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Palonosetron for prevention of acute and delayed nausea and vomiting induced by moderately emetogenic adjuvant folfox-4 regimen in colorectal cancer (CRC) patients: A phase II study of the Gruppo Oncologico dell' Italia Meridionale (GOIM)

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ABSTRACT

Introduction: Folfox-4 is the standard adjuvant treatment in stage III colon cancer and is also recommended in high-risk stage II colon cancer. Oxaliplatin-based regimens are considered moderately emetogenic therapies. Palonosetron, a new selective inhibitor of 5-HT3 receptors, in combination with dexhametasone showed a high antiemetic activity in pivotal trials enrolling patients treated with moderately or high emetogenic regimens. Considering these data, the GOIM started a multicentre phase II trial aiming to evaluate the activity and safety of palonosetron plus dexhametasone in patients affected by radically resected colorectal cancer and treated with adjuvant folfox-4.

Materials and methods: Patients with stage III or high-risk stage II colorectal cancer and receiving folfox-4 as adjuvant treatment entered into the trial. Informed written consent was required. A single pretreatment dose of palonosetron 0.25 mg (intravenous) i.v. followed by dexamethasone 8 mg i.v. was administered. Nausea and vomiting were evaluated on day 1 and over the following 4 d, with a patient diary including vomiting episodes, daily nausea and use of rescue medications. The main end-point of the study was the absence of vomiting in the entire period (5 d) at the first cycle. The absence of moderately or severe nausea and vomiting on days 1–5 was the secondary end-point. Adverse events were evaluated according to the NCI-CTC criteria.

Results: Eighty-five patients entered into the study and were all evaluable for activity and safety. The absence of vomiting on the study period (days 1–5) was observed in 82 (96.5%) patients: one patient on the 1st and two on the 2nd day experienced mild vomiting. With respect to the secondary end-point, the complete control during the acute phase was 96.5% while during the late phase was 92%. The complete responses during the acute and delayed phases were 99% and 89.5%, respectively. The main side-effects (G1 grade) were: constipation 13%, headache 10%, vertigo and insomnia 2%.

Conclusions: Palonosetron is a very active antiemetic drug for the prevention of nausea and vomiting induced by folfox-4 regimen.

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1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) represents one of the most distressing experiences of cancer treatment. CINV significantly impairs quality of life, interferes with daily functions, can cause medical complications such as dehydration, malnutrition or electrolyte imbalance, and may affect the patients' ability to continue with the scheduled chemotherapy influencing survival in this way.[1]

Two major phases of CINV have been identified: an acute phase beginning immediately after the chemotherapy administration and resolving within 24 h and a delayed phase starting 24 or more hours after chemotherapy and lasting up to 120 h, rarely more, depending on the employed regimens.[2] A third category is anticipatory CINV that typically responds better to behavioural modification or non-pharmacological approach.[3] The control of both acute and delayed CINV is a relevant objective for the patient's quality of life and also aims to optimise cancer treatment.

The introduction of 5-HT3 receptor antagonists, ondansetron, granisetron, tropisetron and dolasetron, has determined a better control of emesis when compared with the traditional metoclopramide, and the addition of a corticosteroid to these 5-HT3 receptor antagonists, further improves the control of CINV with a response rate during the acute phase ranging from 50% to 70%.[4,5] In contrast, the effectiveness of the 5-HT3 receptor antagonists in preventing delayed CINV is less well established with some experiences reporting about 50% of the control.[6,7] The toxicity profile of 5-HT3 receptor antagonists is modest, the main side-effects being headache and constipation in 10–15% of patients. Despite some pharmacological differences, all these 5-HT3 receptor antagonists are considered therapeutically equivalent and interchangeable when employed at equipotent doses.[8–10]

Nevertheless, 5-HT3 receptor antagonists have increased the control of CINV, a substantial proportion of patients continue to experience both acute and particularly delayed CINV after moderately and high emetogenic chemotherapy. Therefore, there is a strong need to develop new agents to improve control rate and patient care.

Palonosetron is a highly potent second generation selective 5-HT3 receptor antagonist with a 100-fold stronger binding affinity for the 5-HT3 receptor.[11] In contrast to other 5-HT3 receptor antagonists that exist as racemic mixtures, Palonosetron exists as a single stereoisomer with better pharmacological and pharmacokinetic profiles.[12] In preclinical studies, palonosetron demonstrated potent antiemetic properties in several animal models, and in previous phase I studies Palonosetron was found to be well tolerated and to have mean plasma elimination half-life values of about 40 h,[13] longer than that of ondansetron (4–6 h), granisetron (5–8 h), tropisetron (7 h) and dolasetron (7 h).[14] Both the high binding affinity and the long half-life give palonosetron the possibility to provide more complete and prolonged protection against CINV than that of the other 5-HT3 receptor antagonists. In two randomised studies, a single intravenous dose of Palonosetron 0.25 mg provided a statistically significant improvement in complete response compared with ondansetron 32 mg or dolasetron 100 mg, in patients treated with moderately emetogenic chemotherapy.[15,16] In both these studies, corticosteroids were not added to 5-HT3 receptor antagonist premedication. In another randomised trial enrolling patients treated with highly emetogenic chemotherapy, Palonosetron plus dexhametasone proved to be at least as effective as ondansetron in preventing acute CINV with a slightly higher control of delayed CINV.[17]

Oxaliplatin (L-OHP) plus 5-fluorouracil (5FU) modulated by folinic acid (FA) and administered part in bolus and part in continuous infusion according to the De Gramont's schedule is considered the standard adjuvant treatment in stage III and is recommended in stage II high-risk colorectal cancer (CRC) patients.[18] Oxaliplatin is considered a moderately emetogenic drug[19–21] and the current guidelines recommend to employ a combination of 5-HT3 receptor antagonist plus dexhametasone as prophylactic antiemetic regimen in patients treated with moderately emetogenic chemotherapy.[22]

Considering these data, the GOIM started a multicentre phase II study to evaluate the activity and safety of Palonosetron plus dexhametasone in preventing acute and delayed CINV in adjuvant CRC patients treated with folfox-4 regimen.

2. Patients and methods

2.1. *Patients selection*

Eligible patients were chemonaive males or females $\geqslant$18 years of age with histological diagnosis of stage III or high-risk stage II colorectal cancer and were candidates to receive folfox-4 regimen as adjuvant treatment. Patients had to have a performance status 0–1 (ECOG scale), adequate bone marrow reserve and renal and hepatic function and no cardiovascular impairments. Patients had to be available to complete their diary and to sign written informed consent; fertile women had to use an adequate contraception.

Patients were excluded if they were unable to understand or cooperate with the study procedures and if they had taken any antiemetic drug within 24 h prior to treatment until day 5 post-treatment. Evidence of disorders requiring anticonvulsant therapy, clinical evidence of intestinal subocclusion, electrolytes abnormalities, presence of nausea or vomiting during the screening phase were considered exclusion criteria.

2.2. *Study design and treatment regimen*

This was a multicentre phase II study conducted in four Italian centres. The study protocol was approved by the Ethic Committee of each participating site.

The enrolled patients received a single dose of Palonosetron 0.25 mg i.v. bolus plus dexhametasone 8 mg i.v. on day 1, 30 minutes before the folfox-4 regimen that was administered as follows: oxaliplatin at 85 mg/m^2 on day 1, folinic acid at 100 mg/m^2 on days 1–2, fluorouracil bolus at 400 mg/m^2 on days 1–2 and fluorouracil 22 h continuous infusion on days 1–2, every 2 weeks.

Only dexhametasone was permitted as rescue medication.

2.3. *Efficacy parameters*

The primary efficacy end-point of the study was the overall percentage of patients who achieved a complete response defined as no episodes of vomiting without use of rescue medication for the entire period of study (0–120 h).

The secondary end-points assessed during the acute phase (within the first 24 h after chemotherapy) and during the late phase (24–120 h) separately for each day and for the entire period, included: full control percentage (defined as no episodes of vomiting, without use of rescue medication, with maximum degree of nausea = mild), complete response during acute phase, nausea intensity classified according to Likert's scale (from zero = none to 3 = severe), number and duration of episodes of vomiting, the global satisfaction of the antiemetic therapy, measured with a visual-analogic scale (VAS), and the safety.

2.4. *Study visits and procedures*

Consenting patients were initially screened for 15 d before starting treatment. During this time period the following were recorded: history of nausea and vomiting, physical examination, vital signs, weight and performance status, laboratory tests, concomitant medications.

During the first 24 h after the treatment (day 1) each patient reported on his diary the following: number and timing of emetic episodes, use of rescue medication, severity of nausea and patient global satisfaction.

On days 2–5, each patient reported on his diary the following: emetic episodes, severity of nausea, rescue medication, other side-effects.

Safety was evaluated for a period of 15 d, according to NCI common toxicity criteria NCTC version 2.

2.5. *Statistical analysis*

The statistical analysis was performed according to Fleming's one step study design.[23] Considering $\pi = 0.20$ as null hypothesis and $\pi \geqslant 0.35$ as acceptable hypothesis, with an α error = 0.05 and $\beta = 0.90$, at least 77 patients had to be enrolled. Adding about 5% of patients not eligible, or lost to follow-up or withdrew for major violation, a minimum of 81 patients had to be enrolled.

The evaluation of the primary and secondary end-points was performed according to an intent-to-treat (ITT) analysis.

3. Results

From October 2006 to November 2007, 85 patients entered into the study. Their main characteristics were median age: 67 years (range 27–82), median PS: 0 (range 0–1), primary site: colon 61 (72%) and rectum 24 (28%), stage III: 60 (70%), high-risk stage II: 25 (30%) (Table 1).

All patients were evaluable for activity and safety. With regard to the primary end-point, the number of patients who achieved a complete response (absence of vomiting during the overall treatment period of the study 0–120 h) was 82 (96.5%) (Table 2). With regard to the secondary end-points, the complete control during the acute phase was 96.5%, while during the delayed phase was 92% (Table 3). The complete responses during the acute and late phases were 99% and 89.5%, respectively (Table 4).

Table 1 – Patients' characteristics

Median age	67 years (range = 27–82 years)
Sex	M: 56 points (66%)
	F: 29 points (34%)
PS (ECOG)	0: 68 points (80%)
	1: 17 points (20%)
Primary site of disease	Colon: 61 points (72%)
	Rectum: 24 points (28%)
Stage	IIB: 25 points (30%)
	III: 60 points (70%)

Table 2 – Primary end-point: complete response

	Absent	Present
Vomiting (days 1–5)	82 (96%)	3 (4%)

Table 3 – Secondary-end-point: complete control

	Number of patients (%)
Day 1	82 (96.5%)
Days 2–5	79 (92%)

Table 4 – Secondary-end-point: complete response and number of nausea and vomiting episodes

	Absent	Mild	Moderate	Severe
Nausea (day 1)	72 (85%)	11 (13%)	2 (2%)	0
Nausea (days 2–5)	68 (80%)	13 (15%)	3 (4%)	1 (1%)
Vomiting (day 1)	84 (99%)	1* (1%)	0	0
Vomiting (days 2–5)	83 (97%)	2** (3%)	0	0

* Acute phase.
** Delayed phase.

The treatment was well tolerated. Consistent with previous studies with 5-HT3 receptor antagonists, we observed the following percentage of toxicities: headache 10%, constipation 13%, vertigo 2%, insomnia 2%. All the toxicities were mild in severity. There were no significant treatment-related changes in laboratory measures or vital signs. The median value of patients' satisfaction was very high with 9 points (range 2–10).

4. Discussion

At our knowledge this study is the largest phase II trial evaluating the role of single dose Palonosetron plus dexhametasone in preventing acute and delayed CINV in a homogeneous chemonaive cancer patient population. With regard to the primary end-point, i.e. the number of patients

with a complete response (absence of vomiting for the entire study period), the rate was 96.5%. In the acute phase, the percentage of complete control (absence of vomiting with maximum mild nausea) was 96.5%, while in the late phase the complete control was observed in 92% of patients. The complete responses during the acute and late phases were 99% and 89.5%, respectively. These results are the best reported in the literature. No patients delayed the treatment due to emesis and this result, considering the importance to maintain a correct timing of chemotherapy administration in an adjuvant setting, seems also more relevant to us.

The Palonosetron dose used in this study was based on a phase II dose-ranging study showing Palonosetron 3.0 μg/kg (fixed dose of approximately 0.25 mg) to be the minimally effective dose for the prevention of highly emetogenic CINV.[24] The addition of dexhametasone at 8 mg was based according to the current guidelines for preventing CINV in patients treated with moderately emetogenic chemotherapies. We chose to treat a homogeneous population, regarding the type of cancer and the chemotherapy regimen administered, to evaluate the real impact of Palonosetron in preventing acute and delayed CINV. The pivotal phase III trials exploring the activity of Palonosetron did not use the 5-HT3 receptor antagonist in combination with dexhametasone and enrolled heterogeneous populations of patients with the disadvantage to have no uniform elegibility criteria and to employ different chemotherapy regimens.[15,16] These reasons could explain the better results observed in our experience compared to the others. In another little phase II trial Palonosetron 0.25 mg was administered in combination with dexhametasone at 8 mg, as in our study, to 32 patients receiving at least one qualifying moderately emetogenic agents such as cyclophosphamide, doxorubicin, carboplatin or oxaliplatin. Twenty-seven (84%) patients had a complete response during the acute phase and 19 (59%) had a complete response during the delayed interval.[25] Also these results are slightly inferior to those observed in our experience and maybe reflect the difference in the chemotherapeutic regimens employed.

Palonosetron was well tolerated. Only a small proportion of events were considered possibly or probably related to study medication. Consistent with previous studies of 5-HT3 receptor antagonists the most frequently reported adverse events were mild headache 10%, constipation 13%, vertigo and insomnia 2%, respectively.

The antiemetic treatment was appreciated by the study population with a median value of patients' satisfaction, measured by VAS scale, of 9 points (range 2–10).

In conclusion Palonosetron plus dexhametasone given as pretreatment infusion is effective and safe in preventing acute and delayed CINV in CRC patients receiving moderately emetogenic folfox-4 regimen. This combination is recommended as the most active to prevent acute and delayed CINV in CRC adjuvant setting.

Conflict of interest statement

All authors disclose no financial and personal relationships with industries and organisations that can inappropriately influence this work.

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