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Can we predict chemo-induced hematotoxicity in elderly patients treated with pegylated liposomal doxorubicin? Results of a population-based model derived from the DOGMES phase II trial of the GINECO

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ABSTRACT

Introduction: Use of anthracyclines is often limited in older patients due to cardiac and hematologic toxicities. Thanks to its reduced toxicity profile, Pegylated Liposomal Doxorubicin (PLD) allows an extended use of doxorubicin to this population. We aimed at modeling PLD-induced hematotoxicity in patients with metastatic breast cancer ≥ 70 years old and at finding predictive factors of neutrophil nadir value.

Methods: Sixty patients, enrolled in the DOGMES prospective multicentric phase II trial, were treated with PLD at 40 mg/m^2 every 28 days during six cycles. Trial design included geriatric covariates assessment at inclusion and monitoring of cells count every week for three cycles. A population model was developed to describe hematopoiesis and hematopoietic reserve in these patients. The effect of co-administered G-CSF (granulocyte colony-stimulating factor) was also examined.

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Results: A pharmacodynamic model was built using data from 53 patients not receiving G-CSF. This model assumed an instantaneous effect of PLD on the system. Based on this model, exact neutrophil nadir value was computed and ranged between 0.069 K/mm^3 and 2.63 K/mm^3 confirming the weak hematotoxicity of PLD. The same model was then applied to the 7 patients receiving G-CSF and showed that basal neutrophil count was higher for these patients. No other difference was found between both cohorts. Among the covariates collected, three were predictive of neutrophil nadir value: diabetes, frailty syndrome and assistance at home.

Conclusion: This developed model allowed the identification of predictive factors of nadir ANC and the identification of patients that are more likely to develop hematotoxicity that should be monitored with attention.

1. Introduction

Breast cancer is the first cause of cancer mortality in women worldwide. Nowadays, more than 50% of breast cancers are diagnosed in women age 65 or older and cancer-related mortality rate is threefold higher in this population. Due to the increase in life expectancy, a rise in cancer incidence and mortality is expected in the next decades.[1,2] Despite an improvement in breast cancer care and overall survival, these improvements did not benefit patients over 65 because of a trend towards under-treatment in the elderly and the lack of specific recommendations.[3] It is thus necessary to characterize the age specificity of breast cancer and understand the risks and benefits of treatment in older adults.[4,5]

Anthracyclines play an important role in the management of breast cancer. Due to their cardiac toxicity, they are usually administered with caution to elderly patients and often at adapted dose. A cumulated doxorubicin dose greater than 400 mg/m^2 significantly increases the risk of congestive heart failure for patients older than 65.[6]

Toxicity remains a dose-limiting parameter in clinical trials evaluating anthracyclines in geriatric populations. As compared to the CMF (cyclophosphamide, methotrexate, fluorouracil) protocol, adjuvant anthracyclines induced more grade 3 or 4 toxic events, hospitalizations due to febrile neutropenia according to the Memorial Sloan–Kettering records.[7] Nevertheless, no official recommendation exists to adapt doxorubicin dose with age even if doses lower than 50 mg/m^2 are often preferred in elderly patients.[8] Development of liposomal formulation associated with lower risk of cardiotoxicity allows extending the use of doxorubicin to the geriatric population.

Doxil® is a pegylated liposomal formulation of doxorubicin (PLD): the active substance is encapsulated in liposomal vesicles, which preferentially penetrates tumor tissues, thus reducing plasma concentrations of doxorubicin and its active metabolite, doxorubicinol. Comparisons between standard doxorubicin and PLD have shown that PLD was better tolerated with an equivalent efficacy even though hand-and-foot syndrome was more frequent with PLD.[9,10]

Nowadays the adaptation of medical and surgical care in the elderly is often a matter of debate. Among the leading questions is the better assessment of their individual vulnerability and toxicity risk prediction.[11]

Physiological modifications and comorbidities have a non-negligible influence on drug pharmacokinetics (PK) and pharmacodynamics (PD), translated into an increased inter-individual variability within the geriatric population. Moreover previous studies have shown a progressive decrease of neutrophil nadir upon time in patients over 65 treated with 4 cycles of doxorubicin–cyclophosphamide, whereas it is maintained over time in a younger population.[12] This phenomenon is hypothesized to illustrate the exhaustion of hematopoietic reserve in the elderly.[12]

Hematotoxicity is often dose-limiting[13] and international guidelines consider age as a vulnerability criterion to be taken into account for hematopoietic growth factor use without any insight into hematopoiesis dynamics.[14–16]

The prospective DOGMES phase II study aimed at evaluating response and tolerance of PLD in patients with metastatic breast cancer aged over 70. The impact of age, comorbidities and geriatric covariates on PLD hematotoxicity was also explored.

In this paper, we propose a population pharmacodynamic modeling approach to describe the hematopoietic reserve, hematopoiesis and neutropenic effects of PLD in elderly patients. This model has been used to correlate the risk of neutropenia to patients' characteristics.

2. Patients and Methods

2.1. *Patients*

Sixty patients with metastatic breast cancer over 70 years old were enrolled in the "Doxorubicine liposomale pégylée en Oncologie Gériatrique — Metastases du cancer du Sein" (DOGMES) prospective multicentric phase II study. The main objective of the DOGMES study was to evaluate, in an elderly population, PLD efficacy in terms of objective response.[17] The main eligibility criteria were histologically proven HER2/neu negative invasive breast adenocarcinoma (ductal or lobular) and cytologically or histologically proven first line hormone-resistant metastatic disease at the time of study entry. Details and clinical results of the DOGMES study are reported elsewhere.[18]

Patients received PLD at 40 mg/m^2 every 28 days for at least 6 cycles. Absolute neutrophil count (ANC) was monitored at inclusion and every week for three cycles. In total sixty-six covariates (demographic, biologic, oncologic and geriatric) were assessed at inclusion. Geriatric assessment domains included comorbidities, nutritional assessment, functional assessment, cognitive status, psychological states and autonomy.