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Original Research

Clinical consequences of chemotherapy dose reduction in obese patients with stage III colon cancer: A retrospective analysis from the PETACC 3 study

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KEYWORDS
Colon cancer;
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Abstract ***Background:*** Dose reduction in obese cancer patients has been replaced by fully weight-based dosing recommendations. No data, however, are available on the effects of dose reduction in obese stage III colon cancer patients undergoing adjuvant chemotherapy.
Methods: Survival outcomes and toxicity data of obese (body mass index [BMI] $\geq$30 kg/m^2), stage III colon cancer patients treated within the phase III PETACC 3 trial comparing leucovorin, 5-FU (LV5FU2) with LV5FU2 plus irinotecan were analysed retrospectively according to chemotherapy dosing at first infusion (i.e. fully weight-based dosed - versus dose-reduced group). Multivariate analyses on relapse free survival (RFS) and overall survival (OS) were conducted to adjust for baseline prognostic factors using Cox regression model.
Results: 13.4% (280 of 2094 patients) had a BMI $\geq$ 30 kg/m^2, and 5.3% had both a BMI $\geq$ 30 kg/m^2 and a body surface area (BSA) $\geq$2 m^2. Dose reductions occurred in 16.1% of patients with a BMI $\geq$ 30 kg/m^2 and 32.4% with BMI $\geq$ 30 kg/m^2 and BSA $\geq$ 2 m^2, respectively. In patients with BMI $\geq$ 30 kg/m^2, multivariate analysis demonstrated a trend towards better RFS in the fully dosed compared to the dose-reduced group (Hazard ratio (HR): 0.69,

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95% CI: 0.43–1.09; p = 0.11); however, there was no statistically significant difference in OS. In patients with BMI ≥ 30 kg/m^2 and BSA ≥ 2 m^2, multivariate analysis demonstrated better RFS in fully dosed compared with dose-reduced patients (HR: 0.48, 95% CI: 0.27–0.85; p = 0.01) and a strong trend towards better OS (HR: 0.53, 95% CI: 0.28–1.01; p = 0.052). This group comprised predominantly of men.

Conclusions: Data support the recommendation of using fully dosed chemotherapy for the adjuvant treatment in obese patients with colon cancer.

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1. Introduction

Obesity, defined by a body mass index (BMI) ≥ 30 kg/m^2, is associated with an increased incidence of colorectal cancer [1]. With respect to the prognosis of colorectal cancer, the risk for progression and death in stage IV disease was not elevated in obese patients [2], whereas in stage II/III colon cancer, data are quite controversial: in an analysis among obese women with stage II–III colon cancer, Meyerhardt *et al.* demonstrated a significant increase in overall mortality [3], whereas in a subsequent study in another cohort, BMI was not significantly associated with an increased risk of colon cancer recurrence or death [4]. However, other studies and a meta-analysis have consistently shown that independent of gender, a higher BMI is associated with inferior clinical outcome in obese colon cancer patients undergoing adjuvant chemotherapy [5–7]. Since empiric dose reductions in obese patients and dose capping at a body surface area (BSA) of 2 m^2 were common practice [8] for long, it remains a matter of debate, if chemotherapy dose reduction in obese patients might have contributed to the inferior clinical outcome. Meanwhile, international guidelines clearly recommend full weight-based chemotherapy dosing for obese patients [9], particularly when the goal of treatment is cure. Most data supporting this recommendation come from adjuvant and neoadjuvant trials in breast cancer patients, indicating that dose reductions in obese patients are associated with inferior clinical outcome [10–13]. On the other hand, toxicity was not increased in fully dosed obese cancer patients [14–16].

Data from pooled analysis of obese stage IV colorectal cancer patients treated with chemotherapy indicate that even small dose reductions are associated with significantly decreased relapse free survival (RFS) compared to fully dosed chemotherapy and a trend towards decreased overall survival (OS) was found in this large pooled analysis [17].

Data on the effects of dose reductions in obese patients undergoing adjuvant treatment for locally advanced colon cancer, however, are lacking. Consequently, we aimed to assess the effects of baseline dose reductions in the adjuvant treatment of obese colon cancer patients. Our retrospective analysis is based on the multicenter phase III PETACC 3 trial, which failed to demonstrate an improvement in RFS or OS for the addition of irinotecan to fluorouracil (5-FU) and leucovorin in stage III colon cancer patients [18].

2. Material and methods

2.1. Study population

The PETACC 3 study design has been described previously [18]. In brief, 2094 patients (age ≥18 and ≤ 75 years) with completely resected, histologically proven stage III adenocarcinoma of the colon and a World Health Organisation performance status <2 were randomly assigned to receive 12 cycles of biweekly leucovorin and 5-FU (LV5FU2) plus irinotecan (FOLFIRI) or LV5FU2 alone.

BMI (weight in kilogram/height in square metres) and BSA according to the de Bois formula $(((\text{weight})^{0.425} * (\text{height})^{0.725} * 71.84)/10{,}000)$ were calculated before the first chemotherapy administration. Obesity was defined by a BMI ≥ 30 kg/m^2. For patients with a BSA > 2 m^2, the PETACC 3 study protocol recommended dose capping at 2 m^2 for irinotecan but not for 5-FU. However, dose capping was not performed in all patients with a BSA > 2 m^2. We categorised obese patients as either 'fully dosed' or 'dose-reduced' according to whether or not they received at least 95% of chemotherapy dose for the first cycle (180 mg/m^2 on day 1 for irinotecan and 1000 mg/m^2 on days 1 and 2 for 5-FU) for both 5-FU and irinotecan. Next, we compared overall treatment exposure, toxicities and disease outcomes in patients with a BMI ≥ 30 kg/m^2, who received fully dosed with those who received dose-reduced chemotherapy in their first chemotherapy cycle. In addition, we performed an analysis restricted to obese patients (BMI ≥ 30 kg/m^2) with a BSA ≥ 2 m^2 to focus on the population for which dose capping was explicitly recommended in the protocol.

2.2. Statistical analysis

Overall treatment exposure was summarised using the relative total dose and relative dose intensity over the

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