European Journal of Pharmacology 722 (2014) 192–196

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Prognostic factors for chemotherapy induced nausea and vomiting

David Warr *

Department of Hematology and Medical Oncology, Princess Margaret Cancer Centre, Rm 5-204, 610 University Avenue, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Accepted 8 October 2013
Available online 21 October 2013

Keywords:
Emesis
Prognostic
Chemotherapy
Cancer

ABSTRACT

Purpose: to review the topic of prognostic factors for chemotherapy-induced nausea and vomiting. Multiple patient factors such as age, gender and alcohol intake have been found that affect the likelihood of emesis with a given chemotherapy. Pharmacogenomics has also been explored as a cause for variation in emetic response. In theory these risk factors could be used to optimize antiemetic therapy for individual patients but guidelines for prophylactic antiemetics are based solely upon the type of chemotherapy administered. Attempts to identify subgroups of patients for whom guidelines recommendations are suboptimal have thus far been unsuccessful except for those with a poor experience in a previous cycle of the same chemotherapy. At present, there is no basis for deviating from evidence-based guidelines when prescribing antiemetics prior to the first cycle of chemotherapy.

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1. Introduction

Control of chemotherapy induced emesis has improved substantially over the last 20 years through the use of prophylactic antiemetics. Antiemetics can, however, be costly and may induce annoying side effects. Chemotherapy agents vary greatly in the likelihood of inducing nausea and vomiting; thus the antiemetics administered should be tailored to the emetic challenge. The antiemetics recommended by guidelines groups such as the Multinational Association of Supportive Care in Cancer (Roila et al., 2010) are determined by the probability of a given drug causing emesis when administered without antiemetics. At one end of the spectrum are agents like vinorelbine which have virtually no risk of causing emesis and for which no antiemetics are recommended. At the other end are drugs like high dose cisplatin which cause emesis in virtually 100% of patients and for which a combination of a corticosteroid, 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist and neurokinin$_1$ (NK$_1$) receptor antagonist is recommended. Each chemotherapy regimen is assigned an antiemetic regimen based upon the most emetogenic drug administered.

The evaluation of emetogenicity is complicated by the fact that most chemotherapy protocols consist of combinations of agents and the net result may be a more emetogenic stimulus than a single agent. Only one instance of this enhanced emetic effect

* Tel.: +1 416 946 2260; fax: +1 416 946 6546.
E-mail address: david.warr@uhn.ca

0014-2999/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejphar.2013.10.015

due to combination therapy is recognized in the guidelines (an anthracycline plus cyclophosphamide) in that a combination of two "moderately emetogenic" drugs qualifies as a regimen for which the NK_1 RA aprepitant is part of recommended therapy (Basch et al., 2011; Roila et al., 2010). The rationale is that two large randomized clinical trials have documented a clinically important improvement in the control of emesis when aprepitant is added (Rapoport et al., 2010; Warr et al., 2005). Although even high dose cisplatin is more emetogenic when combined with cyclophosphamide or doxorubicin (Gralla et al., 2005) and a formula for estimating the emetogenicity of the enormous number of possible combinations was proposed (Hesketh et al., 1997), with that one exception, recommended treatment is based upon single agents.

Clinical studies have established that, even with the same chemotherapy, there are patient related factors that alter the risk of emesis such as age, alcohol intake and gender (Hesketh et al., 2010) (Warr et al., 2011). Chemotherapy dose is undoubtedly important but it has been largely unexamined except for high dose cisplatin (Beck et al., 1992; Hesketh et al., 2010).

It has been suggested that risk factors might be used to alter the antiemetics administered (Osoba et al., 1997). For example a patient who is about to receive "moderately emetogenic" chemotherapy but who is predicted to be at much higher than average risk for vomiting could in theory be prescribed the same antiemetic combination (a corticosteroid, 5-HT_3 receptor antagonist and NK_1 receptor antagonist) that would be recommended for patients receiving highly emetogenic chemotherapy. Conversely a patient who is about to receive high dose cisplatin but has a low risk profile might in theory be spared the expense of an NK_1 receptor antagonist.

2. Risk Factors

2.1. Prognostic factors vary in strength of evidence

The table (Table 1) lists risk factors that have been found in at least two clinical trials of substantial size as well as others for which there is less convincing evidence. The number of patient characteristics found in at least univariate analysis to influence the chance of emesis is sufficiently large that it is not possible to list all of them. Indeed, this area is even more complex because nausea and vomiting can be considered separately for risk factors with slightly different predictors in one analysis (Osoba et al., 1997) and emesis during the first 24 h and beyond 24 h may differ in their predictors (Dranitsaris et al., 2012). It has been noted that even in analyses of large databases from antiemetic trials, prognostic factors may be inconsistent across subgroups (Pater et al., 1994). Whether this is true variation or a chance variation due to multiple subgroup analyses is unknown.

2.2. Nausea and vomiting with previous chemotherapy cycle

A course of chemotherapy generally consists of repeated administration of the same agents. Although emesis becomes somewhat more likely with successive cycles (de Wit et al., 2003; Herrstedt et al., 2005), it is not surprising that the strongest predictor of nausea or vomiting after the first cycle of chemotherapy is their presence or absence with the previous cycle with the same chemotherapy (Roila, 1996). Thus, for those patients who are already receiving chemotherapy, patient characteristics do not have a major role in determining the subsequent risk of emesis above and beyond knowledge of what happened with the previous cycle of treatment.

2.3. Commonly cited factors

For patients with no prior chemotherapy, the most commonly cited high risk factors are young age, female gender, limited or no regular alcohol intake and previous emesis e.g. pregnancy associated vomiting or motion sickness. There is no physiological rational for the most commonly cited risk factors. Some factors may simply represent a different threshold for emesis irrespective of the stimulus. For example emesis is more common in females than males in the settings of palliative care (Kirkova et al., 2012), postoperative care (Leslie et al., 2008) and chemotherapy but the reason is unknown. Although female gender has been associated with poorer results in a large number of antiemetic trials, the combined results from two phase III randomized trials of aprepitant suggested that this gender difference disappeared when aprepitant was added to a 5-HT_3 receptor antagonist and dexamethasone i.e. males and females fared equally well in the aprepitant containing arms gender (Hesketh et al., 2006). This surprising finding has not been evaluated in other studies with

Table 1
Risk factors for chemotherapy induced emesis.

Risk factor	Established (2 or more studies)	Limited or contradictory evidence	References
Vomiting with previous cycle	×		Roila (1996), Roila et al. (1989)
Type of chemotherapy administered	×		Pater et al. (1994) Basch et al. (2011)
Antiemetic administered	×		Pater et al. (1994) Warr et al. (2011)
Gender	×		Hesketh et al. (2010), Osoba et al. (1997)
Age	×		Warr et al. (2011) Hesketh et al. (2010)
Alcohol	×		Warr et al. (2011) Hesketh et al. (2010)
Pregnancy associated emesis or motion sickness	×		Warr et al. (2011) Pirri et al. (2011)
Anxiety		×	Molassiotis et al. (2002)
Expectation		×	Roscoe et al. (2004)
Concomitant opioid		×	Shoji et al. (1999)
Concomitant serotonin specific reuptake inhibitors		×	Koriech (1995) Mir et al. (2012)