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Original article

Association among metabolic syndrome, inflammation, and survival in prostate cancer

Vincenza Conteduca, M.D., Ph.D.[a,*], Orazio Caffo, M.D.[b], Luca Galli, M.D.[c], Antonio Maugeri, Pharm.D[d], Emanuela Scarpi, Ph.D.[e], Francesca Maines, M.D.[b], Vincenzo Emanuele Chiuri, M.D.[f], Cristian Lolli, M.D.[a], Stefania Kinspergher, M.D.[b], Giuseppe Schepisi, M.D.[a], Matteo Santoni, M.D. Ph.D.[g], Daniele Santini, M.D. Ph.D.[h], Lucia Fratino, M.D.[i], Salvatore Luca Burgio, M.D.[a], Samanta Salvi, B.Sc.[j], Cecilia Menna, M.D.[a], Ugo De Giorgi, M.D. Ph.D.[a]

[a] *Medical Oncology Department, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[b] *Medical Oncology Department, Santa Chiara Hospital, Trento, Italy*
[c] *Department of Oncology, Azienda Ospedaliero, Universitaria Pisana, Istituto Toscano Tumori, Santa Chiara Hospital, Trento, Italy*
[d] *Oncology Pharmacy Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[e] *Department of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[f] *Medical Oncology Department, Vito Fazzi Hospital, Lecce, Italy*
[g] *Department of Medical Oncology, University Hospital of Ancona, Ancona, Italy*
[h] *Medical Oncology Department, Campus Bio-Medico, University of Rome, Rome, Italy*
[i] *Medical Oncology Department, National Cancer Institute, Aviano, Italy*
[j] *Biosciences Laboratory Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*

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Abstract

Background: Metabolic syndrome (MS) and inflammation (INF) alterations are among the factors involved in cancer progression. The study aimed to assess the relationship between MS and INF and its effect on progression-free/overall survival (PFS/OS) in metastatic castration-resistant prostate cancer (mCRPC) treaed with abiraterone or enzalutamide.

Methods: We, retrospectively, evaluated patients with mCRPC in 7 Italian Institutes between March 2011 and October 2016. MS was defined by modified adult treatment panel-III criteria. INF was characterized by at least one of these criteria: neutrophil to lymphocyte ratio ≥ 3, elevated erythrocyte sedimentation rate or C-reactive protein.

Results: Eighty-three of 551 (15.1%) patients met MS criteria at baseline and 34 (6.2%) during treatment. MS patients (MS+) presented a greater INF profile compared to MS− ($P < 0.0001$). Median PFS was 3.7 for MS+ vs. 8.7 months for MS− (hazard ratio [HR] = 2.77; 95% CI: 2.12–3.61; $P < 0.0001$). Median OS was 6.9 and 19 months in MS+ and MS−, respectively (HR = 3.43; 95% CI: 2.56–4.58; $P < 0.0001$). We also demonstrated INF led to shorter PFS and OS (4.5 vs. 8.5 months, HR = 1.48, 95% CI: 1.15–1.90, $P = 0.002$, and 11.2 vs. 18.8 months, HR = 1.66, 95% CI: 1.26–2.18, $P = 0.0003$, respectively). The combination of MS with INF provided the identification of high-risk prognostic group (MS+/INF+ vs. MS−/INF−) with worse PFS (3.7 vs. 9 months, HR = 2.7, 95% CI: 1.88–3.89, $P < 0.0001$) and OS (6.3 vs. 20.4 months, HR = 4.04, 95% CI: 2.75–5.93, $P < 0.0001$). Multivariable analysis confirmed that MS was independently associated with PFS (HR = 2.07; 95% CI: 1.03–4.18; $P = 0.041$) and OS (HR = 4.87; 95% CI: 2.36–10.03; $P < 0.0001$). The absence of INF as an independent predictor of survival underlined the correlation between MS/INF.

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* Corresponding author. Tel.: +39-54-373-9100; fax: +39-54-373-9151.
E-mail address: vincenza.conteduca@irst.emr.it (V. Conteduca).

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Conclusions: Pretreatment identification of MS and INF alterations might represent an available and easy tool for better prognostication of patients with mCRPC. A prospective evaluation is warranted. © 2018 Elsevier Inc. All rights reserved.

Keywords: Castration-resistant prostate cancer; Abiraterone; Enzalutamide; Metabolic syndrome; Inflammation

1. Introduction

Recently, the introduction of several survival-prolonging drugs has increased cancer-specific survival in patients with metastatic castration-resistant prostate cancer (mCRPC) and, consequently, treatment-related comorbidities, especially secondary to androgen deprivation therapies (ADT), including abiraterone and enzalutamide [1,2]. Anti-androgen receptor (AR) therapies are notoriously characterized by marked reduction in circulating testosterone leading to detrimental changes to body composition, lipid profile and insulin sensitivity [3,4]. Such components comprise the cardiometabolic condition known as metabolic syndrome (MS). It is a group of cardiovascular risk factors including hypertension, central adiposity, hypertriglyceridemia, hyperglycemia, and low level of high-density lipoprotein cholesterol (HDL) with insulin resistance serving as the underlying feature. Insulin resistance in fat cells causes hydrolysis of stored triglycerides and elevated levels of free fatty acids, resulting in increased triglycerides, low-density lipoprotein (LDL) cholesterol, fat mass and decreased HDL-cholesterol and glucose uptake, responsible of the development of hyperglycemia [5] (Fig. 1).

MS is present in approximately 50% of men undergoing long-term ADT (more than 6 months) [6], potentially exposing this population to higher risk of the onset of cardiovascular disease and mortality [7,8]. Furthermore, MS may contribute to prostate cancer risk and worse prognosis [2,9]. To date, the role of other conditions such as inflammation (INF) on the MS emergence is not fully well established.

There is increasing evidence that INF is linked with metabolic disturbances [10] and may represent in turn a central and reversible mechanism through which MS promotes cancer risk and progression. Elevated levels of proinflammatory and proangiogenetic cytokines, interleukins (IL) and growth factors, including IL-6, IL-8, tumor necrosis factor-α, vascular endothelial growth factor, CRP (C-reactive protein), leptin, adiponectin, and insulin-growth factor, are associated with MS [11,12] as well as with advanced prostate cancer, distant metastases, and shorter survival [13]. Hence, it is conceivable that growth of prostate cancer in patients with MS is also associated with "INF status" based on the accumulation of immune cells among adipocytes with consequent inhibition of adiponectin, which stimulates fatty acid oxidation, reduction of inflammation and regulation of cancer survival [1]. Systemic INF can easily be evaluated by means of peripheral blood markers such as serum white blood cells, neutrophils, lymphocytes and platelets, and acute phase proteins. As shown for the presence of MS, neutrophil to lymphocyte ratio (NLR) has been reported to be associated with the prognosis of patients with mCRPC [14–16].

In the last years, several noninvasive factors have been investigated as biomarkers able to predict survival in patients with mCRPC treated with anti-AR therapies. This study aimed to evaluate the prevalence of metabolic or inflammatory alterations in mCRPC patients treated with abiraterone or enzalutamide. Moreover, we firstly provided a preliminary view about the relationship between MS and INF status and its impact on survival in these patients.

2. Patients and methods

2.1. Study design and patients

We, retrospectively, evaluated 551 patients with mCRPC treated with abiraterone or enzalutamide at 7 Italian Institutes between March 2011 and October 2016. Eligibility criteria required histological confirmation of adenocarcinoma of the prostate without neuroendocrine differentiation, progressive disease (PD) despite "castration levels" of serum testosterone (<50 ng/dL), ongoing luteinizing-hormone-releasing hormone (LHRH) analog treatment or prior surgical castration. Additional inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, normal organ and marrow function (defined as hemoglobin >8 g/dL; leukocytes >3,000/μl; platelet count >100,000/μl; bilirubin $<1.5\times$ upper limit of normal [ULN]; alanine transaminase and aspartate aminotransferase $<1.5\times$ ULN; serum creatinine $<1.5\times$ ULN; normal serum potassium level <5.5 mEq/l; cardiac ejection fraction $\geq$ 50%). Excluded criteria were uncontrolled hypertension, myocardial infarction, or arterial thrombotic events in the past 6 months; severe or unstable angina, New York Heart Association (NYHA) III or IV heart failure, or clinical evidence of infection or hematological disease which could influence systemic inflammatory parameters. Additional exclusion criteria was the concomitant use of statin therapy which can influence diagnosis of MS also INF state. The study was approved by the institutional review boards.

2.2. Diagnostic Criteria of MS and Inflammation Status

In this study, we adopted the modified ATP-III criteria [5] (Fig. 1) by which a subject was classified as having MS if 3 of the following 5 criteria were present as obesity (waist circumference >102 cm); hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure $\geq$

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