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Editorial Comment

Potential new agents in the prophylaxis and treatment of chemotherapy-induced emesis

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Results from the first two clinical trials investigating the antiemetic effect of a serotonin$_3$ (5-HT$_3$)-receptor antagonist were published in 1987. The 5-HT$_3$-receptor antagonists were the first group of drugs specially designed as antiemetics, and today they are well-established and have revolutionised the prophylaxis of acute chemotherapy-induced nausea and vomiting.

According to recently published guidelines [1,2], the combination of a 5-HT$_3$-receptor antagonist and a corticosteroid is recommended as antiemetic therapy during the initial 24 h after the start of treatment with moderately or highly emetogenic chemotherapy. Using such a combination, 60–90% of patients receiving cisplatin-based chemotherapy and 70–90% of those receiving moderately emetogenic chemotherapy have no emesis during the initial 24 h after chemotherapy.

There are, however, a number of remaining problems in antiemetic therapy. The 5-HT$_3$-receptor antagonists are more successful in the prophylaxis of vomiting than in prevention of nausea from chemotherapy. Accordingly vomiting, which was the most severe chemotherapy-induced symptom before the introduction of the 5-HT$_3$-receptor antagonists, is now ranked fifth by the patients, whereas nausea is today reported as the most severe [3]. Prophylaxis of delayed emesis (later than 24 h after chemotherapy) is less successful than prophylaxis in the acute phase, and the role of 5-HT$_3$-receptor antagonists is only modest. Therapy should be based on a corticosteroid combined with a dopamine- or a 5-HT$_3$-receptor antagonist [1,2]. Another problem is the declining efficacy of antiemetic therapy during multiple cycles of chemotherapy [4]. The vast majority of studies have investigated antiemetic efficacy during the initial cycle of chemotherapy only. Patients often receive four to six cycles of chemotherapy and the high protection rate against emesis obtained during the first cycle is difficult to maintain [4].

Studies addressing antiemetic protection in patients receiving high-dose chemotherapy and bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT) are small and often heterogeneous, but results indicate that protection rates are lower compared with conventional dose chemotherapy [5]. Little is known about optimal antiemetic therapy in patients with refractory emesis during previous cycles of chemotherapy and in patients with breakthrough emesis. Addition of a dopamine antagonist in patients with refractory emesis after treatment with cisplatin and antiemetic therapy with a 5-HT$_3$-receptor antagonist plus a corticosteroid seems useful [6].

Several attempts have been initiated to develop new antiemetics such as serotonin synthesis inhibitors and drugs acting at different neuroreceptors including 5-HT$_{1A}$, 5-HT$_{2A/2C}$, 5-HT$_4$ and dopamine D$_3$, but none of these agents has so far gone into clinical trials.

The most promising group of potential new antiemetics is the substance P antagonists. The tachykinin substance P was isolated in 1931, but was not purified and sequenced before 1970. Until recently, it was thought that substance P was the only mammalian tachykinin, but now the tachykinin family also include the decapeptides neurokinin A (NKA) and neurokinin B (NKB) and the neuropeptides K (NPK) and γ (NPγ). The receptors for the tachykinins have been cloned and identified as G-protein coupled receptors NK$_1$, NK$_2$ and NK$_3$ [7] with substance P as the preferred ligand at NK$_1$ receptors. The potential therapeutic role of the tachykinin antagonists include emesis, depression and anxiety as the most likely areas for new drug development, but research has also been directed towards the treatment of pain, migraine and respiratory diseases. NK$_1$ receptor antagonists require entry into the central nervous system to have antiemetic effect. An obstacle for the clinical use of NK$_1$ receptor antagonists as

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antiemetics was therefore the inability to penetrate through the blood–brain barrier, but today highly selective non-peptide NK_1 receptor antagonists with nanomolar affinity for human, central NK_1 receptors have been developed [8]. These have shown a broad antiemetic spectrum in different species such as ferrets, *Suncus murinus*, cats and dogs, but species differences in the affinity for the NK_1 receptor, have made it difficult to predict antiemetic potential in humans from animal models.

In this issue of the *European Journal of Cancer*, Cocquyt and colleagues (pp. 835–843) compare the antiemetic effect of L-758,298 (a prodrug for the NK_1 antagonist, MK-0869) and the serotonin antagonist, ondansetron, in a randomised, double-blind study [12]. 53 patients received cisplatin-based chemotherapy 50–100 mg/m^2 and were randomised to antiemetic therapy with a single i.v. dose of L-758,298 or ondansetron (Table 1). It is well known that acute emesis is a prognostic factor for occurrence of delayed emesis in patients receiving cisplatin. It is therefore of interest that, although 52% of the patients receiving ondansetron did not have acute emesis compared with 37% of those receiving L-758,298, the authors found a statistically significant difference in complete protection from delayed emesis in favour of L-758,298 (30 versus 72%, $P = 0.005$).

Four clinical trials (three randomised, double-blind), published in peer-reviewed journals, have investigated the antiemetic effect of one of the non-peptide NK_1 antagonists (Table 1). The studies include a limited number of patients, investigate patients receiving cisplatin-based chemotherapy only, and have been criticised because standard antiemetic therapy was not used in the delayed phase [13,14]. In spite of these limitations, it is noteworthy that all the studies indicate significant effect of the NK_1 antagonists against delayed cisplatin-induced emesis, because results with standard antiemetic therapy are far from optimal.

A few conclusions can be drawn from the preliminary available studies: (1) a NK_1 antagonist is not superior to a 5-HT_3 antagonist (might even be inferior) in the treatment of acute emesis induced by cisplatin, but seems to improve the efficacy of the standard combination of a 5-HT_3 antagonist plus a corticosteroid; (2) NK_1 antagonists are superior to placebo in the treatment of cisplatin-induced delayed emesis; (3) adverse events have been mild.

Table 1
Clinical studies investigating the use of NK_1 receptor antagonists in the prophylaxis of chemotherapy-induced nausea and vomiting

Author [Ref.]	Study design	Patients (*n*)	Chemotherapy (mg/m^2)	Antiemetics	Day 1 (% with no emetic episodes)[a]	Days 2–5 (% with no emetic episodes)[a]
Kris [9]	Uncontrolled	7	Cisplatin ⩾ 80	CP-122,721 p.o.×1 50–200 mg, day 1	15	86
		10		CP-122,721 p.o.×1 50–200 mg plus serotonin antagonist plus DEX day 1	100	80
Hesketh [10]	MC, R, DB, P Two-arm study	61	Cisplatin ⩾ 100	GRA plus DEX day 1 versus	67	37
				GRA plus DEX day 1 plus CJ-11,974 p.o.×2, 100 mg, days 1–5	86	68[b]
Navari [11]	MC, R, DB, P Three-arm study with stratification for sex and additional emetogenic CT	159	Cisplatin ⩾ 70	GRA plus DEX day 1 versus	67	33
				GRA plus DEX day 1 plus L-754,030 p.o×1, 400 mg day 1 and 300 mg days 2–5 versus	93 } 93[c]	82 } 80[c]
				GRA plus DEX day 1 plus L-754,030 p.o.×1, 400 mg day 1	94	78
Cocquyt [12]	MC, R, DB, P Two-arm study with 1.5/1 ratio R to L-758,298/OND	53	Cisplatin = 50–100	OND 32 mg i.v.× 1, day 1 versus	52	30
				L-758,298 i.v.×1, 60–100 mg, day 1	37	72[d]

MC, multicentre; R, randomised; DB, double-blind; P, parallel; GRA, granisetron; DEX, dexamethasone; CT, chemotherapy; OND, ondansetron, p.o., orally.

[a] In [12] patients were observed for 7 days post-cisplatin.

[b] $P < 0.05$.

[c] $P < 0.001$ (arm 2 + 3 combined versus arm 1).

[d] $P = 0.005$.

NK_1 antagonists have potential use as part of the armamentarium of drugs against chemotherapy-induced emesis, but a number of issues still need to be investigated. What is the optimal schedule of NK_1 antagonists? Can NK_1 antagonists add to the efficacy of standard antiemetics in patients receiving multiple cycles of moderately and highly emetogenic chemotherapy? What about the effect in patients receiving highly emetogenic non-cisplatin chemotherapy with BMT or PBSCT? No antiemetics have verifiable efficacy against chemotherapy-induced breakthrough emesis, but NK_1 antagonists might be useful and should be investigated in this setting, because one of the NK_1 antagonists (GR205171) was superior to placebo in the treatment of established postoperative nausea and vomiting [15].

The time has now come for initiation of large phase III trials investigating the use of NK_1 antagonists in patients receiving optimal standard antiemetic therapy both in the acute and delayed phase.

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