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Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer

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ABSTRACT

Background: Recent research suggests a significant relationship between lean body mass (LBM) and toxicity from chemotherapeutic agents. We investigated if higher drug doses per kg LBM were associated with increased toxicity in stage IIIB/IV non-small cell lung cancer (NSCLC) patients receiving a first-line chemotherapy regimen dosed according to body surface area (BSA).
Methods: Data from patients randomised to receive intravenous gemcitabine 1000 mg/m^2 plus orally vinorelbine 60 mg/m^2 days 1 and 8 in a phase III trial comparing two chemotherapy regimens were analysed. LBM was estimated from assessment of the cross-sectional muscle area at the third lumbar level (L3) on computed tomography images obtained before chemotherapy commenced. Common terminology criteria for adverse events (CTCAE) grade 3–4 haematological toxicity and dose reduction and/or stop of treatment after the first course of chemotherapy were defined as primary and secondary toxicity outcomes.
Results: The study sample included 153 patients, mean age was 66 years, 55% were men, 87% had disease stage IV and 75% had performance status (PS) 0–1. Gemcitabine doses per kg LBM varied from 23.2 to 53.1 mg/kg LBM, and vinorelbine doses from 1.5 to 3.3 mg/kg LBM. Higher doses of gemcitabine per kg LBM were significantly associated with grade 3–4 haematological toxicity in bivariate (OR = 1.12, 95% CI 1.03–1.23, $p = 0.008$) and multivariate analyses (OR = 1.15, 95% CI 1.01–1.29, $p = 0.018$), as were also higher doses of vinorelbine per kg LBM. No significant association was found between drug doses per kg LBM and dose reduction and/or stop of treatment.
Conclusion: The study showed that dose estimates according to BSA lead to a substantial variation in drug dose per kg LBM, and higher doses per kg LBM are a significant predictor for chemotherapy-induced haematological toxicity. The results indicate that taking LBM into account may lead to a better dose individualisation of chemotherapy.

1. Introduction

Although several targeted therapies have been developed during the last decade, cytotoxic chemotherapy remains the cornerstone of systemic cancer treatment. Doses are routinely individualised from body height and weight by calculating the body surface area (BSA) according to the formula originally derived by Du Bois and Du Bois in 1916 [1]. It is well known that using BSA

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as the only method for individual dose adjustment is insufficient to avoid severe toxicity, but the continued use mainly relies on the lack of other, more precise methods for dose individualisation and more precise predictors for pharmacokinetic variation [2–4].

Body composition is influenced by several factors such as age, gender and disease, and has been shown to vary considerably between individuals of the same height and weight [5]. The relative proportions of lean body mass (LBM) and fat tissue may affect drug metabolism, and thereby clinical response and adverse effects [3,6]. LBM and BSA are only weakly correlated [7] and as most chemotherapeutic drugs are not lipophilic, LBM might be a better estimate of the volume of distribution for these drugs [8–10].

New image based technology enables precise estimates of human body composition, including LBM and fat tissue. This has been applied within the field of oncology and recent research indicates that chemotherapy administered according to BSA induces higher frequencies of toxicity in patients with low muscle mass [7,11–13]. It has also been shown that BSA-based dosing leads to a considerable variation in mg chemotherapeutic agent per kg LBM, and that higher dose per kg LBM is associated with more frequent toxicity [11].

The majority of patients with lung cancer are diagnosed with advanced non-small cell lung carcinomas (NSCLC) [14], and receive palliative chemotherapy [15]. For most of the routinely used agents, doses are individualised according to BSA. Severe treatment toxicity is frequent, limits the treatment intensity and increases the symptom burden. Subgroups representing large proportions of the NSCLC patients, i.e. the elderly, patients with poor performance status (PS) and those with substantial weight loss are at particular risk [16–18]. Therefore, new strategies that may reduce the risk of severe toxicity are needed.

The aim of the present study was to explore whether chemotherapy doses calculated according to BSA result in a significant variation in dose/kg LBM in advanced NSCLC patients receiving first-line chemotherapy, and to investigate if higher drug doses per kg LBM were associated with increased toxicity.

2. Materials and methods

2.1. Design of the former RCT

The Norwegian multicentre phase III randomised clinical trial (RCT) on which the present study is based, was conducted between September 2007 and April 2009 [19]. The RCT was designed to compare two first-line regimens in advanced NSCLC, i.e. gemcitabine (1000 mg/m^2 intravenously (i.v.)) and vinorelbine capsules (60 mg/m^2) given on day 1 and 8 (VG-arm), or carboplatin (AUC = 5, i.v.) day 1 combined with vinorelbine capsules (60 mg/m^2) day 1 and 8 (VC-arm). All patients were to receive three courses of chemotherapy administered every three weeks. The dose for patients ≥75 years of age was reduced by 25% from the start of treatment. This was recommended in the protocol, based on observations from a previous trial by our study group, where elderly receiving reduced chemotherapy-doses had similar toxicity and overall survival as younger patients receiving a full dose [20]. The inclusion criteria were NSCLC stage IIIB or IV, age ≥18, PS 0–2, adequate bone marrow (absolute neutrophil count (ANC) > 1.5×10^9/L, platelets > 100×10^9/L) and liver function (bilirubin < 1.5 × upper normal limit, alanine amino transferase (ALT) and alkaline phosphatase (ALP) < 3 × upper normal limit). Patients with other active malignancies, or diseases affecting gastro-intestinal absorption were excluded. There were no other restrictions with respect to comorbidity, age or presence of brain metastases, which probably explains the short median survival in our population [19]. Baseline data comprised demographic variables, stage of disease, histology, PS, height, weight and biochemical parameters. A computed tomography (CT) scan of the thorax and upper abdomen performed within 4 weeks before start of chemotherapy was mandatory. Quality of life (QoL) was assessed at baseline and during follow-up (before each course of chemotherapy) using the European Organisation for Research and Treatment of Cancer Quality of life core questionnaire (EORTC QLQ-C30) and its lung cancer specific module (QLQ-LC13) [21,22]. Haematological parameters were registered at day 1, 8 and 15 in every chemotherapy cycle. The local investigators registered non-haematological toxicity as a summary measure after completion of chemotherapy. The trial randomised a total of 444 patients. No significant differences in overall survival (VG: 6.3 months, VC: 7.0 months, $p = 0.802$), or QoL were found between the trial arms, and there were only minor toxicity differences in favour of the VG arm [19].

2.2. Patient selection, present study

Patients who received carboplatin (VC-arm) were excluded from the present study since the carboplatin doses were calculated according to estimated renal clearance, and not BSA. In addition to CT based estimates of body composition, we defined complete data on the following prognostic factors in advanced NSCLC as prerequisite for inclusion; age, gender, PS, stage of disease and loss of appetite [18,23,24]. Appetite loss and weight loss may be regarded as clinical indicators of a general deterioration and therefore affect the occurrence of toxicity from treatment. Loss of appetite was derived from the patients' baseline score on the item "Have you lacked appetite" from the QLQ-C30. The scores were dichotomised with the score "not at all" indicating no appetite loss, while "a little", "quite a bit" and "very much" defined loss of appetite. Weight loss before start of chemotherapy was not registered in the RCT.

2.3. Assessments of body composition

Diagnostic CT scans taken within four weeks before start of treatment were analysed using Slice-O-Matic software (v.4.3 Tomovision, Montreal Canada) by three observers blinded for patient data. The total cross sectional area of skeletal muscle (cm^2) was quantified at the level of the third lumbar vertebra (L3), as this is strongly correlated to whole body skeletal muscle mass [25]. For tissue demarcation, pre-established thresholds of Hounsfield Units (HU) in the range of −29 to +150 HU were used for muscle tissue [26]. The total cross sectional skeletal muscle area (cm^2) was divided by height squared (m^2), and expressed as L3 skeletal muscle index (SMI, cm^2/m^2). We estimated lean body mass (LBM) from the regression equation: lean tissue (kg) = 0.30 × L3 muscle cross sectional area (cm^2) +6.06 [26].

Body mass index (BMI) (kg/m^2) was categorised as follows: BMI < 20 as underweight, BMI [20, 25] as normal weight, BMI [25, 30] as overweight and BMI ≥ 30 as obesity [5].

2.4. Definitions for toxicity outcomes

As the primary outcome, we defined haematological toxicity (anaemia, neutropenia or thrombocytopenia) grade 3–4 according to the Common terminology criteria for adverse events (CTCAE) version 3.0 on day 8, 15 or 21–22 of the first cycle. The secondary outcome was defined as either (1) dose reduction of ≥20% (compared to the starting dose) for one or both drugs (gemcitabine and/or vinorelbine) at day 8 of the first cycle or at day 1 of the second cycle and/or (2) stop of treatment after the first cycle due to registered toxicity.

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