Antiemetics: State of the art

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Introduction

In 1958, the first patient with a solid tumour was cured by chemotherapy. Methotrexate, the antineoplastic agent used, is not highly emetogenic and prophylactic antiemetic therapy was not part of the treatment plan. Ten years later, combination chemotherapy became more and more commonly used and consequently the emetogenic potential of therapy increased, leading to a beginning interest in antiemetic drugs. One of the first clinical trials was done by Moertel and colleagues [1]. They investigated five different drugs in a double-blind randomised trial and demonstrated that two of these had some activity against 5-fluourouracil-induced emesis. The interest in antiemetic drug development was markedly increased when the US Food and Drug Administration (FDA) approved cisplatin in 1978. Patients treated with cisplatin will all vomit within the first 24 h after infusion, and the majority of these within the first 2–4 h [2].

The first effective antiemetic prophylaxis in patients receiving cisplatin-based chemotherapy was high doses of metoclopramide, as described by Gralla and colleagues in 1981 [2]. The effect was thought to be mediated through blockade of dopamine receptors, but the later understanding that the effect was due to antagonism at serotonin$_3$ receptors led to a breakthrough in antiemetic drug development. Today, many patients have the good fortune of receiving combination antiemetic drug prophylaxis from their first course of chemotherapy, as recommended by evidence-based guidelines [3,4].

Antiemetics

Basically, antiemetics can be divided into four groups: dopamine (D)$_2$-receptor antagonists (D$_2$-RAs), corticosteroids, serotonin (5-HT)$_3$-receptor antagonists (5-HT$_3$-RAs) and neurokinin$_1$-receptor antagonists (NK$_1$-RAs). Furthermore, cannabinoids are used as the fourth or fifth choice in some countries, whereas their use is illegal in others.

Although D$_2$-RAs were the first antiemetics to be used, these drugs are today primarily useful as rescue antiemetics, and are not recommended by guidelines as part of first choice antiemetic regimens. The primary reason for the ignorance of these drugs is the frequent induction of extrapyramidal side effects, in particular in younger patients. Two of these drugs, domperidone and metopimazine, do not cause extrapyramidal side effects, but are not distributed worldwide. This is annoying because metopimazine is effective against nausea [12], which today is a more troublesome chemotherapy-induced side effect than vomiting.

The 5-HT$_3$-RAs were the first class of drugs specifically developed for the purpose of antiemesis. Drugs like ondansetron, granisetron, tropisetron, dolasetron and lately palonosetron [13–16] have significantly reduced the number of patients suffering from chemotherapy-induced vomiting, whereas the efficacy against nausea has been less pronounced. These drugs make up the basis of antiemetic drug combinations, particularly against acute emesis (0–24 h after initiation of chemotherapy).

Corticosteroids have been used as antiemetics for more than 30 years. It is therefore thought-provoking that our knowledge about the mechanism of action and optimal dose schedule is still limited. We know that corticosteroids improve the effect of almost all other antiemetics, have some effect against nausea and are well tolerated when administered as antiemetics for 1–5 days.

NK$_1$-RAs were the second class of drugs designed as antiemetics. Aprepitant [5–9] was approved by the FDA in 2003, and the second drug in the class, casopitant, has completed phase III studies and has applied for FDA approval [10,11,17]. The NK$_1$-RAs improve the effect of a 5-HT$_3$-RA plus dexamethasone in patients receiving cisplatin-based chemotherapy and in women treated with a combination of cyclophosphamide plus an anthracycline. The most significant effect is achieved against vomiting, whereas the effect against nausea seems to be limited and restricted to comprising cisplatin-induced nausea only. Contrary to the 5-HT$_3$-RAs, the effect seems more pronounced

Table 1
Phase III studies with the neurokinin$_1$-receptor antagonists, aprepitant and casopitant

Author	Design	Patients	Chemotherapy	Antiemetics[a]	CR			No EE			No Nausea		
					D1	D2–5	D1–5	D1	D2–5	D1–5	D1	D2–5	D1–5
Warr 2005 [5]	R, DB, 2P	N = 866 CT-naive	CTX and DOX/EPI	1. OND D2–3	69%	49%	42%	77%	69%	59%	NA	NA	33%
				2. APR D1–3	**76%**	55%	**51%**	**88%**	**81%**	**76%**	NA	NA	33%
Yeo 2009 [6]	R, DB, 2P	N = 127 CT-naive	CTX and DOX/EPI	1. OND D2–3	73%	58%	42%	74%	67%	50%	60%	60%	36%
				2. APR D1–3	72%	64%	47%	72%	76%	55%	62%	47%	31%
Poli-Bigelli 2003 [7]	R, DB, 2P	N = 569 CT-naive	CIS $\geqslant$ 70 mg/m^2 plus others	All DEX D2–4									
				1. PLA	68%	47%	43%	69%	48%	44%	NA	40%	39%
				2. APR D1–3	**83%**	**68%**	**63%**	**84%**	**72%**	**66%**	NA	**53%**	**49%**
Hesketh 2003 [8]	R, DB, 2P	N = 530 CT-naive	CIS $\geqslant$ 70 mg/m^2 plus others	All DEX D2–4									
				1. PLA	78%	56%	52%	79%	59%	55%	69%	48%	44%
				2. APR D1–3	**89%**	**75%**	**73%**	**90%**	**81%**	**78%**	72%	51%	48%
Schmoll 2006 [9]	R, DB, 2P	N = 489 CT-naive	CIS $\geqslant$ 70 mg/m^2 plus others	All DEX D2–4									
				1. OND D 2–4	79%	63%	61%	81%	64%	62%	NA	NA	NA
				2. APR D1–3	**88%**	**74%**	**72%**	**89%**	**79%**	**77%**	NA	NA	NA
Herrstedt 2009 [10]	R, DB, 4P	N = 1917 CT-naive	CTX and DOX/EPI	All OND D2–3									
				1. PLA	85%	59%	59%	86%	63%	63%	71%	35%	35%
				2. CAS D1 (po)	88%	73%	**73%**	**91%**	**80%**	**80%**	66%	38%	38%
				3. CAS D1–3 (iv D1/po D2–3)	86%	74%	**74%**	88%	**78%**	**78%**	67%	39%	39%
				4. CAS D1–3 po	89%	73%	**73%**	**91%**	**81%**	**81%**	64%	33%	33%
Grunberg 2009 [11]	R, DB, 3P	N = 800 CT-naive	CIS $\geqslant$ 70 mg/m^2 plus others	All DEX D2–4									
				1. PLA	88%	66%	66%	89%	68%	68%	76%	46%	46%
				2. CAS D1–3 (po)	**95%**	86%	**86%**	**96%**	89%	**89%**	**84%**	57%	**57%**
				3. CAS D1–3 (iv D1/po D2–3)	**94%**	80%	**80%**	**94%**	83%	**83%**	**84%**	55%	**55%**

[a] In all study arms patients received OND + DEX D1
$P < 0.05$ for entries in bold.
CTX = cyclophosphamide; DOX = doxorubicin; EPI = epirubicin; CIS = cisplatin; OND = ondansetron; DEX = dexamethasone; APR = aprepitant; CAS = casopitant; PLA = placebo; CR = no emesis and no rescue medication; EE = emetic episode; D = day; CT = chemotherapy; R = randomised; DB = double-blind; 2P, 3P, 4P = parallel design and 2, 3 or 4 arms respectively; NA = data not available;

against delayed emesis (24–120 h after initiation of chemotherapy).

Conclusion

This lecture will include a review of phase III trials with the new 5-HT_3-RA, palonosetron, and the NK_1-RAs, aprepitant and casopitant (Table 1).

The questions: "Are there differences between the 5-HT_3-RAs?" and "Are there differences between the NK_1-RAs?" will be addressed.

Finally, a summary of the latest update (June 2009) of the evidence-based guidelines developed by the Multinational Association of Supportive Care in Cancer (MASCC) and ESMO will be presented.

Conflict of interest statement

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