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Original Study

**FOLFOX as Perioperative Chemotherapy of localized Gastric Cancer: Efficacy and Tolerance**

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**Abstract**

**Background**

Use of perioperative chemotherapy had significantly improved prognosis of localized gastric cancer. Two studies have validated this approach using cisplatin based chemotherapy despite important toxicities. We conducted this study with the aim to evaluate efficacy and toxicity of FOLFOX regimen in this setting.

**Material and Methods**

This is a retrospective study including patients followed for gastric cancer in the Oncology Department of the military hospital Mohamed V in Rabat, Morocco over a period of 7 years from 2007 to 2013. Patients received 4 cycles of mFOLFOX as perioperative regimen. Assessment of tumor response after completion of preoperative chemotherapy was granted by comparative CT scan, tumor markers measurements and R0 surgery rate. Adverse events were graded according to classification of the National Cancer Institute Common Toxicity Criteria version 4.0.

**Results**

Thirty-one patients were included in this study. Use of preoperative chemotherapy showed partial response in fourteen patients (45.1%), stabilization in fifteen patients (48.4%). Tumor markers CEA and CA 19–9 were significantly decreased. R0 resection rate was 83.87%. Only 2 (6.45%) cases of grade 3/4 hematologic toxicity were reported in our study. Achieving programmed postoperative chemotherapy was possible in 72.41% of patients.

**Conclusions**

Our study is limited by the retrospective design and small sample size but FOLFOX chemotherapy seems effective and well tolerated in this setting and its place deserves to be studied in a larger study.

**Keywords**

gastric cancer, perioperative chemotherapy, FOLFOX, efficacy, toxicity

**Introduction**

Gastric cancer is one of the most common digestive cancers. Management of localized stages is well codified with two standards of care: American standard is adjuvant postoperative chemo-radiation \(^1\), and European standard is perioperative chemotherapy. Two studies have validated this approach using for the first and most important one Epirubicin—Cisplatin—Fluouracil protocol \(^2\), or Fluouracil—cisplatin Association for the Study of FFCD \(^3\). The main problem of these two protocols is toxicity for those patients often elderly.

FOLFOX 4 is one of the most used protocols in digestive cancers. Its overall safety and efficacy in advanced gastric cancer has been established through a Phase II study \(^4\). With the objective to evaluate the interest of this regimen as perioperative chemotherapy for localized gastric cancer is the reason why we conducted this study.

**Materials and methods**

This is a retrospective study including patients followed for gastric cancer in the oncology department of

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military hospital Mohamed V of Rabat in Morocco over a period of 7 years from 2007 to 2013. The objective of our study was to assess efficacy and tolerance of mFOLFOX as perioperative chemotherapy for localized gastric cancer.

We included in this study patients aged from 20 to 70 years, with histological confirmation of adenocarcinoma of the stomach or gastroesophageal junction. PS 0–2. Without evidence of distant metastases in body CT scan. Without medical contraindications to chemotherapy or surgery. Without a history of gastric surgery, chemotherapy, radiation therapy or concomitant malignancies. Correct kidney, liver and heart functions were required.

Patients received 4 cycles of mFOLFOX preoperatively with oxaliplatin at 85mg/m² on day 1, leucovorin at 200 mg/m² over 2 hours followed by bolus of 5–FU 400mg/m² on day 1 followed by a continuous infusion of 5FU dose of 2400mg/m² over 46 hours. Cycles were repeated every 15 days. Antiemetics and growth factors were used as needed. A biological assessment was requested systematically before each cycle, including complete blood count, serum electrolytes, liver function and renal function tests. Adverse events were graded according to classification of the National Cancer Institute Common Toxicity Criteria version 4.0.

Assessment of tumor response after completion of preoperative chemotherapy was granted by comparative measurement of target lesion size as RECIST1.1 criteria and by measurement of tumor markers CEA and CA19–9. Responders and stable patients were referred for surgical treatment, while second—line chemotherapy was started in case of progressive disease.

Surgery was performed 3–4 weeks after completion of preoperative chemotherapy. Type of surgery was dictated by tumor location and intraoperative findings. Lymph node dissection type D1, D2 or D1.5 was performed according to the decision of the surgeon.

All samples were histologically examined and the disease was classified according to TNM classification of the 7th edition of American Joint Committee on Cancer (AJCC) TNM staging system for gastric cancer.

Postoperative chemotherapy was started 4 weeks after surgery and comprised four cycles of the same protocol depending on patient’s performance status and residual toxicities. Patients were followed until death or until the date of the last assessment of 15 December 2013.

Statistical analysis was performed using SPSS software version 18.0. Differences were considered as significant for p–value under 0.05.

Results

Between 1 January 2007 and 31 December 2013 thirty—one patients were included in this study. Epidemiological characteristics of this population are described in Table 1.

Therapeutic evaluation after completion of preoperative chemotherapy showed partial response in fourteen patients (45.1%), stabilization in fifteen patients (48.4%). Tumor progression was noted in two patients (6.5%). No complete response could be obtained.

<table>
<thead>
<tr>
<th>Age (Avg)</th>
<th>55.8 years (33–67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>9</td>
</tr>
<tr>
<td>Man</td>
<td>22</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>17</td>
</tr>
<tr>
<td>Distal</td>
<td>8</td>
</tr>
<tr>
<td>Body</td>
<td>6</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Well differentiated Adenocarcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>4</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>6</td>
</tr>
<tr>
<td>Poorly differentiated Adenocarcinoma</td>
<td>14</td>
</tr>
<tr>
<td>Independent cells Adenocarcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Others (mucinous, tubular, etc.)</td>
<td></td>
</tr>
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Pre–treatment Stratification

<table>
<thead>
<tr>
<th>T</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>5</td>
</tr>
<tr>
<td>T3</td>
<td>14</td>
</tr>
<tr>
<td>T4</td>
<td>12</td>
</tr>
<tr>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>N0</td>
<td>5</td>
</tr>
<tr>
<td>N1</td>
<td>13</td>
</tr>
<tr>
<td>N2</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 1: Epidemiological and clinicopathological features.

<table>
<thead>
<tr>
<th>Item</th>
<th>Pre–treatment tumor markers</th>
<th>Post–treatment tumor markers</th>
<th>p–value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>0.86 (0.02–19.40)</td>
<td>0.61 (0.7–16.10)</td>
<td>0.040</td>
</tr>
<tr>
<td>CA 19–9</td>
<td>0.27 (0.1–27.45)</td>
<td>0.15 (0.04–18.36)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2: Tumor marker levels before and after completion of pre–operative chemotherapy

Tumor markers were expressed as folds over upper normal limit. p values for tumor markers were calculated using Wilcoxon test.
Use of perioperative chemotherapy had significantly improved prognosis of localized gastric cancer. Phase 3 multicenter trial MAGIC (2) shows a gain in 5 years overall survival (36% vs. 23%) and R0 resection rate (79% vs 69%) with use of perioperative chemotherapy using ECF regimen. Toxicity of this protocol remains important including 23.8 and 27.8% of grade 3 and 4 neutropenia for respectively preoperative and postoperative chemotherapy. In addiction use of continuous infusion of 5FU could alter quality of life of patients.

Ychou et al. (3) evaluated in their Phase 3 study published in Journal of Clinical Oncology in 2011 interest of perioperative CF regimen (2 to 3 cycles of cisplatin 100 mg/m² on day 1, and 5FU continuous infusion over 5 days at 800mg/m²) compared to surgery alone. This trial was positive in terms of 5 years overall survival (38% vs. 24% respectively) and disease-free survival at the cost of 38% grade 3 and 4 toxicity in the chemotherapy arm essentially hematological.

Since works of Al-Batram et al. (5), Luo et al. (6), and other authors FOLFOX has become one of the most widely used regimens in management of gastric cancer. With overall good safety and easiness of use. This pushed us to conduct this retrospective study evaluating efficacy and safety of FOLFOX chemotherapy as perioperative treatment of gastric cancer.

Use of FOLFOX in perioperative setting is being explored but some series exist in literature. De Vita et al. (7) evaluated post preoperative chemotherapy response and stabilization, partial response, complete response, and progression. Table 3: Post preoperative chemotherapy radiological evaluation

<table>
<thead>
<tr>
<th>Quality of resection</th>
<th>Preoperative chemotherapy</th>
<th>Postoperative chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>R1</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>R2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. Histological results after surgery

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Preoperative chemotherapy</th>
<th>Postoperative chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>T2</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>T3</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>T4</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>N:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>N1</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>N2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>N3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph node dissection type:</th>
<th>Preoperative chemotherapy</th>
<th>Postoperative chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>D1</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>D1.5</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>D2</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Adverse effects of chemotherapy

**Peripheral neuropathy**

- Grade 1–2: Preoperative 7, Postoperative 12
- Grade 3–4: Preoperative 0, Postoperative 5

**Mucositis**

- Grade 1–2: Preoperative 3, Postoperative 6
- Grade 3–4: Preoperative 0, Postoperative 1

**Diarrhea**

- Grade 1–2: Preoperative 9, Postoperative 3
- Grade 3–4: Preoperative 0, Postoperative 0

**Vomiting**

- Grade 1–2: Preoperative 14, Postoperative 20
- Grade 3–4: Preoperative 4, Postoperative 1

**Haematological toxicity**

- Grade 1–2: Preoperative 12, Postoperative 3
- Grade 3–4: Preoperative 2, Postoperative 1

Tumor markers CEA and CA 19–9 were significantly decreased after preoperative chemotherapy (Table 2).

Surgery was performed in 29 patients. R0 resection rate was obtained in 26 (90%) patients. Lymph node dissection was type D1 in 9 patients (31%), D 1.5 in 10 (34%) patients and D2 in 10 (34%) patients. Histological results are detailed in Table 3.

Nearly half of patients (52%) have an adenocarcinoma with signet ring cells. 6 patients (20%) have a poorly differentiated form and 8 patients with well or moderately differentiated adenocarcinoma (28%).

Among the 29 operated patients 21 (72%) received postoperative chemotherapy. Adverse events of pre and post—operative chemotherapy are detailed in Table 4.

Median follow—up of operated patients was 25 months. 5 events (17%) occurred, with two local recurrences, and 3 cases of metastatic relapse.

Discussion

Use of perioperative chemotherapy had significantly improved prognosis of localized gastric cancer. Phase 3 multicenter trial MAGIC (2) shows a gain in 5 years overall survival (36% vs. 23%) and R0 resection rate (79% vs 69%) with use of perioperative chemotherapy using ECF regimen. Toxicity of this protocol remains important including 23.8 and 27.8% of grade 3 and 4 neutropenia for respectively preoperative and postoperative chemotherapy. In addiction use of continuous infusion of 5FU could alter quality of life of patients.

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Use of FOLFOX in perioperative setting is being explored but some series exist in literature. De Vita et al. (7)
relate clinical response rate of 38% using FOLFOX 4 as preoperative treatment of gastric cancer.

FOLFOX 4 protocol yielded response rates of 43 and 41% respectively in two series published by Al–Batran et al. (5) and Luo et al. (6). Use of mFOLFOX regimen in our sample has allowed obtaining significant response rate with 45% of partial response and 48% of stabilization.

Achieving programmed postoperative chemotherapy was possible in only 54.8% of cases in MAGIC trial (2) and 50% in the study published by the Ychou et al. (3) while 72% of our patients have received postoperative chemotherapy.

Toxicity of standard chemotherapy (ECF or CF) remains a concern especially in patients with gastric cancer often elderly. Results of MAGIC trial relate significant rate of grade 3 and 4 toxicities with 23.8% neutropenia and 2–6% extra-hematologic toxicities like vomiting, diarrhea, stomatitis, neurological toxicities and skin change (2).

Compared with this protocol chemotherapy using FOLFOX seems better tolerated. Only 6% of grade 3/4 hematologic toxicity is reported in our study. Series of Al–Batran (5) and Vita (7) do not notice any neurological toxicity of grade 3/4 neutropenia. Neuropathy seems to be principal side effect of FOLFOX regimen with 5 cases of grade 3 during postoperative chemotherapy in our study, all fully resolved after chemotherapy end.

**Conclusion**

Perioperative chemotherapy is a standard of care in management of localized gastric cancer. Two validated protocols exist using Cisplatin with important concern about toxicity. Our study is limited by the retrospective design and small sample size but FOLFOX chemotherapy seems effective and well tolerated in this setting and its place deserves to be studied in a larger study.

**Acknowledgements**

- All authors have equally contributed to the completion of this article.

**Ethics, consent and permissions**

- This study was approved by the ethics committee of the military hospital of Rabat
- All patients enrolled in this study have given their consent to participate

**References:**