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Commentary: A systemic digestive allergic reaction imputable to docetaxel in a breast cancer patient

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Drug-induced hypersensitivity reactions (HSRs) are immunologically mediated dose-independent reactions[1,2]. Most reported cases of chemotherapy-induced HSRs are either immediate and IgE-mediated (type I), or delayed and T-cell mediated (type IV), according to the Gell and Coombs classification[3-9]. In our daily oncological practice, these HSRs mainly involve platinum and taxane, and clinical manifestations range in severity from pruritus to anaphylactic shock.

Docetaxel and paclitaxel are two main taxanes approved for the treatment of breast, lung, ovarian and prostate cancers. HSRs to docetaxel and paclitaxel have been reported in up to 7% of patients in phase I early clinical trials, and may be lethal in 0.05%[10,11]. In large clinical trials, HSRs are not reported (see Table S1 in Hamdan et al., reference 12), probably because their symptomatology and pathophysiology remain unclear[13].

We recently reported a case of severe allergic digestive reaction with hypereosinophilia imputable to docetaxel in a breast cancer patient[12]. Under docetaxel treatment, the patient had diarrhea with blood hypereosinophilia over 4000/mm3 that lasted for three months after the last cycle of docetaxel, leading to performing multiple biopsies of the gut and colon. All etiologies of hypereosinophilia were eliminated except for drug-induced HSR, with the highest imputability score for docetaxel. In particular, she had no DRESS syndrome according to consensus criteria[14]. A complete histological analysis including electron microscopy and multiple fluorescent immunostainings enabled us to confirm this was an immunologically-mediated HSR. In both gut and colon, we found a diffuse infiltration of numerous eosinophils and mast cells. In addition, mast cells from the epithelium were different from mast cells in the lamina propria, as described in bronchial biopsies of severe asthma with blood eosinophilia (Type IVb Th2-mediated immune reaction)[15,16].

Blood hypereosinophilia could thus be a sign of HSR, and provide a biomarker that is easy to monitor. After a search of the Medline database using the following algorithm: ("Eosinophilia"[Mesh] OR "Eosinophilia" OR "eosinophilic" OR "eosinophilic syndrome" OR "hypereosinophilia") AND ("Neoplasms"[Mesh] OR "cancer") AND ("Drug Hypersensitivity Syndrome"[Mesh] OR "Antineoplastic

Table 1 : Chemotherapy-induced hypereosinophilia.

Name/class of drug	References
PI3K inhibitor	Oncologist 2015
Anti-CTLA4	PloS One 2013
Lenalidomide	Eur J Dermato 2012
Aminopeptisase inhibitor	Br J Cancer 2010
Chlorambucil	Pharmacology 2008
Imatinib	Ann Dermatol Venereol 2008 Ann Dermatol Venereol 2006 Lancet Oncol 2005
Dacarbazine	Ann Dermatol Venereol 2006
Fludarabine	Ann Hematol 2002 Ann Hematol 1999
13-cis-retinoic acid	Med Pediatr Oncol 1999
Tegafur	J Gastroenterol 1994

Agents"[Mesh] OR "Drug Therapy"[Mesh] OR "chemotherapy" OR "drug-induced"), with the limits: Species=human and blood eosinophil count>1500/mm3, we identified 13 publications of hypereosinophilia imputable to an anticancer agent (Table1).

Blood hypereosinophilia is rarely reported with anti-cancer treatments. This is probably because there are too few reports from large clinical trials and inadequate pharmacovigilance after drug approval. Blood eosinophilia may also be underestimated because of the high doses of corticosteroids administered systematically with chemotherapy regimens.

A prospective registry would be needed to determine the real incidence of chemotherapy-induced blood hypereosinophilia. This would be the first step in improving the characterization of hypersensitivity reactions, to avoid the discontinuation of efficient anti-cancer treatments as soon as an HSR is suspected.

For patients with breast or ovarian metastatic cancer, survival is compromised in case of severe taxane-induced HSR because the treatment needs to be stopped[13,17].

After a complete history, physical examination, skin tests and drug provocation tests when available, HSR management is limited to antihistaminic and steroid therapy, or to desensitization[9]. This latter method is the most effective but infusion time needs to be prolonged and/or drug concentration progressively increased over a period of 2-3 days (mithridatization). Desensitization aims to deplete the amounts of inflammatory mediators with no effect on IgE. It is a time- and resource-consuming method with no validated protocol. In addition, using low doses of cytotoxic drugs could reduce the treatment efficacy[13,17,18].

An innovative approach could be the specific molecular targeting of mast cells and eosinophils. Indeed, in Th2-mediated immune reaction, Th2 T cells secrete cytokines like IL-5 which induces multiple responses, one of them being the production of IgE and an eosinophilic inflammation[19]. Eosinophils have low-affinity IgE receptors, and even low serum level of IgE will stimulate eosinophil degranulation[20]. In this type of drug-induced HSR, IgE could thus be a possible target.

Omalizumab, an anti-IgE monoclonal antibody, approved for the treatment of severe allergic asthma, is also considered efficient to prevent anaphylactic reactions linked to foods and poisons[21]. It could be a promising approach to treat chemotherapy-induced HSRs.

Conflict of interests

The authors do not have any conflict of interest.

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