Efficacy of controlled-release oxycodone for oxaliplatin-induced peripheral neuropathy in advanced colorectal cancer patients

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ABSTRACT

Oxaliplatin is used in the oxaliplatin-based regimen FOLFOX, a standard chemotherapeutic protocol for the treatment of advanced colorectal cancer (CRC) patients. The principal and dose-limiting cumulative toxicity associated with oxaliplatin-based chemotherapy is neurotoxicity.

These effects might last for several months and have had a significant impact on the continuation of oxaliplatin-based treatment, as these painful symptoms often disrupt the chemotherapy schedule. Furthermore, patients who are unable to complete a planned therapy program might suffer from chronic discomfort and a decreased QoL.

CIPN-related pain is predominantly neuropathic, and controlled-release (CR) oxycodone was found to be efficacious and tolerable for the treatment of neuropathic pain in several clinical settings. A meta-analysis of the role of opioids in the treatment of benign neuropathic pain showed that opioids, particularly oxycodone, were more effective than other agents. The objective of this study was to evaluate the efficacy and tolerability of oxycodone in oxaliplatin-induced peripheral neuropathy (OIPN) and its impact on FOLFOX therapy in cancer patients.

METHODS

A total of 64 advanced CRC patients with stage III or IV disease were included in this study. All eligible patients underwent gross resection of the primary CRC and subsequently received curative-intent FOLFOX therapy. The key inclusion criteria were as follows: ≥ 18 years of age, WHO PS score of 0 or 1, and a life expectancy of ≥ 6 months.

All patients received mFOLFOX6 therapy. mFOLFOX6 comprises, given every 2 weeks. Bevacizumab, cetuximab, or panitumumab was administered prior to mFOLFOX6 in 27 cases. FOLFOX was continued until disease progression (PD), the decision to use alternative therapies, unacceptable toxicities, or patient refusal of further treatment.

Patients with cancer-related pain who had been administered CR oxycodone during the FOLFOX period were defined as the OXY group. Patients who did not receive CR oxycodone treatment were defined as the non-OXY group (Table 1). Neurological toxicities were assessed according to the CTCAE version 3.0. The severity of neurological toxicity was evaluated as the worst score in each patient during FOLFOX therapy. A peripheral sensory neuropathy subscale was applied to grade the clinical severity as follows: grade 1, asymptomatic or with a loss of deep tendon reflex or paresthesia (including tingling) that did not interfere with function; grade 2, sensory alterations or paresthesia (including tingling) that interfered with function, but not with activities of daily living (ADL); and grade 3, sensory alterations or paresthesia that interfered with ADL.

Table 1 Baseline characteristics of eligible patients

	non-OXY (N=35)	OXY (N=29)
Mean age (range)	64.9 (48-76)	62.7 (48-75)
Gender		
Male	20	16
Female	15	13
Stage		
IIIA	1	0
IIIB	4	2
IIIC	7	2
IV	23	25
Chemotherapy regimen		
mFOLFOX	28	9
mFOLFOX +Bmab	7	18
mFOLFOX +Bmab+Pmab	0	2
Dose of CR oxycodone		
10mg		18
15mg		2
20mg		3
30mg		3
40mg		2
160mg		1

RESULTS

Opioids might be effective for the treatment of painful CIPN. In particular, oxycodone provided significant pain relief from peripheral neuropathic pain caused by post-herpetic neuralgia or diabetic neuropathy. Oxycodone could be considered a therapeutic option for CIPN.

We retrospectively investigated the efficacy and tolerability of CR oxycodone for OIPN during FOLFOX therapy in CRC patients. A total of 62.1% of patients in the OXY group continued FOLFOX therapy until PD. Conversely, only 20% of patients in the non-OXY group continued FOLFOX therapy until PD (Table 2). The cumulative oxaliplatin dose was significantly higher in the OXY group than in the non-OXY group (Table 4). Grade 3 sensory neuropathy only occurred in the non-OXY group (Table 3). These results suggest that CR oxycodone might prevent or improve the symptoms of OIPN in CRC patients.

Patients in the OXY group had longer survival than those in the non-OXY group (Figure 1).

Table 2 Causes of FOLFOX therapy discontinuation

	non-OXY (N=35)	OXY (N=29)
Progression disease	7	18
Peripheral neuropathy	10	0
Allergic reaction	6	4
Fever or infection	3	2
Scheduled change	0	3
General debilitation	5	0
Myelosuppression	2	0
Patient's preference	2	2

Table 3 CTCAE grading of sensory neuropathy

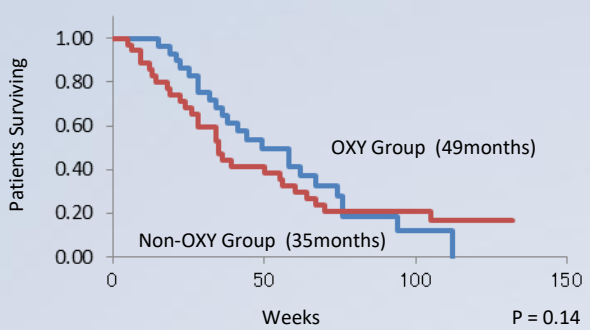
	non-OXY (N=35)	OXY (N=29)
Grade 1	9	4
Grade 2	24	25
Grade 3	2	0
Grade 4	0	0
Grade 5	0	0

Table 4 Frequency of FOLFOX cycles and total oxaliplatin dose

	non-OXY group (N=35)	OXY group (N=29)
Median of FOLFOX cycles (range)	7 (2-18)	13 (6-46) *
Median of total oxaliplatin dose (ramge)	483.0 mg/m^2 (76.2-1414.1)	1072.3 mg/m^2 * (408.7-3385.3)

* $P < 0.05$

Figure 1 Kaplan-Meier Estimates of Survival According to Study Group



CONCLUSIONS

In conclusion, we demonstrated that patients who were administered CR oxycodone received significantly more cycles of FOLFOX therapy and a higher cumulative oxaliplatin dose than did patients who were not administered CR oxycodone. Although this study had several limitations, the results suggest that CR oxycodone can attenuate OIPN and extend FOLFOX therapy in CRC patients.

REFERENCES

Efficacy and tolerability of controlled-release oxycodone for oxaliplatin-induced peripheral neuropathy and the extension of FOLFOX therapy in advanced colorectal cancer patients. Nagashima M, Ooshiro M, Moriyama A, *et al.* Support Care Cancer 22(6): 1579-84, 2014.

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