative mortality rate as low as 1–2% [20–22]. Moreover, long-term survival rates are also possible in patients undergoing surgery after neoadjuvant chemotherapy [23]. Thus the current emphasis on this topic is more than justified.

Potential objectives of chemotherapy for unresectable liver metastases

The title of this paper anticipates two objectives of neoadjuvant chemotherapy for unresectable liver metastases: best response or resection.

Resection of initially unresectable liver metastases, by definition, transits through substantial tumour shrinkage, i.e. a very good objective response. Thus, the two end-points (response and resection) are in sequence, as illustrated in the algorithm of Fig. 1. However, only a minority of these patients will ultimately become candidates for radical surgery upon neoadjuvant chemotherapy. Indeed, it is likely that, out of 100 patients starting chemotherapy for unresectable liver metastases, 10–20 will progress and another 50–70 will never become resectable. Thus only 10–30% of initially unresectable lesions will undergo surgery. In these cases, the most relevant goal becomes R0 (complete) resection, even though a substantial fraction of patients will have micro- (R1) or macroscopic (R2) residual disease (Fig. 1). As we will see, however, even more relevant is the duration of the relapse-free survival (RFS).

Resectability as an objective

There are two major limitations in using resectability as a measure of success: (i) the difficulty of defining

clearly non-resectable liver metastases at baseline, and (ii) the subtle border between a 'feasible' resection and an 'oncologically sound' resection.

The difficulty of defining clearly non-resectable liver metastases at baseline

The definition of resectability suffers from bias. In fact, liver metastases that are clearly unresectable for one surgeon may be resectable for another.

The major problem in interpreting the results of all phase II studies of preoperative chemotherapy in stage IV colorectal cancer is that they have been performed on a category of patients that is not clearly defined: those 'potentially resectable' [24,25].

Furthermore, in conditions where substantial tumour shrinkage has been obtained by preoperative chemotherapy, the enthusiasm may push the surgeon to attempt a resection where indeed the chances of a radical resection are minimal. On the other hand, we may have cases of patients with two or even three metastatic sites that are clearly non-resectable at the beginning, but an excellent response lasting 8–12 months may induce the initial judgement to be revised.

Thus, minimisation of bias, that in general is very difficult, is prohibitive in this peculiar condition.

'Feasible' versus 'oncologically sound' resection

Clinical trials are clearly needed to provide scientific guidance to define the concept of 'oncologically sound' resection. The need comes from the consideration that a technically feasible resection is not always an oncologically sound resection; that is a resection with a reasonable chance to translate into a substantial clinical benefit for the patient. The major difficulty is to indicate objective criteria to define a sub-group of patients who will benefit most from an aggressive therapeutic approach aiming at potential cure. Attempts have been made by several investigators to integrate data on prognostic variables into a scoring system for stratifying patients with hepatic colorectal metastases. In particular, Fong and colleagues [26] examined a series of parameters that were found to be independent predictors of adverse prognosis: (i) extrahepatic disease; (ii) positive surgical margin; (iii) nodal metastases for primary cancer; (iv) short disease-free interval; (v) tumour size greater than 5 cm; (vi) more than one liver metastases; and (vii) carcinoembryonic antigen (CEA) over 200 ng/ml.

More recently, Adam and colleagues [2] have proposed a model to predict survival after surgery in metastatic patients downstaged by chemotherapy, based on four preoperative factors that were found to be independently associated with decreased survival: (i) rectal primary tumour; (ii) $\geqslant$3 metastases; (iii) maximum tumour size >10 cm; and (iv) cancer antigen 19–9 (CA 19–9) >100 UI/l. Strikingly, mean adjusted 5-year survival according to the presence of 0, 1, 2, 3 or 4 factors was 59%, 30%, 7%, 0% and 0%, respectively.

These scoring systems are likely to reflect the probability of disseminated disease at the time of presentation and may aid patient selection for surgery. However, these criteria are necessary, but not sufficient by themselves to fulfil the extremely complex concept of 'oncologically sound' procedure. Combination of these clinical prognostic models with advanced imaging techniques, evaluation of the overall clinical course of the disease and good clinical judgement are, at present, the best foundation for this concept for which no scientific definition is currently available.

Best response as an objective

One of the challenges of clinical decision-making is when to stop chemotherapy and start surgery. There are two possibilities: to operate as soon as the tumour becomes resectable, or to pursue best response. The former is the correct choice.

Best response can be defined as the condition of maximum tumour shrinkage. This implies that one should wait for at least two tumour evaluations showing no further shrinkage before defining maximum response. This is not recommendable for lesions that become resectable following chemotherapy.

In fact, pursuing best response may lead to two conditions where surgery becomes more difficult: when iatrogenic liver damage develops or when the metastases disappear.

In a recent study, 83% of the lesions disappearing on computed tomography scan still contained microscopic disease when the area was excised at surgery, indicating that clinical complete response (CR) reflects pathologic CR in only approximately 10% of cases [27]. This has led the surgeon to conclude that, under these conditions, what has been the dream of the medical oncologist (CR) may be the nightmare of the surgeon (because he or she no longer knows where to resect in the case of CR). Therefore best response is a reasonable end-point only for those patients who are by no means candidates for surgery.

In conclusion, as soon as response allowing surgery is achieved, the surgeon should examine the patient

to make the decision. While response is certainly an objective of chemotherapy in clinical practice, as well as an end-point in clinical trials, best response should not be an adequate end-point in this particular setting.

Response, resectability and resection rates by themselves may be misleading end-points

Let us consider a patient with six massive liver metastases that are clearly unresectable and who receives 4 months of chemotherapy. The patient has a 70% tumour reduction and now there are only three lesions that may be resectable. Let us assume that the patient undergoes surgery and that the margins are clear. This patient has achieved both the end-points under consideration (response and resection); in fact he or she has gone beyond those, because resection has been an R0 resection. This must be viewed as a major success. And this success is universally recognisable if he does not relapse in the next couple of years. But let us now consider that the same patient has recurrent liver metastases 3–6 months after the R0 resection. How beneficial was the resection? Certainly marginal.

The median duration of NED state following R0 resection, i.e. the relapse-free survival (RFS), varies according to the starting conditions, but the most reliable figure for patients with initially unresectable liver metastases that we can derive from the literature is approximately 6 months [3]. This duration of benefit in general should be regarded as too short to make liver resections acceptable.

Relapse-free survival after response-leading-to-resection as the real measure of benefit

From the above it can be concluded that the real indicator of benefit is neither the response nor the resectability, nor the R0 resection rate, but how long the NED state lasts after an R0 resection. That is to say the RFS.

While it is agreed that 6-months RFS is too short an interval, it is our opinion that, despite being ambitious, this cut-off should be 12 months, especially in light of the costs and morbidities of the complex multidisciplinary approach needed.

We should aim for this end-point when we embark on intensive costly and risky programmes of chemotherapy followed by surgery. We may not reach this target, but this therapeutic aim should be clear from the beginning. Anything below this 'high bar' would have little clinical relevance and would be too costly. This concept should hold true both in clinical practice (where exceptions can obviously be made) and clinical trials.

Our group is running a trial in which clearly unresectable advanced colorectal cancer patients are treated with a combination of three biologics and a chemotherapy doublet. The end-point is 12 months RFS > 30%. We call it an 'ambitious trial'. But it is one of the first attempts to innovate this field with an end-point that conjugates clinical relevance with social acceptability.

Conflict of interest statement

None declared.

References

1 Bismuth H, Adam R, Levi F, *et al.* Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996, **224**(4), 509–520; discussion 520–2.

2 Adam R. Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases. *Ann Oncol* 2003, **14**(suppl 2), ii13–16.

3 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), 663–669.

4 Tournigand C, Andre T, Achille E, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004, **22**(2), 229–237.

5 Folprecht G, Grothey A, Alberts S, *et al.* Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005, **16**(8), 1311–1319.

6 Cervantes A, Casado E, Van Cutsem E, *et al.* Cetuximab plus oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFOX-4) for the epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer (mCRC) in the first-line setting: a phase II study. *Eur J Cancer Suppl* 2005, **3**(2), 181, abstract 642.

7 Fisher GA, Kuo T, Cho D, *et al.* A phase II study of gefitinib in combination with FOLFOX-4 (IFOX) in patients with metastatic colorectal cancer. *J Clin Oncol* 2004, **22**(14S), abstract 3514.

8 Folprecht G, Lutz MP, Schoffski P, *et al.* Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. *Ann Oncol* 2006, **17**(3), 450–456.

9 Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004, **350**(23), 2335–2342.

10 Kopetz S, Abbruzzese JL, Eng C, *et al.* Preliminary results from a phase II study of infusional 5-FU, leucovorin and irinotecan (FOLFIRI) plus bevacizumab as first-line treatment for metastatic colorectal cancer (mCRC). *J Clin Oncol* 2006, **24**(18S), abstract 3579.

11 Peeters M, Raoul J-L, Van Laetham J-L, *et al.* Cetuximab in combination with irinotecan/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFIRI) in the first-line treatment of metastatic colorectal cancer. *Eur J Cancer Suppl* 2005, **3**(2), 188, abstract 664.
12 Abad A, Anton A, Massuti B, *et al.* Resectability of liver metastases (LM) in patients with advanced colorectal cancer (ACRC) after treatment with the combination of oxaliplatin (OXA), irinotecan (IRI) and 5-FU: Final results of a phase II study. *J Clin Oncol* 2005, **23**(16S), 275, abstract 3618.
13 Falcone A, Masi G, Murr R, *et al.* Biweekly irinotecan, oxaliplatin, and infusional 5-FU/LV (FOLFOXIRI) versus FOLFIRI as first-line treatment of metastatic CRC (MCRC). ASCO Gastrointestinal Cancers Symposium www.asco.org 2006, abstract 227.
14 Quenet F, Nordlinger B, Rivoire M, *et al.* Resection of previously unresectable liver metastases from colorectal cancer after chemotherapy with CPT-11/L-OHP/LV5FU (Folfirinox): A prospective phase II trial. *Proc Am Soc Clin Oncol* 2004, **23**, abstract 3613.
15 Seium Y, Stupp R, Ruhstaller T, *et al.* Oxaliplatin combined with irinotecan and 5-fluorouracil/leucovorin (OCFL) in metastatic colorectal cancer: a phase I-II study. *Ann Oncol* 2005, **16**(5), 762–766.
16 Van Cutsem E, Nordlinger B, Adam R, *et al.* Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 2006, **42**, 2212–2221.
17 Elias D, Sideris L, Pocard M, *et al.* Results of R0 resection for colorectal liver metastases associated with extrahepatic disease. *Ann Surg Oncol* 2004, **11**(3), 274–280.
18 Guyot F, Faivre J, Manfredi S, *et al.* Time trends in the treatment and survival of recurrences from colorectal cancer. *Ann Oncol* 2005, **16**, 756–761.
19 Poston G. Adam R, Vauthey JN. Downstaging or downsizing: time for a new staging system in advanced colorectal cancer? *J Clin Oncol* 2006, **24**, 2702–2706.
20 Adam R, Delvart V, Valenau A, *et al.* Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004, **240**, 644–657.
21 Masi G, Cupini S, Marcucci L, *et al.* Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. *Ann Surg* 2006, **13**, 58–65.
22 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**, 663–669.
23 Adam R. Developing strategies for liver metastases from colorectal cancer. *Semin Oncol* 2007, **34**(2)(Suppl 1), S7-S11.
24 Alberts SR, Horvat WL, Sternfeld WC, *et al.* Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005, **23**, 9243–9249.
25 Pozzo C, Basso M, Cassano A, *et al.* Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004, **15**, 933–939.
26 Fong Y, Fortner J, Sun RL, *et al.* Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999, **229**, 309–318.
27 Benoist S, Brouquet A, Penna C, *et al.* Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006, **24**, 3939–3945.