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SHORT COMMUNICATION

Incidence of atypical acute nerve hyperexcitability symptoms in oxaliplatin-treated patients with colorectal cancer

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Abstract
Context Peripheral, acute or chronic, neurotoxicity is one of the main dose-limiting adverse effects of oxaliplatin (OXA). Acute neurotoxicity is typically characterized by distal and perioral cold-induced paresthesias and dysesthesias, but other uncommon symptoms might also be present.
Objectives The aim of this post hoc analysis of data extracted from a prospective, multicenter study was to assess the incidence of uncommon acute OXA neurotoxicity symptoms in patients undergoing OXA-based chemotherapy.
Methods One hundred chemotherapy-naïve patients (62 males, 38 females, aged 64.7 ± 8.7 years) with colorectal cancer scheduled to receive OXA-based therapy (FOLFOX-4, FOLFOX-6, and XELOX) underwent neurologic evaluation after the 1st infusion and then after 3 and 6 months of OXA-based chemotherapy (after 6th or 4th and 12th or 8th cycles, respectively, according to regimen). At evaluation, patients were asked to report the presence and characteristics of acute hyperexcitability symptoms.
Results Eighty-two patients presented typical symptoms of acute OXA neurotoxicity in the form of cold-induced paresthesias and dysesthesias. In 45/82 (54.9 %) of patients, uncommon symptoms were also present; shortness of breath (32 %), jaw spasm (26 %), fasciculations (25 %), cramps (20 %), and difficulty in swallowing (18 %) were more frequently reported, while voice (4 %) and visual changes, ptosis and pseudolaryngospasm (1 %) occurred rarely. No significant correlation was disclosed between acute OXA neurotoxicity and chemotherapy regimen, cumulative dose of OXA or patients' age.
Conclusions A high percentage of patients treated with OXA-based chemotherapy develop acute neurotoxicity also with uncommon manifestations. Since OXA acute neurotoxicity might be related to the onset of chronic neurotoxicity, these patients should be closely monitored to avoid this dose-limiting adverse effect.

Keywords Oxaliplatin · Acute neurotoxicity · Hyperexcitability · Uncommon symptoms · Atypical presentation

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Introduction

Oxaliplatin (OXA), a third generation organoplatinum compound is extensively used in the treatment of patients with colorectal cancer (CRC), either in the adjuvant or metastatic setting. Peripheral neuropathy in the form of acute or chronic, cumulative neurosensory toxicity is ranked among its main dose-limiting adverse effects.

Oxaliplatin-induced peripheral neuropathy (OXAIPN) may be mild, but could be also severe and disabling with a negative impact on the quality of life of patients [1].

Published data show that the majority of OXA-treated patients would manifest acute OXAIPN at a dose ranging from 85 to 130 mg/m^2 with incidences rates ranging from 65 to 98 % [2]. Clinically, the acute OXAIPN is typically characterized by the rapid onset of cold-induced paresthesias and dysesthesias affecting the oral and perioral region and distal limbs [3]. These clinical manifestations are usually reversible within hours or days, although there is an increase in both their duration and severity with repeated exposure to OXA and high cumulative OXA doses [2].

In addition to the typical acute hyperexcitability symptoms after OXA exposure, other uncommon symptoms, such as jaw spasm, difficulty in swallowing, voice and ocular changes, pseudolaryngospasm, and ptosis are also occasionally reported [4, 5]. The aim of this post hoc analysis of data extracted from a prospective, multicenter study was to assess and report the incidence of atypical acute OXAIPN symptoms in patients undergoing OXA-based chemotherapy. We also aimed at examining the relationship of the atypical presentation of acute OXAIPN with treatment regimen, single and cumulative OXA dose, and patients' demographic characteristics. The assessment of chronic OXAIPN was not included among the objectives of this study.

Patients and methods

One hundred adult, chemotherapy-naïve patients (62 males and 38 females mean aged 65 ± 8.7 years) with a histologically confirmed diagnosis of CRC, participated in this secondary (post hoc) analysis. The study protocol was approved by the corresponding ethics committee and written informed consent was obtained from all patients.

Enrolled patients were scheduled to receive OXA-based adjuvant or first-line treatment. Patients were included if they had satisfactory liver and renal function, a life expectancy of at least 9 months, and Karnofsky performance score ≥70. Patients with a known history of diseases that may cause or contribute to peripheral nerve damage (e.g., diabetes, renal insufficiency, alcohol abuse, vitamin B12 deficiency, etc.) were excluded.

FOLFOX-4 regimen (OXA 85 mg/m^2 as a 2-h infusion on day 1, 5-fluorouracil 400 mg/m^2 bolus on day 1-2, 5-fluorouracil 600 mg/m^2 22 hours infusion on day 1-2, every 14 days), 6 with FOLFOX-6 (OXA85 mg/m^2 as a 2-h infusion, 5-fluorouracil 400 mg/m^2 bolus and 5-fluorouracil 2400 mg/m^2 46 hours infusion all on day 1, every 14 days), and with XELOX (OXA 130 mg/m^2 as a 2-h infusion on day 1, oral capecitabine 2000 mg/m^2 daily for 14 days, every 21 days). The mean single OXA dose per course was 178 ± 42.9 (range 80–260 mg), while the mean cumulative OXA dose was 1,635 ± 306.5 (range 848–2,280 mg). No prophylactic or symptomatic treatment, including anticonvulsants or Ca/Mg infusions, was given for neurotoxicity during the administration of chemotherapy with OXA.

All patients underwent clinical neurologic evaluation after the administration of the 1st course of OXA-based chemotherapy. The clinical evaluation was repeated after six cycles of chemotherapy with either FOLFOX-4 or FOLFOX-6 regimens and after four cycles of XELOX. The final clinical follow-up assessment was performed after completion of OXA-based therapy at cycle 12 for FOLFOX and cycles 8 for XELOX. Blood counts and general biochemistry were examined before each OXA-based therapy administration.

During the evaluations at the time points mentioned above, patients were asked to report the incidence and characteristics of acute hyperexcitability symptoms. Apart from the typical acute cold-induced neurosensory symptoms, such as perioral paresthesias or pharyngolaryngeal dysesthesias, particular emphasis was given to collect data on the incidence of less common OXA-induced acute hyperexcitability symptoms including shortness of breath, swallowing difficulty, laryngospasm, muscle cramps, jaw spasms, fasciculations, voice and visual changes, and ptosis.

Statistical analysis

Descriptive statistics were generated for all variables. The association between the incidence of uncommon acute OXA-induced neurotoxic symptoms and the demographic and clinical characteristics of patients was assessed with the Student's t test. All tests were two-sided and significance was set at $p < 0.05$. Statistical analyses were performed using the SPSS for Windows (release 17.0; SPSS Inc., Chicago, IL, USA).

Results

Incidence of uncommon symptoms

Eighty-two patients (82 %) presented typical symptoms of acute OXAIPN in the form of cold-induced paresthesias and dysesthesias affecting the oral and perioral region and distal limbs. In 45/82 (54.9 %) of patients, also uncommon symptoms were present either individually or simultaneously (2 or 3 clinical uncommon symptoms). Shortness of breath (32 %), jaw spasm (26 %), fasciculations (25 %), cramps (20 %), and difficulty in swallowing (18 %) were more frequently reported, while voice (4 %) and visual changes (1 %), ptosis (1 %), and pseudolaryngospasm (1 %) occurred rarely.

As mentioned earlier, the formal assessments were performed at the middle and last course of OXA-based chemotherapy. However, during the follow-ups at the aforementioned time points, patients were asked to clarify the onset of symptomatology. All patients reported that atypical symptoms of acute OXAIPN were initially manifested within the first middle of OXA-based chemotherapy, between courses 2–5 for FOLFOX and 1–3 for XELOX, and were afterward presented after each subsequent OXA infusion. These symptoms started 6–24 h after the beginning of OXA infusion, without being triggered by cold, and were transient lasting for 24–72 h.

Atypical symptoms, particularly jaw spasms and cramps, tended to recur several times a day, usually presenting as paroxysmal episodes lasting from 1 to 5 min. However, none of the atypical symptoms significantly interfered with function, and as such no dose reduction or prolongation in the time of infusion was required because of their severity.

Associations of uncommon symptoms

Although a trend to significant correlation was present between the presence of at least one uncommon symptom of acute OXA neurotoxicity and the cumulative OXA dose ($p = 0.09$), no significant correlation was instead present between acute uncommon OXA neurotoxicity and the chemotherapy regimen ($p = 0.66$), single OXA dose ($p = 0.71$) or patients age ($p = 0.72$). No significant correlation was either present between the onset of individual acute OXA neurotoxicity uncommon manifestations and single or cumulative OXA dose (shortness of breath, $p = 0.41$ and 0.9; jaw spasm $p = 0.99$ and 0.39; fasciculations $p = 0.87$ and 0.36; cramps $p = 0.07$ and 0.34; difficulty in swallowing $p = 0.68$ and 0.65; voice changes $p = 0.31$ and 0.36; visual changes, ptosis, and pseudolaryngospasm $p = 1$ and 1). Similarly no association was present with the patient's age (shortness of breath, $p = 0.30$; jaw spasm $p = 0.18$; fasciculations $p = 0.90$; cramps $p = 0.16$; difficulty in swallowing $p = 0.33$). Finally, no correlation was present between the number of manifestations presented and the single and cumulative dose ($p = 0.78$) nor age. When tested individually, no association was found between the incidence of each atypical acute OXAIPN symptom and subsequent manifestation of cumulative OXAIPN. In all cases $p =$ ns.

Discussion

The severity of acute OXAIPN is difficult to quantify because neither cold-related symptoms nor other uncommon hyperexcitability phenomena are well addressed in common neurotoxicity scales, and the scales that are specifically focused on this issue have not yet been validated. In line with existing knowledge, typical cold-induced hyperexcitability phenomena were evident in all of our patients manifesting acute OXAIPN. These symptoms seem to be related to voltage-gated Na^+ channels dysfunction in the axonal membrane of sensory axons after OXA infusion [5]. In addition, cold exposure after OXA administration predisposes to ectopic activity, thus further affecting sodium channel kinetics [6].

Although frequently disregarded in clinical practice, apart from typical symptoms, a significant proportion of our patients presented with uncommon symptoms which remain unrelated to cold exposure, such as jaw spasm, fasciculations, cramps, and difficulty in swallowing. There is evidence that the clinical manifestation of these uncommon symptoms is ascribed to the ability of OXA to evoke an acute, abnormal hyperexcitability state of peripheral sensory and motor nerve fibers, resembling neuromyotonia, which also affects cranial nerves, such as trigeminal nerve fibers in the case of jaw spasm [2, 7]. It has been previously demonstrated that OXA can produce axonal hyperexcitability (neuromyotonia) and repetitive discharges in human nerve cells by evoking persistent sodium channel activity and/or decreased potassium conductance [8].

In our sample, no significant correlations emerged between the presence of acute uncommon neurotoxicity symptoms and the analyzed clinical and baseline characteristics of patients. Thus, we might suggest that this overrepresentation of the reported uncommon acute OXAIPN might be due to the 2-h time of OXA infusion [9]. On clinical grounds, and considering that OXA acute neurotoxicity might be related to the onset of chronic neurotoxicity, our results should alert physicians to closely monitor patients for early recognition of acute OXAIPN. As previously demonstrated [9], a prolonged OXA infusion rate from 2 to 4 or 6 h might be considered in patients with evidence of atypical presentation of acute OXAIPN in order to reduce the hazard of eventually developing treatment-emergent OXA-induced neurotoxicity.

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Conflict of interest The authors have declared no conflicts of interest.

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