Body Mass Index and Prognosis of Metastatic Breast Cancer Patients Receiving First-Line Chemotherapy

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Abstract

Background: The effect of body mass index (BMI) on the prognosis of metastatic breast cancer (MBC) has not been explored so far.

Methods: The relationship between BMI (kg/m²) and progression-free survival (PFS) or overall survival (OS) was assessed in 489 patients with MBC enrolled in three clinical trials of first-line chemotherapy. World Health Organization BMI categories were used: normal, 18.5–24.9 kg/m²; overweight, 25–29.9 kg/m²; and obese, 30+ kg/m². Univariate PFS and OS curves were estimated; multivariate Cox analysis was conducted adjusting for age, menopausal status, performance status (PS), hormonal status and site, and number of metastases.

Results: Overall, 39.9% of the patients were normal or underweight, 37.8% were overweight, and 22.3% were obese. Median age was 57 years (range 25–73); median PS was 0. Median PFS was 10.9 months (interquartile range 5.5 to 19.9) in normal weight women, 13.0 months (IQR 7.8 to 23.7) in overweight, and 12.2 (IQR 7.1 to 23.0) in obese women, \( P = 0.17 \). Median OS was 32.0 months [95% confidence interval (CI), 14.5–88.3] versus 33.2 months (95% CI, 19.4–81.1) and 30.7 (95% CI, 17.6–50.8), respectively. In multivariate analyses, no statistically significant association between BMI category and PFS or OS was observed.

Conclusions: In this study, BMI was not associated with the outcome of patients with MBC treated with first-line chemotherapy.

Impact: In the absence of any evidence in support of a prognostic role of obesity in patients with MBC treated with chemotherapy, dietary restrictions, medical interventions aimed at reducing BMI/insulin resistance, or specific anticancer treatment strategies do not seem to be appropriate.

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Introduction

Overweight and obese subjects show an increased risk of developing many types of cancer, including breast neoplasms, when compared with individuals with normal weight (1–3). The relationship between overweight and increased breast cancer risk was consistently observed in postmenopausal women (4, 5), whereas the association between body weight and premenopausal breast cancer risk is less clear (6–8). Several lines of evidence also suggest that increased body weight is associated with a worse prognosis: a shorter survival has been observed in obese women with early breast cancer (9–12) and in those gaining weight after breast cancer diagnosis (13).

Several hypotheses have been put forward to explain the association between obesity and breast cancer. Among these, the most popular one attributes the increased risk and the worse prognosis to the elevated levels of circulating estrogens that are observed in obese women due to peripheral aromatization of androgens in the adipose tissue (14, 15). A more recent hypothesis postulates an indirect effect of obesity on breast cancer development and progression, caused by the associated condition of insulin resistance, which is characterized by elevated levels of circulating insulin and insulin-like growth factors. These, in turn, result into an increased cancer cell proliferation (16, 17). Finally, chronic inflammation has been involved as the determinant of the above mentioned associations, due the fact that obesity is a recognized proinflammatory state, leading to the release of inflammatory cytokines promoting tumor growth (18).

The association between body weight and prognosis was observed mainly in women with early breast cancer. Even though a similar association seems to be plausible also in women with advanced disease, little
The dismal long-term outcome of metastatic breast cancer (MBC) should not conceal the potential relevance of a negative prognostic impact of obesity in advanced disease. In fact, in recent years a substantial improvement in the life expectancy of these women has been observed, with current median survival times in the range of 36 to 48 months and no less than 25% of patients are alive at 5 years as the diagnosis of metastatic disease (21–23). In this perspective, even a moderate relative increase in the hazard of progression or death associated with overweight or obesity (e.g., HR, 1.3–1.5) would translate into absolute decreases of progression free survival (PFS) or overall survival (OS) of several months (> 8–12), of the same order of magnitude of, or greater than the effects of drugs currently used in the treatment of MBC.

Taking advantage of the database of breast cancer clinical trials conducted by our cooperative group in the past years, we evaluated the prognostic impact of body mass index (BMI) in patients with MBC treated with first-line chemotherapy.

Materials and Methods

Patient selection

Six hundred ninety eight patients with MBC enrolled into three consecutive clinical trials of first-line chemotherapy, conducted between 2000 and 2005, were included in the present analysis.

Eligibility criteria were similar in the 3 studies. Patients were required to have histologically confirmed breast carcinoma and metastatic disease, with at least one bidimensionally measurable lesion, previously untreated with chemotherapy for metastatic disease. Prior adjuvant chemotherapy was allowed if discontinued at least 6 to 12 months before study entry. Other eligibility criteria included age younger than 75 years, Eastern Cooperative Oncology Group (ECOG-PS) Performance Status ≤2, and normal cardiac function.

The methods (including treatment details) and the results of these studies have been reported individually (24–26). All data had been prospectively collected and had been entered into a centralized patient data management system at the Trial Centers of the National Cancer Research Institute of Genoa, Italy and of the IRST, Meldola (FC), Italy.

Statistical methods

All statistical analyses were conducted on the database resulting from pooling the original databases of individual studies that included 698 patients. The analysis reported in the current study was limited to 489 patients, as 209 patients were excluded because no direct information on weight and/or height was available.

The primary aim of this study was to evaluate the relationship between BMI (computed by dividing the weight in kilograms by the square of the height in meters) and PFS or OS.

BMI categories were selected according to the World Health Organization definition: underweight, <18.5 kg/m²; normal range between 18.5 and 25 kg/m²; overweight between 25 and 30 kg/m²; and obese ≥30.0 kg/m². However, as only 10 women (2%) were underweight, these women were considered with normal weight women in our analysis. BMI was assessed at baseline, before treatment administration. All information on prognostic factors and response to treatment was obtained from the original files, whereas OS and PFS data were updated from clinical records.

PFS was defined as the time interval from study entry to disease progression, or death from any cause, whichever occurred first. OS was defined as time from study entry to death from any cause.

Univariate analyses used standard statistical methods such as the χ² test for comparison of proportions and the Kaplan–Meier estimator with the log-rank test for the estimation and comparison of survival curves. Multivariate proportional hazards models were used in analyses of PFS and OS to adjust for differences among BMI categories in baseline factors, including age, menopausal status, WHO Performance Status, hormonal status, site, and number of metastases and trial.

Results

All the 489 patients included in the present analysis received first-line chemotherapy regimens including anthracyclines and taxanes, either in sequence or combination. Patient characteristics are described in Table 1. Median age was 57 years (range 25 to 73); PS was 0 in 68% of the patients, with only 5% of the patients having PS = 2. Median follow up was 18 months (range 0.4 to 88.3). The presence of obesity at baseline (time of study enrolment), as defined by a BMI ≥30.0 kg/m², was observed in 109 of 489 patients (22%); 185 patients (38%) were overweight (BMI between 25.0 and 29.9 kg/m²), 185 (38%) were normal (BMI between 18.5 and 24.9 kg/m²), and 10 (2%) were underweight (BMI <18.5 kg/m²).

Progression-free survival

Overall, 385 progressions were recorded in the 489 women included in the analysis. Median PFS was 12.1 months [interquartile range (IQR) 6.3–21.6 months]. No significant trend or heterogeneity in PFS was observed according to BMI category (Fig. 1). Median PFS was 10.9 months (IQR 5.5–19.9) in normal/underweight women (BMI < 25 kg/m²), 13.0 months (IQR 7.8–23.7) in overweight women (BMI 25–30 kg/m²), and 12.2 (IQR 7.1–23.0) in obese women (BMI ≥30 kg/m²); \( P = 0.16 \).

Four hundred seventy three out of 489 patients were included in multivariate analyses of PFS and the following covariates beside BMI, stratified in three categories, were fitted in the model: age, menopausal status, PS, hormonal status, presence of visceral metastases, and number of metastatic sites. Results of PFS multivariate analysis are reported in Table 2. No relevant association between BMI
category and PFS was observed. As expected, a worse PS, presence of visceral disease and endocrine receptor negative disease were significantly associated with an increased hazard of disease progression. No significant interaction between BMI category and any of the above variables was observed.

Table 1. Characteristics of the patients included in this analysis

<table>
<thead>
<tr>
<th>BMI (kg/m²) category</th>
<th>N of pts (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–24.9</td>
<td>185</td>
<td>185</td>
</tr>
<tr>
<td>&gt;25.0</td>
<td>10</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>WHO PS</td>
<td>1/2</td>
<td>321 (68)</td>
</tr>
<tr>
<td>Positive</td>
<td>252 (52)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Non visceral</td>
<td>210 (43)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>N of sites</td>
<td>1</td>
<td>260 (53)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>82 (17)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

Abbreviation: HS, hormone receptor status (estrogen and/or progesterone receptor).

Figure 1. Kaplan–Meier curves of PFS according to BMI at baseline.
Overall survival
At the time of the analyses, 218 deaths had been recorded in 489 women, for a median OS of 32.9 months (IQR 17.4–72.9 months). No significant trend or heterogeneity in OS was observed according to BMI category (Fig. 2). Median OS was 32.0 months (IQR 14.5–88.3 months) in normal/underweight women (BMI <25 kg/m²), 33.2 months (IQR 19.4–81.1 months) in overweight women (BMI 25–30 kg/m²), and 30.7 (IQR 17.6–50.8 months) in obese women (BMI ≥30 kg/m²); P = 0.6.

The results of the multivariate Cox analysis (Table 3) confirmed the lack of any relevant association between BMI category and OS. A worse PS and visceral disease were significantly associated with an increased hazard of death. No significant interaction between BMI category and any of the covariates included in the multivariate model was observed.

Discussion
Our study failed to detect any significant association between BMI and prognosis in patients with MBC receiving first-line chemotherapy. This finding is in contrast with what predicted on the basis of preclinical models and epidemiologic studies, and, more important, with what seen in patients with early breast cancer, where a strong association between increased BMI and a worse prognosis has been observed in most studies. In advanced breast cancer, to our knowledge, only 2 studies assessed the prognostic relevance of BMI. In the first one, an association between obesity and decreased survival was reported in a small cohort of 96 patients.
women were prospectively enrolled and evaluated for their reliability.

Several explanations are possible for the difference with the strong association reported in early breast cancer. The first one calls into question the mechanism by which overweight and obesity may affect prognosis in early breast cancer. If this, as repeatedly hypothesized, involves fine growth-stimulating mechanisms related to the insulin resistance and the proinflammatory state typical of overweight women, their relevance might be greatly diminished in the presence of a significant tumor burden, where tumor biology is likely to be more important than host factors in determining prognosis. In support of this hypothesis, there are two recent reports on the lack of association between BMI and disease-free or OS in triple-negative early breast cancer (29, 30).

In conclusion, this study suggests that the presence of overweight or obesity at baseline is not an adverse prognostic factor in patients with MBC treated with first-line chemotherapy. However, the potential role of lifestyle or medical interventions aimed at reducing BMI/insulin resistance cannot be ruled out and might be clarified by an ongoing randomized clinical trial specifically evaluating the effect of the addition of metformin to first-line chemotherapy in advanced disease (31).

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

Conception and design: A. Gennari, O. Nanni, D. Amadori, P. Bruzzi
Development of methodology: A. Gennari, O. Nanni, M. Puntoni, P. Bruzzi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Gennari, O. Nanni, E. Scarpi, P. Conte
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Gennari, M. Puntoni, E. Scarpi, P. Conte, G. Antonucci, P. Bruzzi
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