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Original article

Resting energy expenditure in the risk assessment of anticancer treatments

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SUMMARY

Background & aims: Alterations of nutritional and performance status (PS) are associated with higher risk of chemotherapy toxicity. Increased resting energy expenditure (REE) is frequent in cancer patients and may contribute to cachexia. We investigated whether abnormal energetic metabolism could predict early acute limiting toxicities (ELT) of anticancer treatments.

Methods: In this observational monocentric study, REE was measured by indirect calorimetry before treatment initiation. Based on the ratio of measured REE to REE predicted by the Harris–Benedict formula, patients were classified as hypometabolic (<90%), normometabolic (90–110%) or hypermetabolic (>110%). Body mass index, weight loss, PS, albumin, transthyretin, C-reactive protein (CRP) and muscle mass (CT-scan) were studied. Were defined as ELT any unplanned hospitalization or any adverse event leading to dose reduction or discontinuation during the first cycle of treatment.

Results: We enrolled 277 patients: 76% had metastatic disease; 89% received chemotherapy and 11% targeted therapy; 29% were normometabolic, 51% hypermetabolic and 20% hypometabolic. Fifty-nine patients (21%) experienced an ELT. Toxicity was associated with abnormal metabolism (vs normal: OR = 2.37 [1.13–4.94], p = 0.023), PS (2–3 vs 0–1: OR = 2.04 [1.12–3.74], p = 0.023), albumin (<35 vs ≥35 g/l: OR = 2.39 [1.03–5.54], p = 0.048), and inflammation (CRP ≥10 vs <10 mg/l: OR = 2.43 [1.35–4.38], p = 0.004). To predict toxicity, the most sensitive parameter was the REE (83%) followed by PINI (63%), GPS (59%), CRP (55%), PS (41%), NRI (37%), and albumin (16%). In multivariate analysis, elevated CRP was an independent predictor of toxicity (p = 0.047).

Conclusion: Abnormal basal energy metabolism identifies patients at higher risk of treatment-related acute complications.

1. Introduction

Malnutrition is a common complication in cancer patients and is associated with an increased risk of acute toxicity following anticancer treatment, as well as with a reduced response to anticancer agents and shorter survival [1,2]. A negative balance between energy intake and energy expenditure contributes to the development of malnutrition [3]. The resting energy expenditure (REE) is often altered in cancer patients [3,4]. Elevated REE appears as the most common alteration in cancer patients compared to healthy subjects. Around 50% of cancer patients show elevated REE [4]. Decreased REE is also observed and may concern 30% of cancer patients [5] depending on the tumor type, site or stage. Elevated REE is a determinant in the development of cancer induced malnutrition, as it is frequently higher than dietary intakes [3]. Therefore, the REE measurement is potential tool for patient

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management. Presently, indirect calorimeters have the expected characteristics to allow routine evaluation of alterations in energy expenditure in large cohorts of patients as they offer precise, reproducible, noninvasive, portable and rapid measurements of REE [4,6].

Since anticancer therapies have a narrow therapeutic index and potentially life-threatening toxicities, but are prescribed to with comorbidities or elderly patients, the clinical research on toxicity risk assessment is a rapidly emerging field. Deterioration of the performance status (PS) and/or alteration of the nutritional status are parameters associated with increased incidence of early acute toxicities [7,8]. Several scores, such as the Glasgow Prognostic Score (GPS), the Nutritional Risk Index (NRI) or the Prognostic Inflammatory and Nutritional Index (PINI) help to identify inflammatory or malnourished patients at risk for complications [9–11]. Nevertheless, treatment tolerance among patients with an apparently good medical condition remains highly variable.

We hypothesized that alterations in energy metabolism, especially hypermetabolism, as an early feature of precachexia, favoring malnutrition, might be associated with an increased risk of acute toxicity. In this study, we investigated whether REE measurement before initiating anticancer treatments could predict the occurrence of early limiting toxicity.

2. Patients and methods

2.1. Patients

We studied a prospective cohort of consecutive cancer patients with solid tumors, who came in our institution in the outpatient setting for a routine evaluation – including REE measurement – prior to initiate anticancer treatment between June 2012 and April 2014. We included patients who started chemotherapy or targeted therapy within one month. We excluded patients who received hormonal therapy or best supportive care alone. Other exclusion criteria were age under 18 years, psychiatric disorders, respiratory insufficiency, surgery or anticancer treatment during the last month.

Patients were followed until the date of their death, their last examination or the completion of a follow-up period of 18 months after the end of the study.

This study was approved by the local Review Board for Oncology according to the declaration of Helsinki.

2.2. Anthropometric measurements, medical and nutritional assessment

Weight was measured with a medical balance and height was measured with a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Weight loss (WL) and Eastern Cooperative Oncology Group (ECOG) Performance Status were determined by a physician.

Routine biological tests included C-reactive protein (CRP, liquid turbidimetry, Cobas, Roche Diagnostic), alpha 1-acid glycoprotein (α1-GP), serum albumin and transthyretin levels (nephelometry, BN II, Siemens).

GPS was calculated using albumin and CRP levels [9]:

GPS 2: CRP >10 mg/L and albumin <35 g/L;
GPS 1: CRP >10 mg/L or albumin <35 g/L;
GPS 0: CRP ≤10 mg/L and albumin ≥35 g/L.

NRI was computed as: 1.519 × serum albumin (g/L) + {41.7 × present weight (kg)/basal weight (kg)} with risk of complications related to malnutrition when NRI <97.5, as previously described [10].

PINI was calculated as: {CRP (mg/L) × α1-GP (mg/L)}/{Albumin (g/L) × Transthyretin (mg/L)} with risk of complications [7] when PINI >1 [11].

2.3. Resting energy expenditure measurement

Measured REE (mREE, kcal/d) was determined by indirect calorimetry using a face mask system (Fitmate VM®, Cosmed, Italy). The measurement was carried out under standard resting conditions (after a 12 h fasting, complete bed rest for 15 min, in a thermoneutral environment). A first 5 min measurement was performed to reach the steady state – which was defined by an average oxygen consumption (VO_2) variation less than 10% – and was then followed by a 10 min measurement for REE assessment. The calorimeter was calibrated before each measure.

In order to evaluate the extent of the perturbation in energy metabolism compared to a healthy situation, predicted REE (pREE, kcal/d) was calculated using revised Harris–Benedict (HB) formula [12]:

- in males: $\text{pREE (kcal/d)} = 88.362 + 13.397 \times W + 479.9 \times H - 5677 \times A$
- in females: $\text{pREE (kcal/d)} = 447.593 + 9247 \times W + 309.8 \times H - 4{,}33 \times A$

where: W is weight in kilograms, H is height in centimeters, and A is age in years.

While several formulas may be used for the calculation of REE [13,14], the HB formula was chosen as it has a good score for accurate prediction of REE in a relatively large range of BMI [14].

Based on the ratio of mREE to pREE, patients were classified according to the standards of Boothby et al. [15] as hypometabolic (mREE < 90% pREE), normometabolic (90–110% pREE) or hypermetabolic (>110% pREE).

2.4. Muscle mass measurement

Muscle mass was evaluated by the measurement of muscle tissue areas on CT-scan images [16], with the third lumbar vertebra (L3) considered as a reference landmark [17]. CT scans were performed for diagnostic or follow-up purposes less than 30 days before REE measurement. L3 images were analyzed with ImageJ software v1.46r (National Institutes of Health, https://imagej.nih.gov/ij).

Muscles were delimited on their anatomic features, and their area was quantified based on established thresholds of muscle radiation attenuation (−29 to +150 Hounsfield units [16]). Cross-sectional areas (cm^2) of all muscles were computed and the mean value for two consecutive L3 images was calculated for each patient. These values were normalized for stature and expressed in cm^2/m^2. Sex-specific cutoff values were used to define sarcopenia (55.4 cm^2/m^2 for males and 38.9 cm^2/m^2 for females) [18]. Lean body mass (LBM) was estimated from muscle cross-sectional areas [17]: LBM (kg) = 0.30 × (L3 skeletal muscle area (cm^2)) + 6.06.

2.5. Treatment and toxicity assessment

Treatment choice was determined by the treating physician in agreement with national and international guidelines. Chemotherapy or targeted therapy was started within a month after the multidisciplinary evaluation. Targeted therapies were defined as any agent that blocks the growth and spread of cancer cells by

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