Title:

Enrichment of cancer stem cells during androgen deprivation therapy for prostate cancer

Daniel Franco1, Muhammad Ali1, Nafiseh Janaki2, Eswar Shankar1, Gregory T. MacLennan2, Sanjay Gupta1

1Department of Urology, Case Western Reserve University & University Hospitals Cleveland Medical center, Cleveland, Ohio

2Department of Pathology, Case Western Reserve University & University Hospitals Cleveland Medical center, Cleveland, Ohio

Androgen deprivation therapy (ADT), specifically surgical or medical castration, is the first line of treatment against advanced prostate cancer and is also used as an adjuvant to local treatment of high-risk disease. Although patients after ADT treatment without metastatic disease initially undergo disease remission, the benefits of this strategy are not clear. In a high percentage of cases, however, castration-resistant prostate cancer (CRPC) arises in ADT-treated patients, through various unknown mechanisms. The cancer stem cell (CSC) model postulates that tumors contain a reservoir of self-renewing cells highly resistant to conventional therapies such as ADT, and their enrichment in a treated tumor may be a reason for CRPC development and progression. CD133 (also known as Prominin-1) is a membrane-bound pentaspan glycoprotein that is frequently expressed by CSCs, and has been used as a biomarker for isolation and characterization of these cells. In this pilot study we investigated the immunohistochemical expression of CD133 in the prostate cancers of patients who were and were not treated with ADT. Surgical pathology specimens (formalin-fixed, paraffin-embedded blocks) from 28 advanced-stage prostate cancer patients who were treated with ADT were retrieved from Department of Pathology archives of University Hospitals Cleveland Medical Center and were compared with 10 prostate cancer specimens from patients who had not received ADT. Immunohistochemical staining for CD133 antigen using rabbit polyclonal anti-CD133 antibody (Novus Biologicals, Littleton, CO) was performed on cancer-bearing histologic sections from each case. The immunohistochemical expression of CD133 in the cancerous tissue was evaluated in each case, and the intensity of staining was assigned a numerical value on a scale ranging from 0 to 5, wherein 0 represents no staining and 5 represents strong staining. The intensity of CD133 staining in the malignant cells in ADT-treated patient specimens was higher in comparison to the intensity of staining noted in specimens from patients who had not received ADT. The average intensity score in ADT-treated specimens was 2.44 + 0.95, in contrast to a mean intensity score of 1.5 + 0.72 in non-ADT treated specimens. The intensity of CD133 expression in ADT-treated prostate cancers is enhanced, in comparison to CD133 expression in non-ADT-treated cancers. This supports the hypothesis of CSC expansion during ADT therapy. The benefits of ADT need to be weighed carefully against substantial risks of disease relapse and its adverse effects on quality of life of prostate cancer patients.