Long-term survival of patients downstaged by oxaliplatin and 5-fluorouracil combination followed by rescue surgery for unresectable colorectal liver metastases

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SUMMARY

Objectives — To evaluate long-term survival of patients resected for primarily unresectable colorectal liver metastases downstaged by systemic chemotherapy.

Methods — Among a group of 82 patients with advanced colorectal cancer, 39 had unresectable liver metastases. After treatment with systemic 3-weekly 5FU/folinic acid/oxaliplatin chemotherapy, the outcome of 11 patients made resectable thanks to chemotherapy was compared to that of 28 patients who were not. Criteria for non-resectability consisted of diffuse bilobar invasion with inability to achieve complete resection, unilobar or bilobar invasion plus vascular extension (invasion of inferior vena cava or 2 suprahepatic veins plus continuity with the 3rd) or involvement of hepatic pedicle. Before and after surgery, CT scan evaluation was performed every 2 months. Progression free survival was defined as the time between starting chemotherapy and recurrence of the disease. We used Kaplan-Meier survival curves and log-rank test for comparisons, P values were two-sided and considered significant if < 0.05.

Results — Progression free survival times were 14 and 6 months, median overall survival were 60 and 18.5 months, respectively, in favour of secondary resected subjects.

Conclusion — Considering the magnitude of the survival benefit, one may question the need and feasibility for trials to assess more formally the impact of surgery in that setting.

RÉSUMÉ

Impact de la chirurgie sur la survie chez des malades porteurs d’un cancer colorectal avec métastases hépatiques initialement non résécables après une chimiothérapie de type oxaliplatine/5FU

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(2006;30:1349-1353)

Objectifs — Évaluer l’intérêt en termes de survie d’une stratégie combinée associant chimiothérapie systémique et chirurgie chez des malades porteurs d’un cancer colorectal avec métastases hépatiques non résécables d’emblée.

Méthodes — Parmi un groupe de 82 malades présentant un cancer colorectal à un stade avancé, 39 présentaient des métastases hépatiques non résécables. La totalité de ces 82 malades a bénéficié d’une chimiothérapie systémique combinant 5FU/acide folicique/oxaliplatine toutes les trois semaines. Le devenir de 11 malades rendus résécables grâce à la chimiothérapie a été comparé à celui des 28 autres malades dont la résection secondaire n’a pas été possible. Les critères de non résécabilité consistaient en une atteinte bilobulaire avec impossibilité de résection complète de la tumeur, ou en une atteinte unilobaire ou bilobaire avec atteinte du confluent sus-hépato-cave ou un envahissement de la veine cave ou encore un envahissement du pédicule hépatique. L’évaluation tumorale était jugée par la réalisation d’un examen tomodensitométrique dans le mois précédent l’initiation de la chimiothérapie puis par des examens répétés tous les deux mois avant et après l’exérèse chirurgicale. Pour les malades réséqués, la survie sans progression était définie par le temps compris entre l’initiation de la chimiothérapie et la récidive. L’analyse statistique a été réalisée par la méthode de Kaplan-Meier. Le test du Log-rank a été utilisé pour l’analyse comparative. Un P < 0,05 a été considéré comme significatif.

Résultats — La survie sans progression et la survie globale a été en faveur des malades secondairement réséqués, 14 mois versus 6 mois et 60 mois versus 18,5 mois, respectivement.

Conclusion — Considérant l’importance du bénéfice en survie apporté par l’exérèse chirurgicale après une chimiothérapie systémique chez des malades ayant un cancer colorectal avec des métastases hépatiques initialement non opérables, il semble nécessaire dans les futurs essais d’évaluer au mieux l’impact de la chirurgie dans cette situation.
Introduction

It is estimated that 15-20% of colorectal cancer patients present with synchronous liver metastases [1]. On the other hand, half of patients with colorectal cancer will develop liver metastases in the course of their disease [2]. Unfortunately, only 10% to 20% of patients in this situation will benefit from surgical resection [3]. Thus, palliative treatment is the only possibility for these patients. Whatever the strategy, using sequential polychemotherapy [4] or monoclonal antibodies [5, 6] median survival does not exceed 22 months. Surgery could modify the natural history of unresectable colorectal liver metastases when systemic chemotherapy could downstage these patients. The aim of this paper was to study the outcome of patients with initially unresectable liver metastases from colorectal cancer treated by a combination of oxaliplatin and 5FU and to compare the survival between non-operable subjects with those whose tumors become resectable after chemotherapy.

Patients and methods

Study population

Among a group of 82 patients with disseminated colorectal cancer, 39 had liver metastases as the only site of metastases. After chemotherapy, 11 were deemed secondarily resectable. The number of metastases was the same in each group (2-15). However, unilobar invasion was more frequent in resected group (9 versus 4). We retrospectively compared survival of these 11 patients with 28 patients presenting with similar initial conditions but who were not deemed resectable after the same chemotherapy regimen. The resectability status was established before and after chemotherapy by a multidisciplinary team including a radiologist, a medical oncologist and a surgeon. The criteria for non-resectability consisted of diffuse bilobar invasion with inability to achieve complete resection, unilobar or bilobar invasion plus vascular extension (invasion of inferior vena cava or 2 supra-hepatic veins plus continuity with the 3rd) or involvement of hepatic pedicle [7]); vascular extension predominated for unilobar localization. Clinical determinants for survival described by Kohn et al. [8] were used to compare the 2 groups.

One treatment cycle consisted of 5-FU given at the dose of 2.6 g/m² as a continuous infusion with a Pharmacia pump over 24 h, on days 1, 8, 22, 29, 43 and 50 (day 64 = day 1 of next cycle), folinic acid iv, at a dose of 500 mg/m² in 5% glucose over 1 h before 5-FU, and oxaliplatin iv at the dose of 130 mg/m² over 2 h in 5% glucose on days 1, 22 and 43 [9].

Toxicities were graded according to the WHO criteria except for neuro-toxicity. Peripheral neuropathy was graded according to an adapted scale: grade 1 when the duration of symptoms was less than 7 days, grade 2 when the duration of symptoms was less than 21 days, grade 3 when the symptoms were permanent and grade 4 when functional impairment was reported.

Evaluation of response

Response was documented by CT scan in all patients. CT scans were performed before starting chemotherapy (1 month maximum) and then every 2 months before and after resection. At each evaluation, patients were reassessed for resectability.

Progression free survival was defined as survival analysis that evaluates deaths from all causes in the follow-up period from the date of starting chemotherapy until relapse of the disease. Overall survival was calculated from the date of starting chemotherapy until death. Complete resection was defined as R0 resection. For statistical analysis, we used the Kaplan-Meier survival curves and log-rank test for comparisons; P values were two-sided and considered significant if < 0.05.

Results

The patient's characteristics are summarised in table 1. Unilobar invasion was present in 13 patients and bilobar invasion in 26. Among the 11 patients in whom a resection was made possible by neoadjuvant chemotherapy, 4 had received prior adjuvant chemotherapy using the Mayo regimen. Two of these patients relapsed less than 6 months after initiation of treatment. Three patients had first-line therapy with 5FU and leucovorin, but presented with progressive disease within 6 months, and 4 had no prior treatment. In 4 resected patients, the diagnostic of liver metastases was synchronous with the initial diagnosis of colorectal cancer. For these patients, primary tumor was resected before starting chemotherapy. Among the 28 patients who were not resected 2 had prior adjuvant chemotherapy, 24 had first-line therapy with various regimen including infusional 5FU modulated with leucovorin or methotrexate, bolus 5FU with leucovorin, combination of 5FU with CPT-11 and mitomycin C. Two patients received more than 2 regimens of chemotherapy. In 19 patients liver metastases were synchronous with the diagnosis of the primary tumor.

Overall, patients received a median total number of 6 oxaliplatin courses (range: 2-15).

Toxicity was mild to moderate and no dose reduction was performed for oxaliplatin. The worst grades for the main toxicity parameters are reported in table II. Patients who were resected had a median of 2 courses before surgery and 4 courses starting 2 months after surgery in 10/11 patients. Chemotherapy had downstaged 9 patients with unilobar invasion and 2 patients with bilobar invasion for which surgery was achieved with curative intent. Surgery was conducted a mean of 3 weeks after the end of chemotherapy and was considered complete in 8/11 patients. In 2 patients the margins were invaded and in 1 the resection was incomplete. No transfusion was performed during surgery in the 11 resected patients. No embolisation or radiofrequency were performed during the procedure. Postoperative complications occurred in 7 patients and consisted of peri-hepatic abscess in 3, transient liver failure in 2 and pleural effusion in 2.

Recurrence was observed after a median of 14 months (range: 8-31). In 7 patients, recurrence was documented in the liver. Of these patients, 4 also had extra-hepatic localisations (pulmonary for 2 patients, bone for 1 patient and large lateral...
Discussion

Neoadjuvant chemotherapy offers the possibility of downstaging in patients with initially unresectable liver metastases from colon cancer [10]. To date, this approach is the only method allowing long-term survival. Median overall survival time for the 11 resected patients was 60 months with 73% of patients alive at 3 years. In an attempt to validate the apparent long-term survival of this small group of patients, we compared outcome of the 28 patients treated in our institution presenting with isolated hepatic metastases and treated with the same oxaliplatin/SFU-FA regimen as second-line therapy but did not undergo hepatic surgery. Obviously, these patients had a higher proportion of synchronous and diffuse bilobar lesions. Median overall survival time was 18.5 months (range: 9-29 months) for the whole group and 21 months in the 8 responding patients. Survival rate at 3 years was 7%. Several studies have attempted to identify the prognostic factors influencing the survival of patients undergoing surgical resection of hepatic metastases [11-13]. Performance status was comparable in the 2 subgroups. No clinical or biologic prognostic factors were identified due to the small number of patients undergoing resection, according to Ihone criteria [8] (data not shown). Three studies using different oxaliplatin/SFU regimens were reported to be efficient for downstaging colorectal liver metastases [14-16]. In the study by Bismuth et al. [14], a chronomodulated 5-FU with oxaliplatin regimen enabled a therapeutic response sufficient for secondary surgery in 16% of patients (53/330), of which 87% complete resections were possible. After the initial resection, 28% of patients underwent one or several hepatic or extra-hepatic resections in the event of recurrence. Progression-free survival was 42.9 months, with 54% of patients alive at time point 3 years. These results were confirmed by Giachetti et al. [15] in a series of 151 patients; of these, 51% became secondarily operable. The complete resection rate was 75%, with a progression-free survival of 17 months, median survival of 48 months and 60% of patients alive at time point 3 years [6]. In the 74 patients not undergoing surgery, the median survival time was 15.5 months. Recently, in a phase II study using FOLFOX 4 regimen, 17 of 42 patients (40%) initially unresectable underwent surgery [16]. Unfortunately, with a median follow up of 22 months, 73% of them developed recurrence. In our study 28% of patients were secondary resected. Chronomodulated or non-chronomodulated 5-FU with oxaliplatin-based chemotherapy, over 6 months, enables secondary resection of hepatic metastases in 16 to 51% of cases. This difference may be due to patient selection and/or chronomodulated regimen.

Our data confirm these observations and highlight the significant benefit in overall survival for patients responding to chemotherapy enabling surgery as compared to those who could not. Even if we assume that patients who underwent surgery had

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Table II – Percentage of worst grade of toxicity.
Proportion des sévères effets indésirables.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>% Grades 1 and 2</th>
<th>% Grades 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>48.7</td>
<td>10</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>2.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20.5</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.9</td>
<td>7.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30.7</td>
<td>12.8</td>
</tr>
<tr>
<td>Neutrotoxicity</td>
<td>54.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Allergy</td>
<td>7.7</td>
<td>0</td>
</tr>
</tbody>
</table>

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aortic lymph nodes for the fourth). In 3 patients, only extra-hepatic metastases developed (pulmonary and bone metastases for one and peritoneal carcinomatosis for the others). Positron emission tomography (PET-scan) was used in two patients. To date, one patient is still free of recurrence at >39 months. When progression was documented 6 patients received a combination of irinotecan, leucovorin and fluorouracil and patients radiofrequency ablation was used in two while a pulmonary metastectomy was performed in another patient.

In the 28 unresected patients, the objective response rate was 32.1%, with progression-free survival of 6 months (range: 4-10 months) (figure 1). Stabilisation of the disease occurred in 28.6% of the patients. Median survival was 18.5 months (range: 16-34.5 months) (figure 2). Survival rate at 3 years was 7%. For the 11 resected patients, progression free survival was 14 months (range: 11-16 months) (figure 2). Survival rate at 3 years was 73%.

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Fig. 1 – Progression free survival in resected and unresected patients.
Survie sans récidive des malades ayant eu une résection hépatique vs ceux n’en ayant pas eu.

Fig. 2 – Overall survival in resected and unresected patients.
Survie globale des malades ayant eu une résection hépatique vs ceux n’en ayant pas eu.
a better prognostic profile and less tumour burden than those who did not, this cannot, by itself, explain a 25-month difference in median survival. Despite improvements in chemotherapy, long term survival up to 3 years is rare. The role of surgery appears to be essential in achieving such a benefit [17, 18]. Today, PET-scan has a role in the management of colorectal cancer, especially for pre-operative staging in case of complex surgical strategies, and can modify surgical approach in 30 to 40% of cases [19-21]. Moreover, new methods can improve resectability in selected patients. In patients with high risk post-operative liver failure, preoperative portal vein embolization by inducing a compensatory hypertrophy of the remnant liver can allow more patients to benefit from resection [22]. Another technique to avoid post-hepatectomy liver failure consists in two-stage hepatectomy. This option is interesting in case of multinodular metastases involving both lobes of the liver. The first hepatic resection is aimed at clearing the highest possible number of metastases and to make the second hepatectomy potentially curative [23]. Recently, it has been demonstrated that a third hepatectomy is safe and provides an additional benefit in survival similar to that of first and second liver resection in case of recurrence of metastases [24]. An alternative to resection is radiofrequency ablation. This technique is useful as a complement in large hepatectomies [25]. The limits of this method are the size of the tumor, which should not exceed 30 mm, and metastases in contact with major biliary or vascular structures [26]. Today, it seems that extrahepatic colorectal metastases are not an absolute contraindication to hepatectomy. For Elias et al. [27], the total number of metastases has a stronger prognostic effect than the site. Obviously, tumor progression before surgery is associated with a poor outcome. Tumor control before surgery is necessary to offer a chance of prolonged remission in these patients [28]. The main role for chemotherapy is to obtain a response allowing curative surgery to be performed. There is no evidence that prolongation of preoperative chemotherapy or the adjuvant therapy following metastasis resection, would further improve the survival. Considering the magnitude of the survival benefit one may question the need and feasibility for trials to assess more formally the impact of surgery in that setting because “a randomized trial to examine efficacy of surgical resection cannot ethically be performed” [29].

We believe that, today, clinical research should focus on improving oxalipaltin/5FU regimens aiming to obtain better responses, allowing curative surgery to be performed and better define the role of adjuvant treatment.

Table III – Comparative analysis of Bismuth, Giachetti and Baize studies.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Resected patients</td>
<td>53/330 (16%)</td>
<td>77/151 (51%)</td>
<td>11/39 (28%)</td>
</tr>
<tr>
<td>PS 0/1 (S and No S)</td>
<td>NA</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>Unilobar invasion (S)</td>
<td>NA</td>
<td>56%</td>
<td>82%</td>
</tr>
<tr>
<td>Previous CT</td>
<td>NA</td>
<td>61%</td>
<td>64%</td>
</tr>
<tr>
<td>Number of CT courses before S</td>
<td>9.6</td>
<td>NA</td>
<td>5.8</td>
</tr>
<tr>
<td>Complete resection</td>
<td>87%</td>
<td>75%</td>
<td>73%</td>
</tr>
<tr>
<td>2nd resection</td>
<td>28%</td>
<td>NA</td>
<td>0%</td>
</tr>
<tr>
<td>Hepatic recurrence</td>
<td>64%</td>
<td>45%</td>
<td>64%</td>
</tr>
<tr>
<td>Extra-hepatic recurrence</td>
<td>47%</td>
<td>NA</td>
<td>64%</td>
</tr>
<tr>
<td>PFS (S)</td>
<td>42.9 months</td>
<td>17 months</td>
<td>16 months</td>
</tr>
<tr>
<td>Median survival (S)</td>
<td>NA</td>
<td>48 months</td>
<td>60 months</td>
</tr>
<tr>
<td>Median survival (No S)</td>
<td>NA</td>
<td>15.5 months</td>
<td>18.5 months</td>
</tr>
<tr>
<td>% survivors at 3 years S / No S</td>
<td>54%/NA</td>
<td>60% / NA</td>
<td>73% / 7%</td>
</tr>
</tbody>
</table>

CT: chemotherapy, S: surgical resection, No S: non resection outcome, NA: not available, PFS: progression free survival

REFERENCES

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