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The role of second-generation 5-HT_3 receptor antagonists in managing chemotherapy-induced nausea and vomiting in hematological malignancies

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Abstract

Compared with solid tumor patients, those with hematological malignancies are at particular risk of chemotherapy-induced nausea and vomiting (CINV) because of their young age, exposure to highly-emetogenic induction, consolidation and salvage regimens, the high-dose conditioning regimens used before stem cell transplantation (SCT), and the heavy psychological burden of such treatments. In the absence of prophylaxis, around 75% of patients undergoing SCT experience delayed CINV. With first-generation 5-HT_3 receptor antagonists, only about 20% are completely protected from nausea and vomiting, and this frequent and debilitating adverse event has not been fully addressed. In contrast to solid tumors, there are no internationally agreed guidelines for the prevention and treatment of CINV in hematological malignancies. Work on a consensus is urgently required. The second-generation 5-HT_3 antagonist palonosetron is highly effective in preventing CINV in patients with solid tumors. The extended half-life of this agent and its mechanisms of action including allosteric binding, positive cooperativity

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and 5-HT_3 receptor internalization, may make it particularly effective in controlling delayed CINV. Although controlled comparisons against first-generation 5HT_3 agents have not yet been conducted in the setting of SCT, available evidence suggests that palonosetron may prove beneficial in preventing CINV in high risk patients with hematological malignancies.

Keywords: Chemotherapy-induced nausea and vomiting; Antiemetics; 5HT3 receptor antagonists; Palonosetron; Stem cell transplantation

1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common, distressing, debilitating and costly side effect associated with the administration of chemotherapy. Without adequate anti-emetic treatment, CINV is experienced by up to 90% of patients, depending on individual risk factors and the emetogenicity of the chemotherapeutic agents used [1,2]. Conventionally, a distinction is made between acute CINV, occurring within 24 h of chemotherapy, and delayed CINV which occurs between 24 and 120 h after chemotherapy administration. Following repeated chemotherapy cycles, patients may also experience anticipatory vomiting and nausea [3].

Patients suffering moderate-severe CINV rate the experience as worse than treatment-related fatigue, diarrhea and mucositis [4]. Besides greatly impairing patients' quality of life (QoL) and functional status [5,6], CINV compromises anti-cancer treatment through reduced compliance, causes dehydration and electrolyte imbalance [2,7], and may require rehospitalisation [8]. A study of more than sixty thousand chemotherapy patients treated in the United States in 1996 found that, on average, those with CINV spent two days longer in hospital than those without this complication, and the total cost of their treatment was greater by one third [9]. A further relevant aspect, especially valid as applied to delayed nausea and vomiting, is the existence of a clinically significant gap between what is perceived by physicians and what is actually experienced by patients. It has been demonstrated that caregivers usually underestimate the incidence of acute and delayed emesis by nearly 30% and 50%, respectively [10].

Clinical, ethical and financial considerations therefore combine in suggesting that optimum control of CINV should be a high priority in the care of the cancer patient, including those with hematological malignancies.

2. Pathophysiology and prevention of CINV

Enterochromaffin cells in the mucosa of the gastrointestinal (GI) tract respond to chemotherapy (as to other potentially toxic chemical or mechanical stimuli) by releasing serotonin which stimulates the 5-HT_3 receptors on the afferent fibers of the vagus nerve [11]. This causes the chemoreceptor trigger zone to send a signal to areas within the medulla, resulting in increased salivation, respiratory rate, pharyngeal, GI and abdominal muscle contractions and emesis.

In addition, the tachykinin known as substance P (SP), the endogenous ligand acting preferentially on neurokinin-1 (NK-1) receptors, is an important mediator of delayed emesis through both central and peripheral sites of action [11]. Three phase III trials in patients undergoing highly emetogenic chemotherapy and one phase III in patients treated with moderately emetogenic drugs have established the value of adding the NK-1 antagonist aprepitant to standard anti-emetic regimens [12–15].

Given the central role of serotonin (and especially of the 5-HT_3 receptor subtype) in the pathways leading to CINV, the development of agents to selectively block the 5-HT_3 receptor was a logical initial step in efforts to control emesis [16]. The first-generation of 5-HT_3 receptor antagonists, exemplified by the prototype drug ondansetron, resembled serotonin in structure [17]. These agents dramatically improved the quality of life of patients undergoing emetogenic chemotherapy and became the standard of care.

The development of palonosetron, a 5-HT_3 receptor antagonist with a structure different from that of serotonin, marked the advent of a second generation of this class of drugs. Compared with earlier 5-HT_3 antagonists, palonosetron has a longer half life (of forty hours, compared with less than ten hours for old-generation agents) and at least thirty-fold higher *in vitro* binding affinity for the 5-HT_3 receptor [18].

While the first-generation agents, ondansetron and granisetron compete with serotonin for the same binding site, palonosetron binds to a different site on the receptor [19]. Such allosteric binding causes a conformational change, increasing receptor affinity and facilitating the binding of other molecules of the antagonist. Furthermore, palonosetron triggers internalization of the receptor, so maintaining functional inhibition even when the drug itself is gone [19,20]. Finally, recent evidence indicates that palonosetron, although not directly binding to the NK-1 receptors, is able to inhibit both serotonin and cisplatin enhanced SP-mediated neuronal response [21]. The demonstration that palonosetron, but not first-generation 5-HT_3 antagonists, also affects the cross-talk between NK-1 and 5-HT_3 receptors signaling pathways, provides a further explanation for the demonstrated efficacy of this drug in controlling delayed CINV.

3. Clinical trials of palonosetron in solid tumors

A series of pivotal phase III trials has compared palonosetron against old-generation 5-HT_3 antagonists in