Incidence and evolution of oxaliplatin-induced peripheral sensory neuropathy in diabetic patients with colorectal cancer: a pooled analysis of three phase III studies


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Background: The purpose of this study was to determine whether the presence of diabetes mellitus (DM) influences the incidence, severity, and/or course of peripheral sensory neuropathy (PSN) after oxaliplatin (FOLFOX) therapy in patients with colorectal cancer (CRC).

Methods: A retrospective pooled analysis incorporating three phase III studies was conducted: Multicenter International Study of Oxaliplatin, 5-Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) (adjuvant treatment; stage II/III colon cancer), EFC4584 (second-line treatment; metastatic CRC), and EFC2962 (first-line treatment; metastatic CRC). Patients were ineligible for the studies if they had known PSN (EFC4584) or PSN grade ≥1 (MOSAIC and EFC2962) at baseline. The incidence of PSN was evaluated retrospectively in patient subgroups with or without DM at baseline that received FOLFOX. Kaplan–Meier curves were used to assess the probability of PSN with increasing cumulative oxaliplatin dose.

Results: Of 1587 patients enrolled across the three studies, 135 (8.5%) had DM at baseline. The incidence of PSN (non-DM/DM) was 45.0%/46.7% (grade 1), 28.6%/26.7% (grade 2), and 13.0%/12.6% (grade 3). The probability of PSN by cumulative dose of oxaliplatin was similar in DM and non-DM patients.

Conclusions: This retrospective analysis indicates that oxaliplatin-based therapy does not influence the incidence, severity, or time to onset of PSN in asymptomatic DM patients with CRC who meet eligibility criteria for clinical trials.

Key words: colon cancer, diabetes mellitus, FOLFOX, neuropathy, oxaliplatin

Introduction

Colorectal cancer (CRC) accounts for 10%–15% of all cancers. Each year, >945 000 new cases of CRC are diagnosed worldwide and it is the cause of death in nearly 500 000 patients [1]. The introduction of FOLFOX regimen has led to significant improvements in survival rates for patients with CRC [2]. Following the initial trial in Europe (EFC2962) [3] and the subsequent USA study (N9741) [4] that established the efficacy of FOLFOX4 as first-line treatment of metastatic CRC, a wealth of clinical data now support the efficacy and safety of oxaliplatin in CRC. Pivotal trials have demonstrated the effectiveness of FOLFOX regimens in both the adjuvant setting for stage II/III colon cancer [5] and advanced/metastatic CRC [6]. In the adjuvant trial, Multicenter International Study of Oxaliplatin, 5-Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) [5], patients with stage II/III colon cancer who received oxaliplatin plus 5-fluorouracil/leucovorin (5-FU/LV) showed significantly improved disease-free survival and overall survival compared with those who received 5-FU/LV alone. In the other trials, oxaliplatin plus 5-FU/LV prolonged progression-free survival versus 5-FU/LV alone when used as first-line treatment in advanced CRC (EFC2962) [3] and significantly improved objective response rate, time to tumor progression, and relief of tumor-related symptoms versus oxaliplatin or 5-FU/LV alone when used second line in metastatic CRC (EFC4584) [6]. In the United States, the intergroup study N9741 established FOLFOX as standard first-line therapy in advanced CRC, with superiority over the bolus 5-FU plus irinotecan regimen [7].

Oxaliplatin exhibits a good tolerability profile. The most common adverse events (AEs) are hematologic and...
Neurotoxicity is a common AE associated with existing platinum-containing anticancer agents [9]. With oxaliplatin therapy, neurotoxicity usually presents as peripheral sensory neuropathy (PSN), which in its persistent form is the main dose-limiting toxicity of oxaliplatin. Persistent PSN is cumulative, and grade 3 oxaliplatin-induced neuropathy occurs in 10%–20% of patients receiving total oxaliplatin doses >750–850 mg/m² [3]. In the MOSAIC trial, grade 3 PSN occurred in 12.4% of patients who received FOLFOX4 during the 6-month treatment period but it was reversible in the vast majority of cases and resolved after treatment was stopped [5].

The mechanisms responsible for the development of neuropathy in patients receiving oxaliplatin therapy are unknown, although recent studies indicate that certain gene polymorphisms may be predisposition factors of PSN [10, 11]. Nerve conduction studies do not appear useful in understanding the pathophysiology of neuropathy or for clinical monitoring of neurotoxicity in patients receiving oxaliplatin [12]. Axonal excitability techniques appear more sensitive and indicate that neuronal sodium channel dysfunction may play a part in the etiology of oxaliplatin-induced neurotoxicity [13].

Neuropathy is a common complication of diabetes mellitus (DM). Up to 50% of patients with DM develop neuropathy, and its likelihood is associated with both the duration and severity of the DM [14]. Although patients with preexisting symptoms of diabetic neuropathy are thought to have an increased risk of developing PSN while receiving chemotherapy [15], it is not known whether therapy with oxaliplatin or other platinum agents increases the incidence or severity of PSN in such patients. Currently, no data are available regarding the selection of patients with DM for chemotherapy. While patients who have symptomatic PSN have been excluded from clinical trials of drugs with potential to cause neurotoxicity, such as platinum-based agents and taxanes, it is not known if PSN would be induced or exacerbated by such agents in diabetic patients who have no symptoms of PSN at baseline.

The objective of this retrospective analysis of three major randomized studies [3, 5, 6] of FOLFOX regimens in patients with CRC was to determine whether the presence of DM influences the incidence, severity, and/or course of PSN with oxaliplatin therapy.

**Methods**

A pooled analysis was conducted using data from three multicenter, randomized, controlled trials in which FOLFOX4 was included as a treatment arm. MOSAIC (EFC3313) was an international phase III study of 5-FU (bolus and continuous infusion) and LV (LV5FU2) with or without oxaliplatin in adjuvant treatment of patients with stage II/III colon cancer [5]. EFC4584 was a North American three-arm phase III study of bolus/infusional LV5FU2 alone, oxaliplatin alone, or the combination of bolus/infusional LV5FU2 and oxaliplatin in second-line treatment of metastatic CRC [6]. EFC2962 was a European phase II/III study of bolus/infusional LV5FU2 with or without oxaliplatin in first-line treatment of metastatic CRC [3]. These studies were chosen as information regarding the presence of DM was obtained at baseline from patient-reported history and further study information could be obtained from a centralized database maintained by Sanofi-aventis. Details of the treatment regimens used in each study are shown in Table 1.

Patients with DM were not excluded from the three studies provided they had no PSN or PSN grade ≤1. The specific exclusion criteria were ‘known PSN’ (EFC4584) and ‘PSN grade >1’ (MOSAIC and EFC2962). The studies used different scales at screening for assessing neuropathy at study entry and during treatment [3, 5, 6]. The scales used were National Cancer Institute—Common Toxicity Criteria version 1.0 (EFC2962 and MOSAIC) and oxaliplatin-specific neurotoxicity scale (EFC4584).

Data were analyzed retrospectively for the association of preexisting DM and the occurrence of PSN due to FOLFOX. The incidence of PSN was evaluated in patient subgroups with or without DM at baseline in patients who received FOLFOX. Kaplan–Meier curves were constructed to show the probability of PSN in relation to increasing cumulative dose of oxaliplatin.

**Results**

A total of 1587 patients were treated with FOLFOX4 across the three studies (Table 1). Of these, 135 patients (8.5%) [MOSAIC, 86 of 1110 (7.7%); EFC4584, 34 of 268 (12.7%); and EFC2962, 15 of 209 (7.2%)] were identified as having DM at

<table>
<thead>
<tr>
<th>Study identifier and setting</th>
<th>Treatments</th>
<th>Total patients in each arm</th>
<th>Patients with diabetes, n (%)</th>
<th>Overall incidence of PSN grade ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC [5] (adjuvant therapy)</td>
<td>LV5FU*</td>
<td>1109</td>
<td>84 (7.6)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>FOLFOX4b</td>
<td>1110</td>
<td>86 (7.7)</td>
<td>12.4</td>
</tr>
<tr>
<td>EFC4584 [6] (second-line therapy)</td>
<td>LV5FU*</td>
<td>257</td>
<td>37 (14.4)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin*</td>
<td>266</td>
<td>35 (13.2)</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>FOLFOX4b</td>
<td>268</td>
<td>34 (12.7)</td>
<td>11.2</td>
</tr>
<tr>
<td>EFC2962 [3] (first-line therapy)</td>
<td>LV5FU*</td>
<td>208</td>
<td>18 (8.7)</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>FOLFOX4b</td>
<td>209</td>
<td>15 (7.2)</td>
<td>14.2</td>
</tr>
</tbody>
</table>

*LV 200 mg/m² i.v. infusion over 2 h, then 5-FU 400 mg/m² bolus, then 5-FU 600 mg/m² over 22 h; days 1 and 2, every 2 weeks.

†LV + 5-FU bolus and infusion* + oxaliplatin 85 mg/m² i.v. infusion over 2 h, day 1, every 2 weeks.

‡Oxaliplatin 85 mg/m² i.v. infusion over 2 h, day 1, every 2 weeks.

Data reported for paresthesias.

PSN, peripheral sensory neuropathy; LV, leucovorin; 5-FU, 5-fluorouracil.
a total incidence of 6%, regardless of DM status. The probability of PSN of grade any grade (59% and 53% of patients with or without DM, respectively). The probability of PSN of grade 1 was reported in 93% and 92% of patients with and without DM, respectively; the probability of onset of PSN of any severity approached 1.0 for both patient groups at a cumulative oxaliplatin dose above ~800 mg/m² (Figure 1A). The probability of PSN grade ≥3 at this level of exposure was much lower but was still very similar in patients with DM (13%) and those without (12%) (Figure 1B). These Kaplan–Meier curves did not reveal any trends that would indicate differences between diabetic and nondiabetic patients with respect to the cumulative probability of PSN.

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The overall probability of PSN was lower in EFC4584 than in MOSAIC, possibly because of the relatively low cumulative dose of oxaliplatin administered in this second-line trial [median cumulative dose, 510 mg/m² (6 cycles) versus 894 mg/m² (12 cycles) for MOSAIC and 837 mg/m² (12 cycles) for EFC2962]. At this level of oxaliplatin exposure, approximately one-half of all patients in study EFC4584 experienced PSN of any grade (59% and 53% of patients with or without DM, respectively). The probability of PSN of grade ≥3 by cumulative dose of oxaliplatin in EFC4584 was very low (Figure 1D), with a total incidence of 6%, regardless of DM status.

study entry. Forty-one patients (19.6%) who received FOLFOX4 in EFC2962 did not have information regarding their DM status collected at baseline. Across the three trials as a whole, the demographic characteristics of the patients with DM did not differ significantly from those without DM, although patients with DM showed a trend toward being older (median age 63 versus 60 years, respectively) (Table 2). In the two studies that allowed baseline PSN grade ≤1, on review of the case report forms, almost all patients had no subjective symptoms. In EFC4584, four patients had grade 1 PSN (two in each arm); in EFC2962, there were no patients with grade 1 PSN.

The incidence of PSN by grade was similar in patients with DM and in those without DM for each study and when the data from the three studies were pooled (Table 3). In the two studies in which information on DM status was collected consistently at baseline (MOSAIC and EFC4584), the probability of PSN by cumulative dose of oxaliplatin was similar for patients with and without DM (Figure 1).

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Table 2. Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with DM (n = 309)</th>
<th>Patients without DM (n = 3032)</th>
<th>Patients with unknown DM status (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>199 (64.4)</td>
<td>1657 (54.7)</td>
<td>51 (57.3)</td>
</tr>
<tr>
<td>Female</td>
<td>110 (35.6)</td>
<td>1375 (45.3)</td>
<td>38 (42.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>285 (92.2)</td>
<td>2888 (95.3)</td>
<td>86 (96.6)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (2.6)</td>
<td>60 (2.0)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (2.3)</td>
<td>45 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>9 (2.9)</td>
<td>39 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Median (range) age, years</td>
<td>63 (40–88)</td>
<td>60 (15–86)</td>
<td>57 (21–75)</td>
</tr>
<tr>
<td>Age &lt; 65 years, n (%)</td>
<td>179 (57.9)</td>
<td>1967 (64.9)</td>
<td>63 (70.8)</td>
</tr>
<tr>
<td>Age ≥ 65 years, n (%)</td>
<td>130 (42.1)</td>
<td>1063 (35.1)</td>
<td>24 (27.0)</td>
</tr>
</tbody>
</table>

*aAll treatment arms included.

DM, diabetes mellitus.

Table 3. Pooled incidence of PSN by grade in patients who received FOLFOX4

<table>
<thead>
<tr>
<th>Severity of PSN</th>
<th>Incidence, n (%)</th>
<th>Patients without DM (n = 1450)</th>
<th>Patients with DM (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population (N = 1585)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>716 (45.2)</td>
<td>653 (45.0)</td>
<td>63 (46.7)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>450 (28.4)</td>
<td>414 (28.6)</td>
<td>36 (26.7)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>206 (13.0)</td>
<td>189 (13.0)</td>
<td>17 (12.6)</td>
</tr>
</tbody>
</table>

*Including 89 patients in EFC2962 with unknown DM status.

PSN, peripheral sensory neuropathy; DM, diabetes mellitus.

Discussion

This retrospective analysis indicates that the presence of DM is not associated with an increased risk of developing PSN in patients receiving oxaliplatin therapy for CRC. The data indicate that diabetic patients without subjective symptoms of PSN (grade 0) can be treated with FOLFOX regimens with no greater risk of cumulative PSN than nondiabetic patients. Though two of the studies allowed patients with grade 1 PSN to enroll, it is interesting that in the subjects accrued, the vast majority did not have subjective symptoms of PSN.

Although suggestive, the current findings should be interpreted with caution due to the relatively modest sample sizes involved. Other limitations include the retrospective nature of the analysis and the fact that details regarding the duration and type of DM at study entry were not collected. Thus, it is not known if patients who have had DM for a longer duration are more susceptible to PSN when treated with chemotherapy or if susceptibility to PSN is different in patients with insulin-dependent versus non-insulin-dependent DM. It is also not known if patients with preexisting grade 1 PSN are more susceptible to toxicity as very few patients with PSN were included. The pathophysiology of neuropathy induced by oxaliplatin may be different from that associated with DM. In patients with long-standing DM, major factors considered to play a role in the development of neuropathy as a late complication include alterations in endoneuronal metabolism,
defective neurotrophic support, oxidative stress, and reduced blood flow [16–18]. Oxaliplatin- or platinum-induced neuropathy appears to involve a different mechanism [13] and further research is needed specifically in diabetic patients undergoing platinum chemotherapy.

Management of neurotoxicity in patients receiving oxaliplatin could be improved if the ~10%–18% of patients who are susceptible to developing cumulative dose-limiting PSN could be identified before treatment begins. Recent studies indicate that certain genetic polymorphisms may predispose individuals to developing PSN [10, 11]. If such findings are validated in prospective studies, genetic screening of individuals might allow oxaliplatin therapy to be tailored accordingly. Studies are also ongoing with xaliproden, an investigational neurotrophic agent for the prevention of oxaliplatin-associated neurotoxicity. A recent phase III study reported that the addition of xaliproden to FOLFOX4 may reduce the incidence and severity of PSN in patients with metastatic CRC [19]. Recent randomized placebo-controlled studies indicate that calcium and magnesium infusions may reduce the incidence of PSN in both the adjuvant and metastatic settings when given with FOLFOX; however, as these studies were terminated prematurely before full accrual, the benefits are presently unclear [20–22]. A further approach being investigated to help reduce neurotoxicity involves a planned interruption of oxaliplatin therapy to allow any cumulative toxicity to resolve, followed by oxaliplatin reintroduction; this ‘stop and go’ strategy appears to be feasible, may result in a lower incidence of neurotoxicity, and does not lead to any loss of clinical efficacy [23–25]. At present, however, careful monitoring for PSN and appropriate dose reductions should remain as standard practice for all patients treated with oxaliplatin-based regimens.

In conclusion, this retrospective analysis indicates that the incidence, severity, and time to onset of PSN in mostly asymptomatic patients with CRC being treated with FOLFOX are not affected by DM, although appropriately powered prospective studies are required to establish an unequivocal correlation between the risk of PSN and the presence of DM in patients receiving oxaliplatin therapy. The incidence of DM is increasing, particularly among the elderly; ~20% of the USA population >60 years old have diagnosed DM and at least a similar proportion have latent or undiagnosed DM [26, 27]. We recommend that investigators prospectively collect data regarding the type and duration of DM at entry into phase III clinical trials involving agents with potential to cause PSN.

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disclosure
RKR, speaker bureau for Sanofi-aventis; AdeG and RMG, consultants for Sanofi-aventis; SG, employee and holds stock options for Sanofi-aventis; TA, honorarium from Sanofi-aventis; and MLR and CT, none.

references
19. Cassidy J, Bjarnason GA, Hickish T et al. Randomized double blind (DB) placebo (Pb) controlled phase III study assessing the efficacy of calcium-magnesium (CaMg) in reducing the cumulative peripheral sensory neuropathy (PSN) induced by oxaliplatin (Ox) and 5-FU/LV combination (FOLFOX4) in first line treatment of patients (pts) with metastatic colorectal cancer (MCRC). J Clin Oncol 2006; 24 (Suppl): 16S (Abst 3507).