Re-exploring immune-related side effects of docetaxel in an observational study: Blood hypereosinophilia
Diaddin Hamdan, Christophe Leboeuf, Christine Le Foll, Guilhem Bousquet, Anne Janin

To cite this version:
Diaddin Hamdan, Christophe Leboeuf, Christine Le Foll, Guilhem Bousquet, Anne Janin. Re-exploring immune-related side effects of docetaxel in an observational study: Blood hypereosinophilia. Cancer Medicine, Wiley, 2019, Epub ahead of print. 10.1002/cam4.2062. inserm-02124678

HAL Id: inserm-02124678
https://www.hal.inserm.fr/inserm-02124678
Submitted on 9 May 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
INTRODUCTION

Docetaxel, a semi-synthetic taxane inhibiting microtubule depolymerization, is approved for breast and lung cancer treatment. It is frequently responsible for drug-induced hypersensitivity reactions in up to 50% of patients,\(^1,2\) thus leading to deleterious treatment interruptions. Rapid drug desensitization protocols are effective in the management of...
HAMDAN et al.

nonsevere hypersensitivity reactions, thus limiting treatment interruptions.3–7 However, severe delayed visceral hypersensitivity reactions, potentially lethal from visceral complications, are excluded from desensitization protocols.

We recently reported a case of docetaxel-induced blood hypereosinophilia with a severe digestive allergic reaction.8 We hypothesized that drug-induced blood eosinophilia, probably underreported, could be a biological sign of hypersensitivity reaction, and could also predict severe delayed visceral hypersensitivity reactions.

In this observational study, we aimed to determine the incidence of docetaxel-induced eosinophilia, and whether it could be an early biological event predictive for the risk of delayed visceral hypersensitivity reactions.

2 | MATERIALS AND METHODS

2.1 | Inclusion criteria, clinical, and biological data

This study was approved by our local Institutional Review Board -IRB 00006477.

One hundred and forty-nine patients were included over a period of 1 year. All of them were being treated with docetaxel monotherapy for breast or lung cancer, as specified in the inclusion criteria (Table 1).

For each patient, blood eosinophil counts were recorded at the beginning of docetaxel treatment, before each cycle, and up to 3 months after the end of docetaxel treatment when data were available. At this last time-point, data were available for 79% of the patients (Figure 1). For the whole population, the blood eosinophil count was retrieved at 1 week before the beginning of docetaxel, at the end, and at 3 months after the end of docetaxel treatment.

For each patient, we considered that the increase in blood eosinophil counts was significant when it was at least twice as high compared to the count before initiation of docetaxel treatment.

For patients with blood eosinophil count >1000/mm³, various tests were conducted to eliminate other possible causes of eosinophilia (Table S1).

For pharmacological imputability of docetaxel, we calculated an imputability score using the French and the North American validated pharmacovigilance scales.9,10

For each patient, docetaxel-induced hypersensitivity reactions of any type (wheal-and-flare reactions, maculopapular eruptions, urticaria, itching, angioedema, local edema, bronchospasm, gastrointestinal symptoms, anaphylaxis, etc) were recorded and graded according to CTCAE-NCI grading scale version 5. Immediate and delayed hypersensitivity reactions were considered, and delayed hypersensitivity reactions occurred at least 6 hr after each administration of docetaxel.11

| Inclusion criteria | Exclusion criteria |
|-------------------|-------------------|
| Breast or lung cancers | Cancers of other origins |
| Localized or metastatic cancer | |
| Docetaxel monotherapy | Docetaxel combination therapy |
| Available blood analyses before, during and after docetaxel treatment | Blood analyses not available during docetaxel treatment |

TABLE 1 Inclusion criteria

![Flow-diagram](image-url)
2.2 | Tissue analyses and characterization of eosinophils and mast cells

Among the four patients with blood hypereosinophilia >1000/mm³, we were able to perform tissue analyses for two patients with eosinophil counts for whom tissue samples were obtained at the time of blood eosinophilia.

We used anti-tryptase and anti-eosinophil peroxidase (EPO) antibodies to differentiate and count mast cells and eosinophils. These two immunostainings were performed on 5 µm-thick tissue sections using indirect immunoperoxidase staining, with rabbit polyclonal anti-human EPO (ab104530, Abcam, Cambridge, UK) and monoclonal mouse anti-human tryptase (clone G3, Santacruz, Heidelberg, Germany) as primary antibodies. Controls included omitting the primary antibody and using an irrelevant antibody of identical isotype. The analysis focused on the number and distribution of mast cells and eosinophils in the different tissue sections. Tissue sections were analyzed using an Olympus AX 70 microscope with a 0.344-mm² field size at 400× magnifications (Olympus, Tokyo, Japan). Images were systematically taken using SAS software for each immunostaining image.

For the ultrastructural analysis, tissue samples were fixed in 2% glutaraldehyde-buffered 0.1 M. cacodylate and embedded in epoxy resin. Ultra-thin sections were stained with uranyl acetate and lead citrate and analyzed using a Hitachi-7650. The images of the distribution of mast cells and eosinophils and their state of degranulation were captured.

2.3 | Statistical analysis

Categorical variables were summarized as the number (percentage) and continuous variables were summarized as the mean or the median.

A comparison of the median value of the three matched-sample of blood eosinophil count was performed (ie, pre-treatment period, at the end, and at 3 months after the end of docetaxel treatment) using the Wilcoxon's test.

All tests were two-sided and the threshold for statistical significance was set to \( P < 0.05 \). The data were analyzed using the BiostaTGV site (http://marne.u707.jussieu.fr/biostatgv, accessed in Avril 2018).

3 | RESULTS

3.1 | Patients

Patients were recruited from January 2017 to December 2017, and inclusion criteria are detailed in Table 1. A total of 149 patients with breast or lung cancers treated with docetaxel mono-therapy were included during this period. Their characteristics are detailed in Table 2:81% had breast cancer, with a median age of 55 and 61 years for breast and lung cancer patients, respectively.

3.2 | Blood eosinophil counts under docetaxel chemotherapy

We have compared the median of blood eosinophil counts before, at the end and three months after the end of docetaxel treatment. Among the 149 patients, 73 (49%) had at least a twofold increase in their blood eosinophil counts during the follow-up period (Table 2). We have compared the median of blood eosinophil counts before, at the end and 3 months after the end of docetaxel treatment. Median blood eosinophil counts significantly increased under docetaxel chemotherapy, from 77/mm³ before treatment, to 135/mm³ and 221/mm³ at 3 and 6 months respectively (\( P < 0.01 \)) after docetaxel initiation (Figure 2A). Three months after the last cycle of docetaxel, blood eosinophil counts remained higher than 500/mm³ in 7% of the patients (Figure 2A and Figure S1), with comparable results in the two cancer types (Figures S2 and S3).

3.3 | Docetaxel-induced hypersensitivity reactions

When we looked at all-grade docetaxel-induced hypersensitivity reactions other than blood eosinophilia, they

| Patients | Breast | Lung | Whole cohort | At least twofold increase in blood eosinophil count during follow-up period |
|----------|--------|------|--------------|------------------------------------------------|
| Number (%) | 122 (81) | 27 (18) | 149 (100) | 73 (49) |
| Mean age (years) | 55 | 61 | 58 | 60 |
| Allergic history (%) | 18 (13) | 2 (7) | 20 (13) | 9 (12) |
| Mean number of docetaxel cycles | 2.89 | 4.63 | 3.76 | 2.58 |
| Mean dose of cycle 1 (mg) | 160.72 | 123 | 141.86 | 151.46 |
| HSRs other than blood eosinophilia | G1-2a (%) | 42 (34) | 8 (29) | 50 (33) | 30 (41) |
| G3-4 (%) | 9 (7) | 2 (7) | 11 (7) | 7 (9) |

Bold values are corresponding to percentages. HSR: hypersensitivity reactions.

*G: Grade according to Common Terminology Criteria for Adverse events of the United States National Cancer Institute, CTCAE-NCI v.5.0.
**Patient 3 - Skin biopsy**

- **Immunostainings**
  - Anti-trypase
    - x40
  - Anti-EPO
    - x40

- **Electron microscopy**
  - Mastocyte
    - x10550
  - Eosinophil
    - x62400

**Patient 4 - Tumor biopsy**

- **Immunostainings**
  - Anti-trypase
    - x10
  - Anti-EPO
    - x40

- **Electron microscopy**
  - Mastocyte
    - x61200
  - Eosinophil
    - x49950
occurred for 66 of the 149 patients (40%) (Table 2). Interestingly, among the 52 patients with a significant increase in blood eosinophil counts, 50% had a hypersensitivity reaction manifestation other than blood eosinophilia (Table 2). Table 3 reports the different types of hypersensitivity reactions, and shows that all-grade hypersensitivity reactions occurred in 21 patients (14%), leading to a premature discontinuation of planned docetaxel treatment. Four patients (2.6%) had blood eosinophil counts over 1000/mm³ (Figure 2B). We eliminated other possible etiologies of eosinophilia and thus confirmed the imputability of docetaxel using drug-imputability scales (Table 4). Patient 1 had an NCI-CTCAE-v5 grade II diarrhea without severe complications; Patient 2 had an NCI-CTCAE-v5 grade III cardiac flutter at the end of the docetaxel treatment despite the absence of any cardiac risk factor. For Patient 3, blood eosinophilia persisted well beyond 6 months after the discontinuation of docetaxel, with severe chronic pruritus justifying a skin biopsy. Patient 4 received docetaxel and had hypereosinophilia at the time of breast surgery.

On the skin of Patient 3 and the breast cancer of Patient 4, specific immunostainings (anti-eosinophil peroxidase, anti-tryptase) and electron microscopy found numerous degranulating mast cells and eosinophils; for Patient 4, we found clustered tryptase-expressing mast cells at the invasive front of the tumor (Figure 2B,C).

### 3.4 Literature review

For the literature review of hypereosinophilia cases imputable to anticancer drugs, we used an ad-hoc algorithm composed of both thesaurus and free text terms to search the Medline database up to 2 May 2018. We used 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 Agents”[Mesh] OR “Drug Therapy”[Mesh] OR “chemotherapy” OR “drug-induced”). With the limits: Species = human and blood eosinophil count >1500/mm³, 818 articles were initially identified. We screened the papers retrieved initially on title and abstract, and finally on full text. Twenty-three publications on hypereosinophilia imputable to an anticancer agent were identified, 19 were case reports, two others were phase I clinical trials, one was an observational cohort, and the last was a literature review (Table 5).

### DISCUSSION

Our study confirmed our hypothesis that docetaxel-induced blood eosinophilia is largely underestimated since a two-fold increase in blood eosinophil count occurred in half of the treated population. It was frequently associated with other clinical manifestations of immediate and delayed hypersensitivity reactions, supporting our hypothesis that blood eosinophilia is a biological sign of hypersensitivity reaction. In addition, it was severe, over 500/mm³, and durable over time for 7% of the patients, comparable to the 7% of patients with grade 3-4 hypersensitivity reactions in phase I clinical trials with docetaxel. It led to visceral complications for four of the 149 patients, and in all four
cases the increase in blood eosinophil count preceded the visceral complication. Blood eosinophilia could be thus an early biological sign predictive for the risk of docetaxel-induced delayed visceral hypersensitivity reactions.

Strikingly, eosinophilia is not reported in clinical trials using docetaxel, possibly because of corticoid premedication which limits the increase in blood eosinophil counts, and also because blood eosinophilia can occur after the end of docetaxel treatment when systematic blood counts are no longer performed. Even for other drugs, drug-induced blood eosinophilia is rarely reported, as our literature review shows.

In case of drug-induced blood eosinophilia, a desensitization protocol, similar to those implemented for immediate hypersensitivity reactions,3–7 might be useful to avoid delayed visceral complications.

One limitation to our observational study is the limited number of patients and tissue samples analyzed. Despite this, we were able to demonstrate that docetaxel-induced eosinophilia is a frequent biological sign of hypersensitivity reaction that can predict delayed visceral complications. In addition, with only two biopsy samples obtained at the time of hypereosinophilia with visceral complications, we confirmed the tissue infiltration by degranulating eosinophils and mast cells, as reported in our previous publication.8

Docetaxel-induced hypersensitivity reaction is an inflammatory reaction resulting from the activation of eosinophils and

### Table 4

| Drugs | Adverse drug reaction probability scale | French imputability score |
|-------|----------------------------------------|---------------------------|
|       | Score | IS | C | S | Intrinsic imputability |
| **Patient 1** | | | | | |
| Docetaxel | 6 | 2 | 3 | 3 | I6 |
| Ondansetron | 0 | 2 | 1 | 2 | I2 |
| Prednisone | 0 | 2 | 1 | 2 | I2 |
| Metoclopramide | 0 | 2 | 1 | 2 | I2 |
| Paracetamol | -2 | 2 | 1 | 2 | I2 |
| Loperamide | -2 | 2 | 0 | 2 | I0 |
| Lansoprazole | -2 | 2 | 0 | 2 | I0 |
| Phloroglucinol | -2 | 2 | 0 | 2 | I0 |
| Diosmectite | -2 | 2 | 0 | 2 | I0 |
| **Patient 2** | | | | | |
| Docetaxel | 6 | 2 | 3 | 3 | I6 |
| Ondansetron | 0 | 2 | 1 | 2 | I2 |
| Prednisone | 0 | 2 | 1 | 2 | I2 |
| Metoclopramide | 0 | 2 | 0 | 2 | I0 |
| Esomeprazole | -2 | 2 | 0 | 2 | I0 |
| Hydroxyzine | -2 | 2 | 0 | 2 | I0 |
| Sotalol | -2 | 2 | 0 | 2 | I0 |
| Nicopatch | -2 | 2 | 0 | 2 | I0 |
| Levetiracetam | -2 | 2 | 0 | 2 | I0 |
| Clofazimine | -2 | 2 | 0 | 2 | I0 |
| **Patient 3** | | | | | |
| Docetaxel | 6 | 2 | 3 | 3 | I6 |
| Ondansetron | 0 | 2 | 1 | 2 | I2 |
| Prednisone | 0 | 2 | 1 | 2 | I2 |
| Metoclopramide | 0 | 2 | 1 | 2 | I2 |
| **Patient 4** | | | | | |
| Docetaxel | 6 | 2 | 3 | 3 | I6 |
| Ondansetron | 0 | 2 | 1 | 2 | I2 |
| Prednisone | 0 | 2 | 1 | 2 | I2 |
| Metoclopramide | 0 | 2 | 1 | 2 | I2 |
| Lansoprazole | -2 | 2 | 1 | 2 | I2 |

Bold values are corresponding to calculated scores according to each pharmacological scales.

IS: Informativeness score, C: chronology, S: semiology
mast cells, themselves able to enhance their own recruitment and activation through an autocrine loop. IL-5 and IL-13 auto-secretion boost IgEs and also induce eosinophil activation and degranulation through their low-affinity IgE receptor. One way of treating hypersensitivity reactions could be by targeting IgEs with omalizumab, an anti-IgE monoclonal antibody approved for the treatment of severe allergic asthma, and successfully used in food and poison-induced anaphylactic reactions.15

In conclusion, our observational study demonstrated that docetaxel-induced blood eosinophilia is a frequent early biological sign of hypersensitivity reaction that can predict delayed visceral complication.

ACKNOWLEDGMENTS

We would like to thank Dr. Christine Dosquet for her valuable advice and criticisms. We would like also to thank Ms. Angela Swaine and Sarah Leyshon for revising the English language.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

ETHICS

This work was approved by the local Institutional Review Board -IRB 00006477 under the number: 16-053. It was also approved by the National Committee on private freedoms (CNIL) under the number: 1988828 v 0.

Informed consent from each patient was obtained prior to inclusion in the study.

ORCID

Diaddin Hamdan https://orcid.org/0000-0002-2212-0287

REFERENCES

1. Rive CM, Bourke J, Phillips EJ. Testing for drug hypersensitivity syndromes. *Clin Biochem Rev*. 2013;34(1):15-38.
2. Picard M, Castells MC. Re-visiting hypersensitivity reactions to taxanes: a comprehensive review. *Clin Rev Allergy Immunol*. 2015;49(2):177-191.
3. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;122(3):574-580.
4. Castells Guitart MC Rapid drug desensitization for hypersensitivity reactions to chemotherapy and monoclonal antibodies in the 21st century. *J Investig Allergol Clin Immunol*. 2014;24(2):72-79; quiz 2 p following 9.
5. Castells M, Sancho-Serra Mdel C, Simarro M. Hypersensitivity to antineoplastic agents: mechanisms and treatment with rapid desensitization. *Cancer Immunol Immunother*. 2012;61(9):1575-1584.
6. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saïf MW. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met Based Drugs*. 2010:2010.
7. Rose PG, Fusco N, Smrekar M, Mossbruger K, Rodriguez M. Successful administration of carboplatin in patients with
clinically documented carboplatin hypersensitivity. *Gynecol Oncol*. 2003;89(3):429-433.

8. Hamdan D, Leboeuf C, Pereira C, et al. A digestive allergic reaction with hypereosinophilia imputable to docetaxel in a breast cancer patient: a case report. *BMC Cancer*. 2015;15:993.

9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.

10. Arimone Y, Bidault I, Dutertre J-P, et al. Updating the French method for the causality assessment of adverse drug reactions. *Therapie*. 2013;68(2):69-76.

11. Demoly P, Adkinson Nf, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69(4):420-437.

12. Tomiak E, Piccart Mj, Kerger J, et al. Phase I study of docetaxel administered as a 1-hour intravenous infusion on a weekly basis. *J Clin Oncol*. 1994;12(7):1458-1467.

13. Rosing H, Lustig V, van Warmerdam L, et al. Pharmacokinetics and metabolism of docetaxel administered as a 1-h intravenous infusion. *Cancer Chemother Pharmacol*. 2000;45(3):213-218.

14. Vandezande Lm, Wallaert B, Desreumaux P, et al. Interleukin-5 immunoreactivity and mRNA expression in gut mucosa from patients with food allergy. *Clin Exp Allergy*. 1999;29(5):652-659.

15. Shankar T, Petrov AA. Omalizumab and hypersensitivity reactions. *Curr Opin Allergy Clin Immunol*. 2013;13(1):19-24.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Hamdan D, Leboeuf C, Le Foll C, Bousquet G, Janin A. Re-exploring immune-related side effects of docetaxel in an observational study: Blood hypereosinophilia. *Cancer Med*. 2019;00:1-8. [https://doi.org/10.1002/cam4.2062](https://doi.org/10.1002/cam4.2062)