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Original article

Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel

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SUMMARY

Background: Body composition may influence clinical outcomes of certain chemotherapeutic agents. We examined the prognostic significance of skeletal muscle mass and adipose tissue on docetaxel toxicity and overall survival in patients with metastatic castrate resistant prostate cancer (mCRPC).

Methods: A retrospective review of patients medical records with mCRPC, treated with docetaxel was conducted. Body composition parameters (skeletal muscle mass, muscle attenuation [MA], visceral and subcutaneous adipose tissue) were measured at L3 by computed tomography (CT) and defined using previously established cut points. Toxicity profile was assessed after 3 cycles of the drug and graded according to the National Cancer Institute Common Toxicity Criteria (version 4). Overall survival was analysed.

Results: Overall 63 patients, mean age 69 years (SD 8.3), were included. Sarcopenia was present in 47% ($n = 30$) and of these 26.7% (8/30) were sarcopenic obese. Common toxicities (all grades) observed included fatigue (80.9%), pain (46%), and constipation (34.9%). DLT occurred in 22 (34.9%) patients; of these 10 patients (15.8%) experienced dose reductions and 12 patients (19%) experienced dose terminations. Measurements of adiposity were not predictive of DLT, however 59.1% patients who had a combination of both sarcopenia and low MA experienced DLT compared to 29.3% of patients without sarcopenia and low MA ($p = 0.021$). Skeletal muscle index and MA were significantly lower in patients who experienced neutropenia (grade I–II) (46.5 cm^2/m^2 vs. 51.2 cm^2/m^2, $p = 0.005$) compared to their counterparts (24.6 HU vs. 32.2 HU, $p = 0.044$). Neither sarcopenia nor sarcopenic obesity was associated with overall survival. In multivariate analysis, BMI $\geq$25 kg/m^2 (HR: 0.349, CI: 0.156–0.782, $p = 0.010$) was a significant predictor of longer overall survival and both visceral fat index $\geq$ median 58.7 cm^2/m^2 (HR: 2.266 CI: 1.066–4.814, $p = 0.033$) and anaemia (HR: 2.81, CI: 1.297–6.091, $p = 0.009$) were significant predictors of shorter overall survival.

Conclusions: Sarcopenia and low MA are associated with neutropenia (grade I–II). Furthermore, presence of anaemia, high volume of visceral fat and BMI <25 kg/m^2 are associated with reduced survival in patients with castrate resistant prostate cancer being treated with docetaxel chemotherapy.

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1. Introduction

Prostate cancer is the most common solid tumour in men in the developed world and accounts for 27% of male cancers [17]. Ten percent of men diagnosed with prostate cancer develop metastatic disease, and the 5-year survival for these patients is 30% [33]. Androgen deprivation therapy (ADT), i.e. gonadotropin-releasing hormone (GNRH) analogues, is standard of care in locally advanced and metastatic disease [32,20]. ADT can reduce serum prostate-specific antigen (PSA) and slow down the progression of cancer by its direct action of reducing the production of testosterone, the hormonal driver of prostate cancer. Undesirable side effects of ADT include substantial alterations in body composition [1] with significant gains in body fat and losses in skeletal muscle mass [40]. Low skeletal muscle mass (sarcopenia) can be significant, especially in men over 70 years of age [35], and the quality of muscle (muscle attenuation) can also be adversely affected by ADT [8].

Sarcopenia has emerged as a prevalent body composition phenotype in many cancers and is important because it is predictive of reduced functional ability, shorter time to tumour progression, shorter survival, and higher incidence of dose limiting toxicity (DLT) to many cytotoxic chemotherapy drugs [29,38,10]. Despite initial favourable oncologic responses to ADT, predictable and irreversible resistance to ADT will occur in the vast majority of patients within a median of two years, signifying castrate resistant prostate cancer (CRPC), i.e. progression of disease despite castrate levels of testosterone [31,13]. Chemotherapy is often prescribed to those men with CRPC who have increasing symptoms of progressing disease, e.g. bone pain and fatigue. Toxicity however is of concern, especially as most patients are elderly and may have pre-existing age- and ADT-related sarcopenia, as well as medical comorbidities.

Docetaxel (TAXOTERE®) has been a standard first line therapy for metastatic CRPC (mCRPC) and exhibits wide inter-patient variability in pharmacokinetics, given it is a narrow therapeutic index drug [12]. Variability in clearance has been correlated with toxicity and treatment efficacy in patients treated with docetaxel [30,34]. Body composition influences the pharmacokinetics of certain cytotoxic agents, as hydrophilic drugs will distribute into the lean compartment whereas lipophilic drugs will distribute into the fat compartment. Thus, changes in adipose tissue and skeletal muscle tissue could lead to increased incidence and severity of chemotherapy toxicities. There is growing literature to suggest that skeletal muscle mass may be a better basis for normalising drug dosages in cancer patients, especially of hydrophilic drugs [22,29]. Likewise, increased adipose tissue may increase volume of distribution for highly lipophilic drugs prolonging their elimination half-lives and a recent publication by Prado et al. [25] identified that both muscle and adipose tissue may play a role in predicting toxicity for hydrophobic agents. Docetaxel is highly lipophilic, binds to plasma proteins (>90%; albumin, lipoproteins, and α1-acid glycoprotein) and is primarily eliminated from the body via CYP3A4 mediated hepatic metabolism (70–80%) [9]. The lipophilic profile of docetaxel would suggest a larger volume of distribution in adipose tissue however animal models suggest a greater distribution of docetaxel in muscle tissue compared with adipose tissue [36].

In addition to being linked to chemotherapy toxicity, body composition parameters have been linked to prognosis and overall survival in cancer patients. Sarcopenia has been shown to be independently prognostic of reduced survival in cancers of the biliary tract [21], lung [43] and colon [43]. The results concerning adipose tissue are conflicting, especially in prostate cancer. Higher mortality has been observed in prostate cancer patients with a high body mass index (BMI) [6]. Conversely, some studies have reported that a high BMI [16] and high volume of subcutaneous adipose tissue [3] are prognostically favourable in mCRPC.

For the current study we wanted to examine whether body composition was associated with toxicity secondary to docetaxel treatment. Secondary endpoints included the prognostic significance of body mass parameters and other clinical parameters on overall survival.

2. Patients and methods

2.1. Study population and toxicity evaluation

Ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, according to good clinical practice and applicable laws.

We performed a retrospective analysis of patients with mCRPC treated with first line docetaxel-based systemic chemotherapy in 3 Irish University teaching hospitals over a 6 year period (from January 2008 to December 2013). All patients had received ADT prior to commencing chemotherapy for mCRPC. Patients received 75 mg/m^2 of docetaxel every 3 weeks or 50 mg/m^2 every 2 weeks (during the analysis period a randomized study reported improved toxicity profiles using the 50 mg/m^2 schedule [19]). All patients had a histologic diagnosis of prostate adenocarcinoma and a baseline CT scan within 6 weeks of commencing their 1st cycle of chemotherapy. In addition, the following data was recorded: comorbidities, Gleason scores, PSA levels, Eastern Cooperative Oncology Group (ECOG) performance status, C-reactive protein (CRP) and albumin levels. Two age groups were defined for this analysis (<75 years and ≥75 years), a range that has been used previously in mCRPC age subgroup analyses [18]. Toxicity profiles were obtained for all cycles of docetaxel however tolerance and toxicity were assessed over the first 3 treatment cycles as we had incomplete toxicity data >3 cycles of docetaxel for all patients. Adverse events were classified according to the common terminology criteria for adverse events (CTCAE) version 4.0. For further analyses, toxicity was divided into grade I–II and grade III–IV. Dose limiting toxicity (DLT) was defined as any grade III or higher toxicity leading to a dose reduction, temporary or permanent discontinuation of treatment. Reported toxicities were fatigue, pain, neutropenia (neutrophils < 1.5 × 10^9/L), anaemia (Hb < 10 g/dL), neurosensory, constipation, diarrhoea, dyspnoea and nausea and vomiting.

2.2. Body composition assessment

Body mass index was calculated by dividing the patients weight in kilograms by height (in meters) squared. Patients with a BMI 18.5–24.9 kg/m^2 were defined as normal and patients with a BMI ≥25 kg/m^2 were defined as overweight or obese (≥30 kg/m^2) as per WHO criteria [42]. Cross-sectional area of muscle and adipose tissue was averaged from two consecutive axial images within the same series at the third lumbar vertebra (L3), using OsiriX software version 5.0 (Pixmeo, Geneva, Switzerland). Different tissue compartments were manually outlined and segmentation of the tissue of interest was based on Hounsfield Unit (HU) thresholds (from −29 to +150 for skeletal muscle, −190 to −30 for subcutaneous adipose tissue and −150 to −50 for visceral adipose tissue). Hand adjustment of the selected areas was performed if necessary and the total cross sectional area of the segmented tissue area was calculated automatically (Fig. 1). Muscle area and total adipose tissue area, were normalized for stature in metres squared (m^2) and reported as skeletal muscle index (SMI; cm^2/m^2), adipose tissue index (ATI; cm^2/m^2) respectively [23,28]. Subcutaneous fat (SAT)