Postoperative chemoradiotherapy after surgical resection of gastric adenocarcinoma: can LV5FU2 reduce the toxic effects of the MacDonald regimen?

A report on 23 patients

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SUMMARY

Aim of the study — A North American phase III trial has recently shown that postoperative chemoradiotherapy using the FUFOX Mayo Clinic regimen improves overall survival and relapse-free survival after surgical resection of gastric cancer. However, severe grade 3-4, hematologic and gastrointestinal toxicities were frequent. The aim of this retrospective and multicentric study was to determine the tolerance of a postoperative chemoradiotherapy regimen using LV5FU2 instead of the Mayo Clinic regimen.

Patients and methods — Twenty-three patients with resected adenocarcinoma of the stomach or gastroesophageal junction at high risk of recurrence were treated with LV5FU2 chemotherapy and radiotherapy (45 Gy in 25 fractions and 5 weeks) delivered to the tumor bed and regional nodes. Nineteen patients were treated with two to four cycles before radiotherapy, then three cycles during radiotherapy, and finally four cycles after radiotherapy; four patients were only given three cycles during radiotherapy.

Results — Of the 23 patients assigned to this protocol, 20 completed treatment (87%). There was only one interruption of treatment because of hematologic or gastrointestinal toxicity. Tolerance of LV5FU2 regimen associated with radiotherapy was excellent: one toxic death, grade 3-4, hematologic and gastrointestinal toxicities were frequent. The objective of this study was to evaluate the tolerance of a postoperative chemoradiotherapy regimen using LV5FU2 instead of the Mayo Clinic regimen.

Conclusion — Radiotherapy combined with LV5FU2 appears to be better tolerated than the Mayo Clinic regimen used in the North American study. These results have to be considered when elaborating future postoperative chemoradiotherapy trials for gastric cancer.

RÉSUMÉ

Radiochimiothérapie postopératoire après gastrectomie pour cancer de l’estomac : peut-on réduire la toxicité du schéma de Mac Donald en utilisant le protocole LV5FU2 simplifié ? Résultats chez 23 malades

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But de l’étude — Un essai de phase III nord-américain a récemment montré une amélioration significative de la survie globale et de la survie sans rechute après gastrectomie pour cancer avec une radiochimiothérapie utilisant le protocole FUFOX Mayo Clinic ; les toxicités hématologiques et digestives grade 3 et 4 étaient cependant fréquentes. L’objectif de cette étude rétrospective multicentrique était d’évaluer la tolérance d’une radiochimiothérapie postopératoire en remplaçant le protocole FUFOX par le protocole LV5FU2 simplifié.

Malades et méthodes — Vingt-trois malades opérés d’un adénocarcinome gastrique ou du cardia à haut risque de rechute ont reçu une chimiothérapie de type LV5FU2 simplifié et une radiothérapie de 45,5 Gy en 25 fractions et 5 semaines dans le lit opératoire et les adénopathies régionales. Dix-neuf malades ont reçu 2 à 4 cures de chimiothérapie avant la radiothérapie, puis 3 cures concomitantes, puis 4 cures après la radiothérapie ; quatre malades ont reçu seulement 3 cures concomitantes de la radiothérapie.

Résultats — Le traitement a pu être achevé chez 20 des 23 malades (87 %). Il n’y a eu qu’un seul arrêt de traitement pour toxicité digestive et aucun pour toxicité hématologique. La tolérance du schéma LV5FU2 associé à une radiothérapie a été excellente : une toxicité digestive grade 3 ou 4, une neutropénie grade 3 (4,3 %) et aucun décès pour cause de toxicité.

Conclusion — La tolérance de l’association LV5FU2-radiothérapie paraît meilleure que celle du schéma nord-américain utilisant le FUFOX Mayo Clinic. Ces résultats méritent d’être pris en compte dans l’élaboration des futurs essais de radiothérapie chimio adjuvante dans les cancers gastriques.

Introduction

Poor prognosis is still the rule for patients with adenocarcinoma of the stomach or the gastroesophageal junction. Five-year survival rates are in the 5% to 20% range [1]. After curative resection, 40% to 65% of patients have locoregional recurrence involving the tumor bed, the anastomosis or lymph nodes. Postoperative treatments have been shown to be ineffective [2, 3].

A multicenter study conducted in North America and reported by MacDonald et al. [4] in 2001 showed significant improvement in overall and relapse-free survival in patients given postoperative chemoradiotherapy in comparison with patients treated by surgery alone. While encouraging, these results must be balanced against the insufficient nodal dissection and the high rate of toxic effects (54% grade 3 and 4 hematologic toxicity and 33% grade 3 and 4 gastrointestinal toxicity) in...
patients treated with the Mayo Clinic FUFOL chemotherapy regimen. This regimen has been progressively abandoned in Europe, particularly for patients with metastatic colorectal cancer. Regimens using continuous infusion of 5FU, for example the LV5FU2 regimen, are preferred because of the lesser toxicity for an equivalent antitumor effect [5]. The regimen has been subsequently simplified to limit hematologic toxicity [6].

The purpose of this retrospective study was to evaluate tolerance to adjuvant chemoradiotherapy after resection for gastric adenocarcinoma in patients given the simplified LV5FU2 regimen instead of the FUFOL Mayo Clinic regimen.

Patients and method

Inclusion criteria

This was a retrospective study conducted in four French centers (Marseille, Paris, Reims, Lyon). Patients treated between January 2000 and August 2002 for histologically proven resectable non-metastatic stage II or III adenocarcinoma of the stomach or the gastroesophageal junction were included.

There were 23 patients (19 men and 4 women) in the study group. Demographic and clinical features are summarized in Table I. Mean age was 63 years (range: 38-79). General health status was satisfactory (WHO ≤ 2) in 21 of the 23 patients.

Subtotal gastrectomy was performed in nine patients and extended total gastrectomy in 14. An exclusive abdominal approach was used for all patients. Macroscopically and microscopically complete resection (R0) was achieved in 16 patients, macroscopically complete resection but with invaded surgical margins (R1) in three patients, and macroscopically incomplete resection (R2) in four patients. We retained the R1 and R2 patients as well as the R0 patients for analysis since the aim of the study was to evaluate treatment tolerance and not its efficacy. Nodal dissection was performed: D0 (N = 6 patients), D1 (N = 12 patients), D2 (N = 2 patients).

The UICC TNM classification, as revised in 1997 [7], was also applied: 21 patients had T3 or T4 tumors and nodal invasion (generally N1) was found in 22.

Postoperative treatment

All patients were given postoperative chemotherapy using the simplified LV5FU2 regimen: 2-hr infusion of leucovorin 200 mg/m^2 on day 1 followed by a 400 mg/m^2 bolus of 5FU on day 1, then a continuous infusion of 5FU 2400 mg/m^2 over 46 hr. Cycles were repeated every 14 days.

Nineteen patients (group 1) were given a chemotherapy regimen similar to the one used by MacDonald et al. [4]: chemotherapy before radiotherapy (2 to 4 cycles of simplified LV5FU2), then three cycles during radiotherapy (weeks 1, 3 and 5), and finally four cycles after radiotherapy.

Four patients treated in one center (group 2) were given radiotherapy and chemotherapy concomitantly (3 simplified LV5FU2 cycles during the radiation protocol in weeks 1, 3 and 5) but were not given chemotherapy before or after radiotherapy. Since the objective was to evaluate tolerance to the chemoradiotherapy combination, we retained for analysis all 23 patients, also reporting separately results for the 19 patients in group 1.

Radiation dose was 65 Gy per week delivered to the tumor bed and regional nodes in five 1.8 Gy fractions (19 patients in group 1). For patients with R1 or R2 resection, the radiotherapist determined whether a complementary dose of 5 or 10 Gy was delivered to the macroscopically or microscopically suspect area. The preradiotherapy work-up included a simulation scan to identify the operative bed, the residual gastric tissue and the anastomosis, as well as neighboring organs at risk (kidney, liver, spinal cord). Dosimetry was established with 3D dedicated software. The nodal areas to be included were selected individually depending on the localization of the gastric tumor. The celiac region was included in all cases. Balistic parameters were determined by virtual simulation using scan slices taken in the treatment position. 25 MeV beams were delivered by a particle accelerator using the routine 3-door anterior, right and left lateral entry configuration. Protection was fashioned individually or using a multilaminar collimator.

Clinical data (weight, WHO status, gastrointestinal tolerance), and laboratory results (mainly hematologic tolerance) were noted every 15 days.

Results

Treatment

Among the 23 patients given chemoradiotherapy, 20 (87%) completed the scheduled treatment cycles. Time from surgery to onset of the chemoradiotherapy protocol was 43 days on average (range: 21-71); time from surgery to onset of radiotherapy was 79 days on average (range: 40-180).

Treatment was interrupted in three patients, due to worsening general status and asthenia in one, tumor progression in one, and grade 3 gastrointestinal toxicity in one. The radiotherapy protocol had not been completed in the first two patients. The third had received the entire radiation dose. Only one interruption was definitely treatment-related.

There were no deaths during treatment.

Toxicity

Tolerance to the LV5FU2 regimen combined with postoperative radiotherapy in the 23 patients (summarized in Table II) was good.

Grade 3 or 4 gastrointestinal toxicity was observed in one patient (4.3%). Other toxic events were grade 1 or 2 nausea (56.5%), grade 1 or 2 diarrhea (21.7%), and grade 1 or 2 mucositis (13%).
Table II. – Hematologic and gastrointestinal toxicity of chemoradiotherapy (maximal toxicity per patient).

<table>
<thead>
<tr>
<th>Toxicité digestive et hématologique de l’association LV5FU2-radiothérapie, évaluée en toxicité maximum par patient.</th>
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</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal toxicity</strong></td>
</tr>
<tr>
<td>- Nausea</td>
</tr>
<tr>
<td>- Vomiting</td>
</tr>
<tr>
<td>- Diarrhea</td>
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<td>- Mucositis</td>
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<tr>
<th><strong>Hematologic toxicity</strong></th>
<th>Grade 1-2 (%)</th>
<th>Grade 3-4 (%)</th>
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<tbody>
<tr>
<td>- Neutropenia</td>
<td>4 (17.4)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>- Anemia</td>
<td>9 (39.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Thrombopenia</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- Neutropenia + fever</td>
<td>1 (4.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Hematologic toxicity included grade 3 or 4 event (fever with neutropenia) in one patient (4.3%), grade 1 or 2 neutropenia (17.4%), and grade 1 or 2 anemia (39%).

The WHO performance score remained stable during the postoperative treatment in 20 patients and worsened by one point in three patients (table I). Weight loss was noted in 18 patients (3-20% body weight) and was greater than 10% of body weight in six of them. Body weight remained unchanged in two patients and three patients gained weight.

There were no toxicity-related deaths.

Among the 19 patients in group 1 (who received the entire intended chemoradiotherapy sequence), treatment was interrupted early in two patients (10.5%): for tumor progression in one and for grade 3 gastrointestinal toxicity in one. We also noted fever and neutropenia in one patient (5.2%), and other toxic events included grade 1 or 2 nausea (58%), grade 1 or 2 diarrhea (26%), grade 1 or 2 mucositis (15%), grade 1 or 2 neutropenia (15%), and grade 1 or 2 anemia (4%).

**Discussion**

The overall prognosis of adenocarcinoma of the stomach or the gastroesophageal junction has not improved over the last decade. Locoregional relapse is frequent in operated patients despite use of different adjuvant treatments. Postoperative chemoradiotherapy trials have not demonstrated efficacy in improving survival [8]. Although the clinical impression is that postoperative treatment does provide some benefit, several meta-analyses on adjuvant chemotherapy have not been able to demonstrate its efficacy [9, 10]. One phase III radiotherapy trial has shown a significant improvement in survival after preoperative radiation in patients with cancer of the gastroesophageal junction [11]. However, a British study which included a large number of patients was unable to demonstrate any benefit from postoperative radiotherapy [12].

Overall, the low 5-year survival rate, the high rate of relapse, and the results of these different therapeutic trials do not allow the conclusion that adjuvant treatment can be beneficial for patients with gastric cancer.

The study published by MacDonald et al. in the *New England Journal of Medicine*, was the first multicentre prospective randomized trial conducted in a large number of patients demonstrating a large significant beneficial effect of adjuvant treatment [4].

Between August 1991 and July 1998, the authors included 603 patients with non-metastatic adenocarcinoma of the stomach or the gastroesophageal junction who had undergone macroscopically and microscopically complete resection (RO). Among these patients, 556 with satisfactory general health (WHO ≤ 2), no major organ failure, and sufficient oral or enteral caloric intake (> 1500 kcal/d) were randomized to two treatment arms: surgery alone (N = 275) and surgery with postoperative chemoradiotherapy (N = 281). The two groups were comparable: 100% of patients had a high risk of relapse (T3/T4 and/or N+) and 85% were N+. 20% had a tumor of the gastroesophageal junction. Adjuvant treatment, initiated between the 27th and 48th postoperative day, used the Mayo Clinic FUOFL regimen: five cycles delivered every 28 days. The first cycle began 5 days before radiotherapy (d1-d5) with 425 mg/m2/d 5FU and 20 mg/m2/d leucovorin. The following two cycles, given during radiotherapy, used a lower dose: 4-day cycle (400 mg/m2/d 5FU) during the first four days of radiotherapy and 3-day cycle during the last three days of radiotherapy; finally, 28 days after the end of the radiotherapy, two complete 5-day cycles were delivered 28 days apart. Radiotherapy began on day 29 of the first chemotherapy cycle and delivered 45 Gy in 25 fractions over five weeks. Radiation was delivered to the operative bed and regional nodes. The entire chemoradiotherapy regimen was completed by 64% of patients and was the cause of grade 3 or 4 toxicity due to hematologic or gastrointestinal events in 54% and 33% of patients, respectively. Treatment had to be interrupted because of toxicity in 17% of patients. Finally, three patients (1%) died from the toxic effects of the treatment (pulmonary fibrosis, heart failure, sepsis). Surgically, D2 dissection was recommended, however considering the number of reported node resections reported this was achieved in only 10% of patients. D1 dissection was performed in 36% of the patients and less extensive dissection, termed D0, was performed in the majority (54%). The type of nodal dissection was not found to have any influence on the beneficial effect of postoperative treatment. The authors thus generalised their conclusions. At a median of 5 years follow-up, the 3-year survival was significantly better in the chemoradiotherapy arm (50%) compared with the surgery alone arm (41%, P = 0.05). Median survival was 36 months versus 27 months, respectively. Relapse-free survival was 30 months in the chemoradiotherapy arm versus 19 months in the surgery alone arm (P < 0.001). Globally, the reduction in the relative risk of relapse was 33%. The risk of death was reduced by 26%. In terms of the favorable effect of treatment, there was no difference in treatment arms for gender, ethnic origin, tumor localization or type of nodal dissection.
The authors concluded that the chemoradiotherapy combination after curative resection of adenocarcinoma of the stomach or gastroesophageal junction significantly improves overall and relapse-free survival, irrespective of the type of nodal dissection.

Two criticisms could be formulated concerning this trial. First, the insufficiency of the nodal dissection, which was less than D1 in the majority of patients (54%), might explain the positive results, as if the chemoradiotherapy simply palliated insufficient surgery. Multivariate analysis did not however show any difference in outcome as a function nodal dissection. The second criticism concerns the high rate of toxicity reported with this combination. Despite this risk, the MacDonald regimen is the option proposed for postoperative chemoradiotherapy in many centers. In their recommendations for therapeutic management of gastrointestinal cancer, the FFCD (Federation of French-speaking Gastrointestinal Cancer Specialists) proposed this adjuvant treatment whenever nodal dissection is insufficient (less than 15 nodes examined) or for T3 or N+ tumors in young well-informed subjects, irrespective of the quality of the nodal dissection [13].

The question is whether the use of another chemotherapy regimen would be able to reduce the high rate of grade 3-4 hematologic or gastrointestinal toxic events and improve compliance. In Europe, the Mayo Clinic FUFO regimen has been progressively replaced by regimens using less toxic continuous FU infusion protocols which appear to be more effective for the treatment of metastatic colonic cancer [5, 6]. It was demonstrated in a French trial including 448 patients with metastatic colorectal cancer, that the LV5FU2 regimen is superior to the Mayo Clinic low-dose FU/leucovorin protocol, in terms of objective response (33% versus 14%, P = 0.0004) and in terms of progression-free survival (median 28 weeks versus 22 weeks, P = 0.012). Furthermore, this regimen appears to be less toxic [5]. The better tolerance to LV5FU2 regimen was demonstrated when it was used as an adjuvant in a trial including 905 patients [14]. The regimen was later modified to further improve tolerance [6].

This better tolerance to the simplified LV5FU2 protocol led our four groups to use it instead of the Mayo Clinic protocol in an adjuvant setting in the treatment of gastric cancer. We thus compared retrospectively in our patients with gastric adenocarcinoma given adjuvant chemoradiotherapy with that reported by MacDonald in similar patients given the Mayo Clinic FUFO regimen.

Our results demonstrate that tolerance was excellent in patients given the simplified LV5FU2 regimen in association with radiotherapy: 20/23 patients (87%) were able to complete the treatment protocol, compared with 66% in the study by MacDonald et al. [4]. We only had one patient who developed grade 3 or 4 gastrointestinal toxicity compared with 33% of the patients in the MacDonald trial. We also had only one patient with a grade 3 or 4 hematologic toxic event (4.3%), compared with 54% of the patients in the North American trial. Three patients (13%) did not terminate their treatment in our study versus 34% in the study by MacDonald et al. [4]. We had two treatment interruptions related to toxicity (8.7%), one for asthenia and one for severe gastrointestinal toxicity, versus 17% in the previous trial (table III). Nevertheless, one must remain prudent when comparing these results because the time to administration of chemotherapy after surgery was long in some of our patients and because of the lack of standard inclusion criteria in this retrospective analysis.

In conclusion, after gastrectomy, patients tolerate well the simplified LV5FU2 plus radiotherapy combination. If postoperative chemoradiotherapy improves overall and progression-free survival of patients with cancer of the stomach or gastroesophageal junction, the chemotherapy protocol must be optimized to improve tolerance, particularly with the simplified LV5FU2 regimen which may replace the Mayo Clinic FUFO regimen. These results should be taken into consideration when elaborating future therapeutic trials for adjuvant chemoradiotherapy in gastric cancer patients.

REFERENCES

5. de Gramont A, Bosset FJ, Milan C, Rougier P, Bouche O, Etienne PL, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorour-

Table III. – Comparison of results between the original MacDonald regimen and as modified in the present study.

<table>
<thead>
<tr>
<th></th>
<th>MacDonald [4]</th>
<th>modified MacDonald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>273</td>
<td>23</td>
</tr>
<tr>
<td>Time from surgery to chemotherapy in days (range)</td>
<td>NA a (27-48)</td>
<td>42.8 (21-71)</td>
</tr>
<tr>
<td>Time from surgery to radiotherapy in days (range)</td>
<td>NA (50-76)</td>
<td>79.6 (40-180)</td>
</tr>
<tr>
<td>% treatment interruption</td>
<td>34</td>
<td>13.04 (3/23)</td>
</tr>
<tr>
<td>% interruption for toxicity</td>
<td>17</td>
<td>8.6 (2/23)</td>
</tr>
<tr>
<td>Grade 3-4 gastrointestinal toxicity (%)</td>
<td>89 (33)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Grade 3-4 hematologic toxicity (PMN b) (%)</td>
<td>148 (54)</td>
<td>1 (4.3)</td>
</tr>
</tbody>
</table>

a NA: data not available
b Polymorphonuclears
Postoperative chemoradiotherapy for gastric cancer


