review

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Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis

S. M. Grunberg*

Department of Medicine—Hematology/Oncology, University of Vermont, Burlington, VT, USA

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Background: Chemotherapy and radiotherapy remain the standards of treatment for many patients with cancer, but these modalities are often limited by distressing side-effects, most notably chemotherapy-induced nausea and vomiting (CINV).

Methods: This paper considers the role of corticosteroids in CINV prophylaxis. Clinical trial results and treatment guidelines indicate that even with the emergence of new serotonin and neurokinin receptor antagonists, corticosteroids continue to play an important role in antiemesis for oncology patients. Numerous clinical trial results have demonstrated that both dexamethasone and methylprednisolone are effective as monotherapy and in combination with older and more recently developed antiemetic agents in patients receiving a wide range of chemotherapeutic regimens used for treatment of different cancers.

Conclusions: With the increasing number of antineoplastic regimens and factors specific to individual patients, it is important to frequently review antiemetic treatment options and continually monitor therapeutic progress to establish the optimal therapy for each patient.

Key words: antiemetic, corticosteroid, dexamethasone, methylprednisolone

introduction

Although molecular therapies are finding increased use in cancer treatment, chemotherapy and radiotherapy remain the standards of treatment for many patients. The effective use of both modalities is limited by a wide range of side-effects. Nausea and vomiting are among the most distressing and feared of these toxic effects [1–3]. These complications can lead to serious medical problems, such as dehydration and electrolyte imbalances, increased duration of hospital stay and an associated rise in treatment costs, and impaired quality of life (QoL) for patients and their caregivers [1]. The impact of chemotherapy-induced nausea and vomiting (CINV) on cancer patients has resulted in a very large body of basic and clinical research aimed at discovery of agents that can provide protection against these treatment complications.

classification, prevalence, and impact of CINV

classification of CINV

CINV can be broadly categorized by onset latency, previous patient experience with CINV, and relationship to antiemetic treatment. Acute CINV is typically defined as occurring within 24 h of therapy. Delayed CINV commences >24 h following treatment and can persist for as long as 6–7 days. Anticipatory nausea and vomiting are responses conditioned by prior exposure to chemotherapy and result from poor emetic control during previous therapy cycles. Additional categories distinguish uncontrolled CINV as either breakthrough (nausea and vomiting that occur despite antiemetic prophylaxis) or refractory (nausea and vomiting unresponsive to treatment). Good control of CINV during the acute period has been shown to decrease the risk of delayed emesis. Conversely, failure of prophylaxis during the first 24 h after chemotherapy is highly predictive for delayed emesis during the same cycle [1, 3]. For example, findings reported by Glaus et al. [4] indicated that 13% and 38% of 247 patients who received chemotherapy and antiemetic medications experienced acute or delayed CINV, respectively. However, 65% of those with acute symptoms had CINV recurrence on one or more subsequent days [4].

emetogenic risk of chemotherapeutic agents

The emetogenicity of cancer chemotherapy varies substantially. In addition to patient-related variability, therapeutic factors associated with emetogenic potential include the specific antineoplastic agent utilized, dose, route of administration, and treatment schedule [5–7]. Although no consensus for a single classification scheme of emetogenic potential has emerged, several groups have categorized chemotherapeutic drugs

*Correspondence to: Dr S. M. Grunberg, Fletcher Allen Health Care, Hematology/Oncology Unit, UHC Campus/St Joseph 3400, 1 South Prospect Street, Burlington, VT 05401, USA. Tel: +1 802-847-3827; Fax: +1 802-847-5946; E-mail: steven.grunberg@uvm.edu

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according to their intrinsic risk for CINV [5–8]. In general, risk for CINV is categorized into four (or more) levels: high (>90% probability of nausea/vomiting without prophylaxis) for cisplatin, dacarbazine, mechlorethamine, streptozotocin, and cyclophosphamide (≥1500 mg/m^2); moderate (30–90%) for a large number of agents, including oxaliplatin, cyclophosphamide (<1500 mg/m^2), cytarabine (>1 g/m^2), doxorubicin and related agents, and irinotecan; low (10–30%) for methotrexate, mitomycin C, paclitaxel, cetuximab, trastuzumab, and others; and minimal (<10%) for bleomycin, bulsulfan, vinblastine, and others (Table 1) [5–8].

impact of CINV

As noted above, CINV has a substantial negative impact on patients' QoL and can deter them from continuing treatment [3]. Delay of needed therapy may occur in as many as 50% of patients experiencing CINV or other chemotherapy-related toxic effects [1]. Results obtained with the Functional Living Index-Emesis (FLIE) questionnaire indicated that 75% of patients with nausea and 50% of those with vomiting reported a negative impact of these conditions on performance of activities of daily living [4]. In another study, FLIE scores after 3 days of treatment indicated that patients with CINV perceived that vomiting and, to a slightly lesser extent, nausea substantially reduced their ability to complete household tasks, enjoy meals, spend time with family and friends, and maintain daily function and recreation. Patients who did not experience CINV had no reduction in FLIE scores from pretreatment levels [9].

Table 1. Emetogenicity for single-dose, intravenous chemotherapeutic and biologic agents [8]. (Reprinted with the kind permission of Springer Science and Business Media)

Degree of emetogenicity (incidence)	Antineoplastic agent
High (>90%)	Cisplatin
	Mechlorethamine
	Streptozotocin
	Cyclophosphamide ≥ 1500 mg/m^2
	Carmustine
	Dacarbazine
Moderate (30–90%)	Oxaliplatin
	Cytarabine >1 g/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide < 1500 mg/m^2
	Doxorubicin
	Daunorubicin
	Epirubicin
	Idarubicin
	Irinotecan
Low (10–30%)	Paclitaxel
	Docetaxel
	Mitoxantrone
	Topotecan
	Etoposide
	Pemetrexed
	Methotrexate
	Mitomycin C
	Gemcitabine
	Cytarabine ≤ 100 mg/m^2
	5-Fluorouracil
	Bortezomib
	Cetuximab
	Trastuzumab
Minimal (<10%)	Bleomycin
	Busulfan
	2-Chlorodeoxyadenosine
	Fludarabine
	Vinblastine
	Vincristine
	Vinorelbine
	Bevacizumab

CINV prophylaxis

A wide range of treatments is now available for prophylaxis against CINV in patients undergoing cancer chemotherapy. The most frequently employed antiemetic agents include corticosteroids [methylprednisolone (MP), dexamethasone], serotonin type 3 (5-HT$_3$) receptor antagonists (ondansetron, granisetron, tropisetron, dolasetron, palonosetron), and neurokinin-1 (NK-1) receptor antagonists (aprepitant). Metoclopramide, lorazepam and other benzodiazepines, and cannabinoids have also been used. Other agents with possible antiemetic efficacy include gabapentin, an antiepileptic drug, and olanzapine, an atypical antipsychotic [3, 6, 10]. Currently, a 5-HT$_3$ receptor antagonist in combination with a corticosteroid and, in certain instances, an NK-1 antagonist is the treatment of choice for prophylaxis against acute emesis following chemotherapy with moderate potential for CINV [11].

MP and dexamethasone have been used safely and effectively as both monotherapy and in combination with other agents for the management of patients with CINV for many years, and have been described as appropriate agents for management of delayed CINV [6]. The remainder of this paper considers the mechanism of action of corticosteroids in preventing CINV, describes how employment of these agents in the management of CINV has evolved over more than four decades of use, assesses clinical trial results for corticosteroids in single-agent and combination therapy, and reviews recommendations for corticosteroid use in current practice guidelines.

mechanisms underlying corticosteroid impact on CINV

Corticosteroids are effective as prophylaxis against CINV, but the mechanisms underlying this effect are still unknown. Results from one *in vitro* study showed that MP substantially decreased cisplatin-induced 5-HT release from peripheral blood mononuclear cells [12]. The possibility that at least part of the therapeutic benefit of MP arises from its ability to decrease 5-HT release is consistent with the fact that emesis is associated with increased levels of this indoleamine in the gut and brain stem [13]. Results from experiments in pigeons indicate that dexamethasone's antiemetic actions may be at least partially due to its activity in the central nervous system (CNS) in both

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the acute and delayed phases of cisplatin-induced emesis. However, the mechanism underlying this effect was probably unrelated to two factors that have been suggested as contributing to cisplatin-induced CINV: prostanoid synthesis and influx of cisplatin into the medulla oblongata [14]. There is also evidence that corticosteroids may exert central antiemetic action through activation of glucocorticoid receptors in the nucleus of the solitary tract in the medulla [15].

It has been shown recently that both MP and dexamethasone antagonize 5-HT_{3A} receptors expressed in *Xenopus* oocytes. The half-maximal effective concentrations (EC_{50} values) for these effects were 1 μM and 1 mM, respectively, and the mode of action was noncompetitive and additive to that of the 5-HT_3 receptor antagonist ramosetron [16]. Thus, antagonism of 5-HT receptors known to be involved in emesis may contribute to the prophylactic effects of corticosteroids in cancer patients.

corticosteroid monotherapy in the management of CINV

Corticosteroids are seldom used as monotherapy for management of emesis and nausea induced by moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC). However, results from a number of studies carried out before the widespread use of 5-HT_3 antagonists have documented the antiemetic efficacy of MP and dexamethasone.

MP has been shown to have substantial efficacy as prophylaxis against CINV in patients receiving chemotherapeutic agents with all levels of emetogenicity. In women treated for breast cancer with an initial course of cyclophosphamide, methotrexate, and 5-fluorouracil, prophylaxis with MP was superior to metoclopramide and prevented CINV at least partially for 63% of patients [17]. In a second trial, MP provided complete antiemetic protection in 67% of women [18]. In a small-scale comparative study, MP provided complete protection against vomiting and nausea, respectively, for 100% and 93% of patients treated with doxorubicin. The response rates for MP in this trial exceeded those for either metoclopramide or domperidone, but the between-treatment differences did not reach statistical significance [19]. Results from a crossover study in 57 chemotherapy-naive patients receiving non-cisplatin-based chemotherapy showed that 250 mg MP was as effective as 500 mg MP in protecting patients against CINV [20]. These results are consistent with the view that the dose–response curve for MP is relatively flat and that adequate protection can be obtained with a 250-mg dose in patients receiving chemotherapy regimens that do not include cisplatin.

Dexamethasone has also been demonstrated to be effective as monotherapy for the management of CINV. High-dose intravenous (i.v.) dexamethasone reduced the risk for nausea and vomiting in patients receiving doxorubicin (a total of 22 cycles), but not for those being treated with combinations based on cisplatin (35 cycles), despite the use of two-fold higher doses of the corticosteroid [21]. In contrast, Goedhals et al. [22] reported that dexamethasone, given as monotherapy or combined with granisetron, provided complete emetic protection (no vomiting or rescue medication) in >50% of patients overall and >70% of patients during days 4–6 following administration of cisplatin-based chemotherapy [22]. Results from a double-blind, randomized, crossover study that included 40 patients receiving non-cisplatin-based therapy indicated that dexamethasone was superior to metoclopramide in preventing CINV. Overall, 58% of patients had no vomiting with dexamethasone compared with 28% of those receiving metoclopramide [23]. Meta-analysis of results from 5613 patients who received HEC or MEC for multiple types of cancer in 32 studies indicated that dexamethasone was superior to placebo or no treatment for complete protection against both acute (OR = 2.22; 95% CI 1.89–2.60) and delayed emesis (OR = 2.04; 95% CI 1.63–2.56). Results were similar for complete protection against nausea. The pooled risk difference for complete protection from emesis was 16% for both the acute and delayed phases [24].

corticosteroid combination therapy in the management of CINV

Before the advent of 5-HT_3 receptor antagonists, the combination of high-dose metoclopramide plus a corticosteroid and diphenhydramine or lorazepam was regarded as the standard of care for CINV [25]. The combination of MP plus metoclopramide has been shown to be superior to metoclopramide alone for prophylaxis against CINV in 200 patients undergoing cisplatin-based chemotherapy [26]. The combination of MP and metoclopramide with or without lorazepam was reported as being highly effective in two studies, one of 100 cisplatin chemotherapy cycles in 50 patients [27] and another of 282 cisplatin or non-cisplatin chemotherapy cycles in 163 patients [28]. The addition of lorazepam to MP plus metoclopramide provided relatively little added benefit with respect to protection against emesis but did reduce patient anxiety and nausea [27, 28]. Clinical trial results have also shown that combinations of either MP or dexamethasone with metoclopramide and diphenhydramine are effective for prevention of CINV in patients receiving cisplatin- or non-cisplatin-based therapy [29, 30]. No substantial difference was noted in emetic protection between regimens containing MP or dexamethasone [30].

The advent of 5-HT_3 receptor antagonists altered standards of care for CINV prophylaxis, but management with these agents alone is not completely effective in many patients [1]. The suboptimal efficacy of 5-HT_3 receptor antagonist monotherapy, especially for delayed symptoms, was evident in results reported by Gebbia et al. [31] for the granisetron arm of a comparative study: on days 2–5 following cisplatin-based chemotherapy, complete emetic protection was achieved with granisetron in only 33% of patients. In addition, 21% of patients received no protection [31]. Another indicator of treatment failure is the requirement for antiemetic rescue medication. A comparison of the 5-HT_3 receptor antagonist dolasetron alone or in combination with dexamethasone showed that 22% of patients receiving antiemetic monotherapy required rescue medication versus 6% of those treated with the combination (Figure 1) [32].

Several controlled clinical trials provide further support for the view that combination of a corticosteroid with a 5-HT_3 receptor antagonist is more effective than monotherapy for prophylaxis against CINV (Table 2). Ramosetron plus

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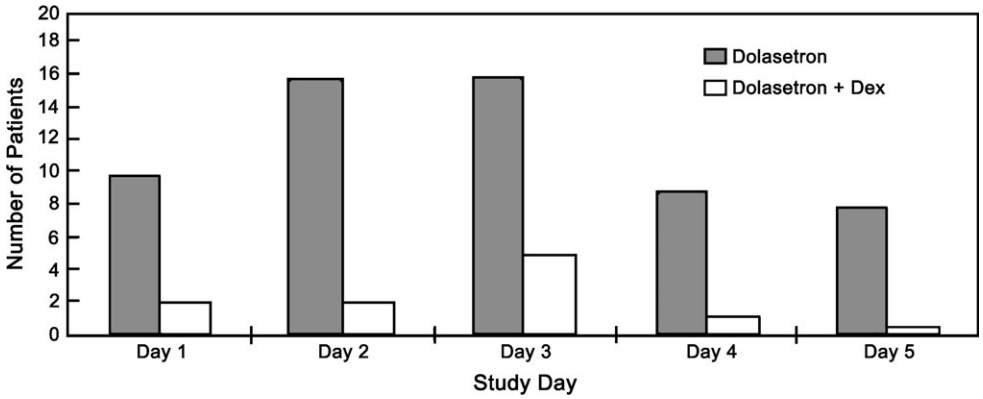


Figure 1. Requirement for rescue medication following fractionated cisplatin chemotherapy in patients who received dolasetron monotherapy or in combination with dexamethasone [32]. (Reprinted with the kind permission of Springer Science and Business Media).

Table 2. Efficacy of 5-HT_3 receptor antagonists plus corticosteroids versus 5-HT_3 receptor antagonist monotherapy for prevention of CINV

Study	Regimen			End point: percentage of patients with complete CINV protection (combination versus monotherapy)	
	Chemotherapy	5-HT_3 antagonist	Corticosteroid	Acute CINV	Delayed CINV
Villalon and Chan [33]	Cisplatin	Ramosetron, i.v. then daily oral	Dexamethasone, i.v. then daily oral	68% versus 54% ($P = 0.034$)	56/64% versus 32/41% ($P = 0.001$)[a]
Janinis et al. [35]	Epirubicin	Ondansetron, i.v. then daily oral	Dexamethasone, i.v.	80% versus 54% ($P = 0.0062$)	N/A
Fauser et al. [32]	Cisplatin	Dolasetron, daily i.v. infusions	Dexamethasone, daily i.v. infusions	73% versus 41% ($P < 0.0001$) over treatment days 1–5	
Garcia-del-Muro et al. [36]	Cisplatin	Tropisetron, i.v. then daily oral	Dexamethasone, i.v. then daily oral	71% versus 46% ($P = 0.0002$)	51% versus 27% ($P = 0.0001$)
Matsuoka et al. [37]	Various high dose	Granisetron i.v.	Dexamethasone, i.v.	92% versus 72% ($P = 0.06$)	N/A
Italian Group for Antiemetic Research [38]	Various	Granisetron i.v.	Dexamethasone, i.v. then several oral doses	70% versus 49% ($P < 0.001$)	51% versus 34% ($P < 0.002$)
Kleisbauer et al. [40]	Cisplatin	Granisetron i.v.	MP, i.v.	78% versus 59% ($P < 0.001$)	N/A
Gebbia et al. [31]	Cisplatin	Granisetron, daily oral	MP, i.m. daily	N/A	47% versus 33% ($P < 0.002$)
Chevallier et al. [41]	Cisplatin	Ondansetron, i.v. then daily oral	MP, i.v. then daily oral	90% versus 71%[b]	56% versus 43%

[a]No composite end point, ratios represent nausea/vomiting percentages.
[b]End point was complete protection or major response, *P* values stated as 'significant' but not actually specified.
5-HT_3, serotonin type 3; i.v., intravenous; N/A, study design or data analysis/presentation did not allow comparison; i.m., intramuscular; MP, methylprednisolone.

dexamethasone was shown to be superior to ramosetron alone (68% versus 54%) in controlling emesis at both 24 and 72 h following chemotherapy in a study of 283 patients treated with cisplatin (≥50 mg/m^2) alone or in combination with other antineoplastic agents [33]. In another multicenter study, the addition of dexamethasone substantially improved prevention of both acute and delayed emesis in 1050 tropisetron-treated patients receiving either cisplatin- or non-cisplatin-containing regimens [34]. In a parallel group study of 113 patients undergoing their first course of chemotherapy with high-dose epirubicin, Janinis et al. [35] reported that ondansetron given i.v. in combination with dexamethasone before chemotherapy was more effective than ondansetron alone in the control of acute emesis. Response rates were 80% versus 54%, respectively, for complete protection against CINV on the first day, the only day on which the corticosteroid was administered [35]. A more prolonged benefit of combination antiemetic therapy was demonstrated in another trial, in which i.v. dolasetron plus dexamethasone was superior to i.v. dolasetron alone for the management of fractionated cisplatin-related nausea and

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vomiting over 5 days in 210 patients. Overall, a complete protective response was obtained in 73% versus 41% of these patients, respectively, and between-group differences were substantial for each day [32]. Similarly, tropisetron in combination with dexamethasone was much more effective than tropisetron plus placebo in the prevention of both acute (76% versus 55%) and delayed (60% versus 39%) emesis in a cohort of 282 chemotherapy-naive patients receiving high-dose cisplatin. Overall control of nausea and vomiting was comparable during acute and delayed phases with response rates of 71% versus 46% and 51% versus 27% [36].

Other studies have compared the antiemetic efficacy of the 5-HT_3 receptor antagonist granisetron alone versus in combination with MP or dexamethasone. Most of these trials also demonstrated substantial superiority of combination therapy over single-agent treatment. Results from 50 patients receiving high-dose chemotherapy with or without total body irradiation for stem-cell transplantation showed that granisetron plus dexamethasone provided acute emetic control superior to that observed with granisetron alone. Response rates for the two treatments were 100% versus 63.2%, respectively, for total-body-irradiated patients and 92% versus 72% for the entire patient cohort [37]. Similarly, the Italian Group for Antiemetic Research [38] showed that the combination of dexamethasone plus granisetron was much more effective than either agent alone in providing complete protection from vomiting and nausea for 24 h after chemotherapy and also on subsequent days in 482 consecutive patients who received MEC (600–1000 mg/m^2 cyclophosphamide, ≥50 mg/m^2 doxorubicin, ≥300 mg/m^2 carboplatin, or ≥75 mg/m^2 epirubicin, alone or in combination). Results from this study also indicated that single-day treatment with dexamethasone was as effective as single-day treatment with granisetron in preventing acute emesis and better in preventing delayed emesis [38]. However, Goedhals et al. [22] reported different results regarding the efficacy of dexamethasone alone versus granisetron plus dexamethasone for protection against cisplatin-induced nausea and emesis. In this study of 654 patients treated with ≥69 mg/m^2 cisplatin, no additional benefit above that of dexamethasone alone was conferred by the addition of granisetron. Response rates for days 1–6 following chemotherapy were 54% and 52%, respectively, and 72% and 71% for days 3–6 [22].

MP has been repeatedly shown to enhance the emetic protection afforded by granisetron in patients receiving high-dose cisplatin therapy for gastric, head and neck, lung, or ovarian cancers [31, 39, 40]. For all efficacy variables measuring acute and delayed emetic protection, oral follow-on therapy with MP plus granisetron was much more effective against cisplatin-induced nausea than granisetron alone [40]. Gebbia et al. [31] reported results of a three-way comparison of antiemetic regimens for treating delayed CINV in 262 patients who responded to i.v. granisetron during the acute phase. During days 2–5 of the first cycle of cisplatin (≥80 mg/m^2) therapy, intramuscular (i.m.) metoclopramide plus MP or oral granisetron plus i.m. MP were each much more effective than oral granisetron alone. Complete protection rates in the three treatment arms were 53%, 47%, and 33%, respectively [31]. Ondansetron combined with MP has been shown to have efficacy superior to that of ondansetron alone for protection against both acute and delayed nausea and vomiting in patients receiving cisplatin-based therapy [41]. Ondansetron combined with MP is also superior to MP plus metoclopramide in preventing CINV in patients receiving non-cisplatin-based therapy for lymphoma [42].

dexamethasone dose for prevention of CINV

The optimal dose and regimen for combining dexamethasone with 5-HT_3 receptor antagonists for managing CINV were explored by the Italian Group for Antiemetic Research in two studies [43, 44] that included only groups receiving combination therapy. In 587 patients receiving chemotherapy with anthracyclines, carboplatin, or cyclophosphamide, the combinations of ondansetron with one of three regimens—a single i.v. 8-mg dose of dexamethasone before chemotherapy, prophylactic i.v. dexamethasone 24 mg, or dexamethasone 8 mg given i.v. before chemotherapy plus four doses of oral dexamethasone 4 mg given every 6 h—all produced very similar rates of protection from CINV. The rates of complete protection against nausea/vomiting were 89.2/61.0%, 83.6/56.9%, and 89.2/61.0%, respectively. Accordingly, a prophylactic i.v. dose of 8 mg of dexamethasone was viewed as most appropriate for preventing acute emesis induced by anthracyclines, carboplatin, or cyclophosphamide [43]. In a separate dose-ranging study of single i.v. doses of 4, 8, 12, or 20 mg dexamethasone administered 45 min before cisplatin-based chemotherapy, the 20-mg dose was shown to be most efficacious for use in combination with a 5-HT_3 antagonist for prevention of cisplatin-induced acute emesis. Complete protection from acute vomiting and nausea was achieved by 69.2% and 60.9% of patients, respectively, who received 4 mg of dexamethasone, by 69.1% and 61.0% of those who received 8 mg, by 78.5% and 66.9% of those who received 12 mg, and by 83.2% and 71.0% of those who received 20 mg [44].

addition of an NK-1 antagonist for prevention of CINV

The effectiveness of corticosteroids as part of combination treatments extends to the most recently developed antiemetic agents. In a study of 523 assessable patients with cancer receiving high-dose cisplatin-based chemotherapy, prophylaxis consisting of the NK-1 antagonist aprepitant plus a standard regimen of ondansetron and dexamethasone provided superior antiemetic protection compared with standard therapy alone. On the first day of chemotherapy, the antiemetic response rates for complete protection were 82.8% for the aprepitant combination therapy group and 68.4% for the standard therapy group; for days 2–5, the complete response rates were 67.7% and 46.8%, respectively [45]. Data from the multiple-cycle extension of a clinical trial of oral aprepitant plus standard therapy (a 5-HT_3 antagonist plus dexamethasone) versus standard therapy alone indicated substantially better antiemetic protection with the three-agent combination over multiple cycles of HEC. Complete responses were noted for 64% and 59% of patients after the first and sixth cycles for patients who received all three agents versus 49% and 34% of those managed with standard therapy [46]. An advantage for the addition of aprepitant to the

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standard regimen of dexamethasone and ondansetron has also been noted with MEC. In a recent randomized trial of 857 assessable patients [47], 76% of patients achieved complete response with the aprepitant-containing regimen compared with 69% with the standard regimen during the acute period and 55% of patients achieved complete response with the aprepitant-containing regimen compared with 49% of patients with the standard regimen in the delayed period. However, since aprepitant is a CYP 3A4 inhibitor and can interfere with dexamethasone metabolism, the dose of dexamethasone should be reduced when used in combination. In the regimen for HEC [45], the dose of dexamethasone was reduced from 20 mg day 1 followed by 8 mg b.i.d. for 3 days to 12 mg day 1 followed by 8 mg o.d. for 3 days when aprepitant was added. In the regimen for MEC [47], dexamethasone was reduced from 20 mg day 1 to 12 mg day 1.

safety of corticosteroids in prevention of CINV

Dexamethasone and MP are generally safe when used as monotherapy and in combination with other antiemetic agents [7]. Although there has been a theoretical concern that corticosteroids could interfere with the antitumor effects of chemotherapy through immunosuppressive mechanisms, this possibility has not been supported by current clinical evidence [7]. However, one must be aware of potential toxic effects of corticosteroids. Treatment with corticosteroids may result in metabolic abnormalities, CNS effects, glaucoma, cataracts, acne, impaired wound healing, dyspepsia, myopathy, hypertension, increased risk of infection, or hypothalamic–pituitary–adrenal axis suppression. Longer term treatment may increase the risk of osteoporosis or osteonecrosis [48, 49]. A dose-dependent sensation of perineal pruritus lasting for several minutes after administration of dexamethasone has also been reported [21]. In a recent survey designed to detect potential corticosteroid-related toxic effects, moderate-to-severe side-effects noted for patients receiving dexamethasone for prophylaxis against delayed CINV included insomnia (45%), gastrointestinal symptoms (27%), agitation (25%), increased appetite (18%), weight gain (17%), rash (15%), depression on cessation of treatment (7%), hiccups (7%), and oral candidiasis (3%) [50].

treatment guidelines

Guidelines for prophylaxis against CINV have been set forth by the American Society of Clinical Oncology, the American Society of Health-System Pharmacists, the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology, and the Multinational Association of Supportive Care in Cancer (MASCC) [1, 6, 11, 51] (Table 3). A key principle followed by all recommendations is that effective management of delayed or anticipatory emesis requires adequate antiemetic therapy for acute symptoms [1, 6, 52]. Thus, a highly effective antiemetic regimen should be employed at the onset of chemotherapy as opposed to follow-on in the event of CINV breakthrough with initially suboptimal antiemetic treatment.

Table 3. Current treatment guidelines for prophylaxis against CINV (modified from 7 and reprinted with the kind permission of Elsevier Ltd)

Emesis risk	Acute phase (day 1)	Delayed phase (days 2–5)
High	5-HT_3 antagonist corticosteroid and NK-1 antagonist[a]	Corticosteroid and NK-1 antagonist[a]
Moderate	5-HT_3 antagonist and corticosteroid (and NK-1 antagonist)[a]	Monotherapy with 5-HT_3 antagonist or corticosteroid or metoclopramide (or corticosteroid and NK-1 antagonist)[a]
Low	Corticosteroid	None
Minimal	None	None

[a]The more recent guidelines by Multinational Association of Supportive Care in Cancer and National Comprehensive Cancer Network recommend using an NK-1 antagonist in combination with a 5-HT_3 antagonist and/or corticosteroid for all patients receiving highly emetogenic chemotherapy and for selected patients receiving moderately emetogenic chemotherapy. CINV, chemotherapy-induced nausea and vomiting; 5-HT_3, serotonin type 3; NK-1, neurokinin-1.

Treatment guidelines support the use of a 5-HT_3 receptor antagonist plus a corticosteroid for prophylaxis against CINV in patients receiving chemotherapy or radiotherapy of high emetogenicity [11, 52]. The MASCC and NCCN guidelines also recommend aprepitant as an additional component of this combination [7, 52]. In patients treated with high-risk non-cisplatin chemotherapy, the guidelines recommend use of a 5-HT_3 receptor antagonist plus a corticosteroid for prophylaxis against CINV followed by a corticosteroid with or without a 5-HT_3 receptor antagonist or metoclopramide for delayed CINV. Recent guidelines recommend aprepitant as well [6, 7]. Corticosteroids are advised as an option for patients receiving chemotherapy with low emetogenicity, but should not be routinely administered if CINV risk is minimal [53].

Optimal antiemetic treatment during the first treatment cycle should diminish the risk of anticipatory CINV in subsequent cycles. However, if anticipatory CINV occurs, behavioral therapy or use of benzodiazepines is recommended [6, 7, 54]. An adequate regimen must also include evaluation of the patient's individual risk factors, counseling about the importance of treatment compliance in the outpatient setting, and close monitoring of therapeutic outcomes [1].

conclusions

Even with the emergence of new 5-HT_3 receptor and NK-1 antagonists, corticosteroids continue to play an important role in antiemesis for oncology patients, and treatment guidelines distinguish a number of clinical scenarios in which these agents should be used to help achieve optimal antiemetic effects. Both dexamethasone and MP are effective as monotherapy and in combination with older and more recently developed antiemetic agents in patients receiving a wide range of chemotherapeutic regimens used for treatment of different cancers. With the increasing number of chemotherapeutic and targeted agents available, it is important to frequently review antiemetic

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treatment options and continually monitor therapeutic progress to establish the optimal therapy for each patient.

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