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COMMENTARY

Is antihistaminergic H2 really useful in prevention of hypersensitivity induced by paclitaxel?

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Worldwide drug shortages are a recent and growing concern which involves all drug classes, including antineoplastic [1]. Successive shortages disrupt and disorganize the activity of oncology practitioners who must find adaptive solutions [2]. Drug shortage can also impact the management of patients with cancer, with potential consequences in term of overall survival [3]. However and interestingly, successive drug shortages have refocused oncology specialists on evidence-based medicine (EBM) [4]. For example, folate shortage has pushed oncology practitioners to experiment a standardized low dose protocol, and first results appear to be consistent with a similar efficacy [5].

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Recent successive parenteral ranitidine shortage (the only parenteral antihistaminergic H2 (antiH2) on the French market) has concerned oncology practitioners. Parenteral ranitidine is used as a premedication of hypersensitivity reaction (HSR) to paclitaxel [6]. During a previous shortage in the USA, De Lemos et al. have already proposed pharmacokinetic bioequivalence with oral drug formulation without clinical validation in terms of EBM [4]. Beyond adaptive propositions and in the light of literature the clinical efficacy of antiH2 medication for prevention of paclitaxel HSR should be questioned.

After the discovery of paclitaxel as an antimitotic drug, the first clinical trials with paclitaxel have revealed a high rate of HSR (up to 40 %) [7]. Clinical observations have linked this HSR with those observed with radiocontrast Media (RCM), which appears to be, at least in part, histaminergic [7]. Trial investigators and the National Cancer Institute have transposed premedication for RCM for clinical trials with paclitaxel (association of a corticoid, antiH1, and antiH2). This was followed by a significant decrease of HSR (around 1 %).

Histaminergic receptors are present ubiquitously and divided according to subtypes. While H1 receptors are preferentially involved in bronchoconstriction and edema mechanisms, H2 receptors are mostly involved in gastric acid secretion. They are also involved in bronchodilation and possibly in hypotension phenomenon. Whereas role of H1 in HSR mediated by histamine is clearly demonstrated, implication of H2 receptors in HSR mediated by histamine is debated. Recent in vivo data based on a gene knockout approach suggest that both H1 and H2 take part in anaphylaxis [8]. A clinical study shows in 12 healthy or

mildly asthmatic subjects that minimal plasmatic histamine concentration to obtain headache or flush was significantly higher only with combination of antiH1 and antiH2 and no with antiH1 or antiH2 alone. However, antiH2 also failed to influence histamine level required to elicit tachycardia whereas antiH1 or combination did it [9]. Furthermore, a controlled clinical study demonstrated the benefit of both antiH1 and antiH2 in prevention of HSR mediated by RCM compared to corticoid or antiH1 or placebo. However, no group received corticoid and antiH1 in the design study [10]. On the other hand, in vitro data indicate that H2 agonism appears to induce paradoxical effect like bronchodilation and inhibition of mast cell and leukocyte secretions [11]. Several in vivo studies show that antiH2 are not effective for prevention on HSR [9–12]. Greenberg et al. evaluated 857 cases of HSR by RCM and shows that prevention by prednisone and diphenhydramine or prednisone, diphenhydramine, and ephedrine significantly decreased the rate of HSR down to 10.8 and 5.0 %, respectively, whereas cimetidine appears to be ineffective [13]. Based on this data, Boehm and Maksymiuk have proposed for the prevention of HSR induced by paclitaxel the combination of a corticoid, an antiH1 and ephedrine but they do not recommend the use of an antiH2 [7]. In clinical practice, other studies have shown that antiH2-related side effects like hypotension and bradycardia pro arrhythmogenic with coronary ischemia risk [14]. Along with this, some cases report anaphylactic reaction with antiH2, especially ranitidine [15, 16], and a retrospective observational Japanese study reports increasing risk of hand-foot syndrome and facial erythema in breast cancer patients receiving docetaxel and antiH2 as premedication [17]. Moreover, Berger et al. shows in two retrospectives studies in a breast cancer population that discontinuation of premedications prior to paclitaxel administration beyond the second dose (in the case of no previous HSR) is safe and not associated with increased rate of rescue medications use [18, 19]. Finally, a systematic review from the Cochrane database on using antiH2 for urticaria underlines the lack of data and the large risk of bias of few small size and old studies [20].

In the light of these elements, efficacy of antiH2 for prevention of HSR induced by paclitaxel still appears to be controversial. However, because HSR can be life threatening, the decision to remove antiH2 from premedication of paclitaxel should be based on EBM. We propose an implementation of an institutional randomized clinical trial to compare a classical prevention protocol (in accordance with SPR) versus a prevention protocol without antiH2. The aim of this study would be to evaluate the non-superiority of the impact of HSR or to estimate the incidence of rescue medication usage during paclitaxel infusion in patients in the study group. Observations and knowledge from this study should be useful for oncology practitioners to better protect patients from HSR induced by paclitaxel.

Compliance with ethical standards

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