Anti-emetics 2005: an overview and the MASCC guidelines applied in practice

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Development of anti-emetic therapy

Twenty-five years ago, anti-emetic therapy was limited to use of corticosteroids, antihistamines and dopamine D_2-receptor antagonists. The first major step in the development of effective anti-emetic therapy, took place in 1981 with the recognition that metoclopramide in high doses is effective in the prophylaxis of emesis induced by cisplatin. The second important step was the development of serotonin$_3$-receptor antagonists (5-HT$_3$-RAs). For the first time a new class of drugs was developed specifically for the purpose of antiemesis. Since the publication of the first clinical trial in 1987, a large number of randomised studies have established the 5-HT$_3$-RAs as essential in the prophylaxis of acute emesis (0–24 hours) after chemotherapy (Table 1). Until recently, the combination of a 5-HT$_3$-RA and a corticosteroid was considered the standard prophylaxis of acute emesis after highly- and moderately emetogenic chemotherapy (HEC and MEC).

New drugs

The finding that substance P is involved in the induction of chemotherapy-induced emesis was another step forward. Substance P is the preferred ligand at neurokinin (NK)$_1$-receptors, and the first agent of this class, aprepitant, has been investigated in 5 phase II, and 3 phase III trials [1–3]. These studies have shown, that aprepitant is not a replacement for the 5-HT$_3$-RAs, but increases the anti-emetic effect of a 5-HT$_3$-RA (ondansetron) plus a corticosteroid (dexamethasone) against acute emesis induced by HEC [1,2] or MEC [3]. None of the phase III trials was specifically designed to investigate the use of aprepitant in delayed emesis (24–120 hours after chemotherapy), but with this limitation in mind, and considering results from phase II trials, it seems reasonable to conclude that aprepitant improves the effect of dexamethasone in delayed emesis [1,2] induced by HEC.

Table 1
Important stages of development in the management of chemotherapy-induced emesis

1979	A corticosteroid is superior to placebo against chemotherapy-induced emesis.
1981	High-dose metoclopramide (hd-MCP) is effective against cisplatin-induced emesis.
1983	A corticosteroid improves the effect of hd-MCP against cisplatin-induced emesis.
1987	First publications of clinical trials with a serotonin receptor antagonist (5-HT$_3$-RA).
1990	A corticosteroid improves the effect of 5-HT$_3$-RAs against cisplatin-induced emesis.
1994–95	A corticosteroid improves the effect of 5-HT$_3$-RAs against emesis induced by MEC.
1997	First publication of a clinical trial with a neurokinin$_1$-receptor antagonist (NK$_1$-RA).
1998	MASCC evidence-based recommendations.
1999	ASCO evidence-based recommendations.
2001	ESMO Minimum Clinical Recommendations.
2003	The NK$_1$-RA, aprepitant, improves the effect of a 5-HT$_3$hyphen;RA plus a corticosteroid against cisplatin-induced emesis.
2004	Development of ' global recommendations' (representing nine international societies).
2005	The NK$_1$-RA, aprepitant, improves the effect of a 5-HT$_3$hyphen;RA plus a corticosteroid against emesis induced by MEC.
2005	Update of MASCC evidence-based recommendations.
2005	Update of ESMO Minimum Clinical Recommendations

A large number of different 5–HT_3–RAs have been developed. With palonosetron as a possible exception, it is the general impression that there are no major differences in effect or toxicity of these agents [4,5]. Palonosetron, has been investigated in five phase I–II trials. It has a potent and selective binding affinity for the 5-HT_3 receptor and a long elimination with a half-life of approximately 40 hours. Three randomised, double-blind phase III studies have compared the effect of palonosetron, with dolasetron and ondansetron respectively [6–8]. The studies were designed as non-inferiority studies and showed that palonosetron was at least as effective as ondansetron and dolasetron. In the two studies including patients receiving MEC [6,7], a number of parameters significantly favoured palonosetron as compared with ondansetron and dolasetron.

Guidelines

The Multinational Association of Supportive Care in Cancer (MASCC) developed their first set of evidence-based guidelines for chemotherapy- and radiotherapy-induced nausea and vomiting in 1997 [4]. Also the American Society for Clinical Oncology (ASCO) [5], the European Society for Medical Oncology (ESMO) [9], the National Comprehensive Cancer Network (NCCN), the American Society of Health-System Pharmacists (ASHP) and The Canadian Consensus Group have developed anti-emetic guidelines.

' Global' guidelines were developed in 2004 by representatives from nine international organizations. MASCC has published these guidelines in the journal of Supportive Care in Cancer. The guidelines include a redefinition of the emetic risk potential of cytotoxins, including new agents [10]. The guidelines recommend that aprepitant is included in the prophylaxis of emesis from HEC [11]. At the time of the consensus meeting, no published studies had investigated the use of aprepitant in patients treated with MEC. Consequently, the recommendation is (May 2005) to use the combination of a 5-HT_3-RA plus dexamethasone in these patients [12,13]. An updating of the guidelines is expected end of May and will probably change recommendations.

Implementation of guidelines

Several studies have shown that implementation of anti-emetic guidelines is difficult, but worth-while, because patients, who receive evidence-based anti-emetic therapy, do better [14] and because implementation of guidelines can be cost-saving [15]. A survey, done during the 27th Congress of ESMO 2002, showed, that the ESMO web page is the preferred way to access guidelines. The MASCC guidelines are published on www.mascc.org., and updated every six months.

Conclusion

Although prevention of chemotherapy-induced nausea and vomiting has been one of the most successful areas of supportive care, improvements are still needed. The new agents have been less effective in prevention of nausea, and also delayed nausea and vomiting continue to be disturbing adverse events to chemotherapy. Recent data suggest that pretreatment genotyping could be a suitable way to optimise anti-emetic therapy in individual patients.

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