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Clinical trials

Geriatric assessment and biomarkers in patients with metastatic breast cancer receiving first-line mono-chemotherapy: Results from the randomized phase III PELICAN trial

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ABSTRACT

Objectives: To determine predictive/prognostic factors for patients with metastatic breast cancer (MBC) receiving first-line monochemotherapy using biomarker analysis and geriatric assessment (GA).
Materials and Methods: Karnofsky Performance Status (KPS) and GA as clinical parameters, and prognostic inflammatory and nutritional index (PINI), and Glasgow prognostic score (GPS) as biomarkers were analyzed for association with clinical outcome within the randomized phase III PEg-LIposomal Doxorubicin vs. CApecitabin iN MBC (PELICAN) trial of first-line pegylated liposomal doxorubicin (PLD) or capecitabine.
Results: Of 210 patients, 38% were >65 years old. GA (n = 152) classified 74% as fit, 10% as compromised, and 16% as frail. Biomarkers showed no age dependency. In multivariate analysis (n = 70) KPS, GA, cumulative illness rating scale-geriatrics (CIRS-G), and GPS were significantly associated with time to progression, and KPS, CIRS-G, and instrumental activities of daily living (IADL) from GA, and PINI showed a significant correlation with overall survival.
Conclusion: GA evaluation was feasible. KPS significantly correlated with efficacy outcomes. Items of a GA and biomarkers of inflammation and nutrition may have prognostic significance in patients with MBC.

1. Introduction

Cytotoxic therapy is associated with severe and potentially lethal complications, especially in older or medically non-fit patients. Therapeutic decisions must be carefully considered to avoid harm to the patient by either treatment-related toxicity or ineffective therapeutic measures. However, there are few data from randomized trials to guide physicians on how to treat older or medically non-fit patients with cancer.

A prospective survey carried out in France collected data from 107 oncologists on the diagnosis and treatment of older women with

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metastatic breast cancer (MBC). Respondents who participated in this survey did not consider geriatric covariates in their routine clinical practice. Prospective clinical trials in older patients with MBC are needed to help reduce heterogeneity in decision-making and define standards of care in this population [1]. A comprehensive geriatric assessment (CGA) could predict severe toxicity and overall survival (OS) of older patients with advanced ovarian cancer [2]. In breast cancer, the value of performing CGA is still unclear. No uniform format for a CGA has been defined; however, most groups recommend assessment of activities of daily living (ADL), instrumental ADL (IADL), comorbidity (e.g., by the Cumulative Illness Rating Scale Geriatrics [CIRS-G]), documentation of daily co-medication, screening for depression and dementia, and a balance and mobility test [3–5].

Assessments of markers of inflammation and nutrition have a long-standing history in the evaluation of different conditions of compromised health. More than 20 years ago, the prognostic inflammatory and nutritional index (PINI), using a formula that included C-reactive protein (CRP), alpha-1 acid glycoprotein (AGP), albumin, and prealbumin (transthyretin), was developed in critically ill patients [6]. Since then, it has been tested in many other patient populations, including patients with advanced solid tumors, where altered PINI correlated with risk of severe hematological toxicity [7]. More recently, the Glasgow prognostic score (GPS), which is based solely on albumin and CRP, has been developed; a GPS of 2 has shown correlation with adverse survival in patients with advanced renal, pancreatic, and breast cancer [8–10].

The pegylated liposomal doxorubicin or capecitabine (PELICAN) trial is a multinational, randomized, open-label study comparing pegylated liposomal doxorubicin (PLD) and capecitabine as first-line treatment for MBC. Details about the safety and efficacy analysis of first-line treatment within the PELICAN trial are reported elsewhere [11]. Interestingly, a similar trial design has been reported from a Dutch phase III trial; however, this trial had to be closed prematurely after enrolling 78 of 154 planned older patients [12]. In this trial, the number of geriatric conditions correlated with grade 3–4 toxicities, and frailty correlated with shorter survival [13]. An open phase II trial evaluated an adapted dose of PLD in older patients with MBC, and found the feasibility of this regimen to be poor in unselected older patients. In addition, several factors that correlated with toxicity, progression-free (PFS) and OS were identified, among these decreased PFS and OS with living in residential homes [14]. Within the PELICAN trial, prospective collection of data and blood samples was incorporated for an exploratory analysis. The main objective of this analysis was to evaluate the prognostic and predictive value of GA and biomarkers of inflammation and nutrition in patients with MBC treated with first-line chemotherapy.

2. Materials and Methods

2.1. Patients

Enrolment criteria for PELICAN are published in detail elsewhere [11]. The study included women aged ≥18 years with MBC whose clinical condition allowed monotherapy treatment or who desired monotherapy and had an Eastern Cooperative Oncology Group (ECOG) performance status 0–2. Exclusion criteria included prior chemotherapy for metastatic disease; eligibility for hormone or trastuzumab therapy; central nervous system metastasis unless asymptomatic for ≥3 months; dyspnea on exertion; and cardiac disease of New York Heart Association (NYHA) class II or greater, or clinical evidence of congestive heart failure or myocardial infarct within six months or a left ventricular ejection fraction (LVEF) < 50%.

2.2. Treatment

Patients in PELICAN were randomized to receive either PLD 50 mg per meter squared ($mg/m^{2)}$ every 28 days or capecitabine 1250 mg/m^2 twice daily for 14 days every 21 days. Detailed dose reduction information was given in the protocol in case of toxicities. Treatment continued until disease progression or unacceptable toxicity.

2.3. Geriatric Assessment

Geriatric assessment was conducted on the PELICAN study population at baseline and consisted of assessment of ADL [15], IADL [16], comorbidity assessed by CIRS-G [17], and documentation of daily co-medications. Performance status was evaluated using the Karnofsky scale (KPS). According to the GA, patients were classified into the following three groups as suggested by Balducci et al. [18] group 1, fit; group 2, compromised; and group 3, frail. Patients without ADL or IADL limitations and without serious comorbidities were classified as fit, patients without ADL limitations and ≤2 limitations in IADL and ≤2 comorbid conditions were classified as compromised, and all other patients were classified as frail.

2.4. Biomarker Analysis

Blood samples (serum or plasma) were collected at baseline (before treatment) and shipped at room temperature to the Laboratory of Experimental Oncology in Hamburg. Samples were aliquoted after centrifugation and stored at −80 °C until analysis at the Department of Clinical Chemistry, University Medical Center Hamburg. Blood samples of 86 patients were available for analysis. Biomarker analysis included C-reactive protein (CRP), alpha-1 acid glycoprotein (AGP), albumin, prealbumin (transthyretin), and serum amyloid A (SAA). AGP, prealbumin, and SAA were measured with a nephelometric assay on the BN II-analyzer (Siemens, Germany). For AGP, the inter-assay coefficient of variation (CV) is 1.7% at 1.12 g per litre (g/l), and 3.5% at 0.46; for prealbumin, 1.1% at 0.19 g/l, and 2.3% at 0.38 g/l; and for SAA 2.8% and 4.7% for concentrations between 7 and 192 mg per litre (mg/l). The measurement of CRP and albumin was performed on the modular analyzer (ROCHE). Albumin was determined by a colorimetric endpoint method with bromcresol green, and CRP by an immunoturbidimetric assay. For albumin, the run to run precision is 2.0% at 30 g/l, and 1.4% at 28 g/l. For CRP, the run to run precision is 2.1% at 41 mg/l and 2.7% at 3.1 mg/l. All assays were performed per manufacturer instructions.

The composite biomarker PINI score was calculated as CRP (mg/l) × AGP (mg/l) / albumin (g/l) x prealbumin (mg/l), with a higher score indicating worse status. The composite biomarker GPS score was defined as follows: patients were allocated a score of 2 if both CRP >10 mg/l and albumin <35 g/l. If only one of these abnormalities was present, a score of 1 was allocated. Patients with none of these abnormalities were allocated a score of 0.

2.5. Statistical Analyses

Data collection, management, and analysis were performed using SAS.

Comparisons between groups were done using a nonparametric Wilcoxon rank-sum test for quantitative parameters. The Kruskal-Wallis test was used for comparisons between 3 or more groups in case of quantitative variables. Categorical variables were compared using Fishers Exact Test or Chi Square Test. The Cochran-Armitage Trend Test was applied for comparisons of categorical variables with ordered categories.

The Kaplan–Meier method was used to estimate the distribution of time to event variables. The survival curves were compared using a log-rank test. The simultaneous impact of geriatric assessments on OS, time to progression (TTP), and time to treatment failure (TTF) were investigated using multivariate Cox Proportional Hazard Models. Starting with a model containing all candidate parameters, the variable with the highest p-value was removed respectively until the model consisted of

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