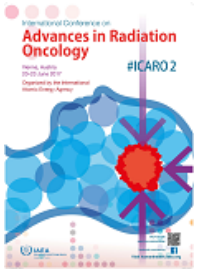

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Potential biomarkers for personalized oncology radiation in uterine cervical cancer

Tuesday 20 June 2017 15:45 (5 minutes)

Uterine cervical cancer (UCC) is one of the most prevalent malignant neoplasms in the world. UCC develops beyond the stage in situ and is frequently treated by a combination of intracavitary radiation therapy and external beam radiation therapy; 30 to 40% of patients with similar prognosis factors not respond equally to a comparable standard treatment. Therefore, the study and identification of prognostic biomarkers, which indicate the probable course of the disease in an untreated individual, and predictive biomarkers, which allow identification of subpopulations of patients most likely to respond to a given therapy, would be extremely useful in the selection of patients for the development of innovative and effective therapies for locally advanced, metastatic and refractory uterine cervical cancer. A comparative analysis of UCC in the context of other cancers may reveal that it is relatively smaller number of targeted molecular agents that have been tested. Some studies indicate that there may be a significant association between the response to treatment and the tumor phenotype, characterized by changes in gene, protein and metabolic expression. The phenotypes that characterize the tumor microenvironment are hypoxia (HIF-1α), glycolysis increase (GLUT1, HKII, GAPDH) and acidosis (CAIX). Activation of the IGF system (IGF1, IGFII, IGF1R) by ionizing radiation induces accelerated cellular senescence. Activation of IGF-1R can result in signaling through two pathways, PI3K/AKT and Ras/MAPK, and as a consequence increases proliferation, protein synthesis and glucose metabolism, and decreased apoptosis. The development of therapeutic approaches directed against IGF1R and signaling pathways related to accelerate cellular senescence can reduce radiation-mediated tissue damage. IGF1R&EGFR may be considered as potential targets for radiosensitization within DNA repair pathways. Within work that we have been developing, reported that gene expression of IGF1R is a strong predictive marker for lack of response to radiotherapy (p=0.018, 95% CI(1.7-41.2)), patients (HPV16 (+), European variants (+), Non-European variants (+)) have 28.6 times higher risk of failure treatment; the presence of anemic hypoxia (hemoglobin (Hgb) ≤11 g/dl) and the expression of GLUT1 and/or HKII influence treatment response and are associated with a lower overall and disease free survival; GAPDH overexpression and co-expressing IGF2 and IGF1R in the presence of Hgb≤11g/dl suggest a possible role of GAPDH as a regulator of tissue response to hypoxia (p=0.04). Objective: To determine whether expression of IGF-IR, GAPDH, HIF-1 alpha, Survivin, GLUT1, CAIX, HKII, presence of HPV16 variants and clinicopathological parameters can be used as prognostic and predictive biomarkers to treatment outcome and as possible molecular targets. Patients & Methods: This prospective cohort study included 149 patients with squamous cell carcinomas of the uterine cervix in FIGO stages IIB (n=53) and IIIB (n=96) between 2008 and 2011. The mean age was 46 years. Of the 149 patients, 61 were treated with radiotherapy and 88 with concurrent radiochemotherapy. Expression of the proteins CAIX, GLUT-1, HIF1α, HKII, IGF-IRα, IGF-IRβ and Survivin, was determined by immunohistochemistry, and presence of HPV16 variants was detected by PCR-SSCP and Reverse line Blot in biopsies taken before treatment. Results: The highest increase was found in expression of GAPDH (100%), Survivin (87%), followed of, IGF-IRα (76.5%), IGF-IRβ (74.5%), IGF-IRα and IGF-IRβ concordance in the expression(73%), HIF1α (74.1%); strong expression was observed with low frequency for GLUT-1 (31.1%), CAIX (16.2%), HKII (10.6%). Hgb level was significantly correlated with treatment response (p=0.01). With a median follow-up of 2.1years, OS was decreased for patients over-expressing IGF-1R β (p=0.04). A similar trend with GLUT-1 over-expression was observed (p=0.18). The OS of the sub-group of patients with anemia (Hgb < 11g/dL) and concomitantly over-expressing IGF-1R and GLUT-1 was significantly decreased compared to the opposite control group (p=0.015). The European variants of HPV16 was identified in 88% and non-European variants in 12%. Greater presence of European variants

E-350G and non-European (eg.AA) with overexpression of IGF1R in the non-complete response group compared to the complete response group was observed. Conclusions: The presence of E-G350 and non-european (eg. AA) variants and overexpression of IGF1R in the non-complete response group could be related with radio-resistance. The expression of GLUT-1, IGF-1R and Hgb (≤ 11g/dl) are associated with poor prognosis, and thus appear to be interesting biomarkers of radiation resistance. If pre-clinical studies suggested such proteins to be part of the biological pathways leading to radio-resistance, the present clinical study confirms their role among UCC patients. Using the expression of GLUT1, IGF-1Rß and Hgb (≤ 11g/dl) as therapeutic molecular targets could contribute to an appropriate therapeutic management as individualized neoadjuvant treatment.

Institution

National Cancer Institute

Country

Bogota, Colombia

Author: MORENO-ACOSTA, Pablo (Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogota, Colombia)

Co-authors: VALLARD, Alexis (Department of Radiation Oncology, Institut de cancérologie de la Loire-Lucien Neuwirth, France); ROMERO-ROJAS, Alfredo (Group of Pathology Oncology, National Cancer Institute, Bogota, Colombia); HUERTAS, Antonio (Tumor Bank, National Cancer Institute); RANCOULE, Chloe (Department of Radiation Oncology, Institut de cancérologie de la Loire-Lucien Neuwirth, France); MAYORGA, Diana (Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogota, Colombia); ACOSTA, Jinneth (Pathology Group, National University of Colombia); COTES, Martha (Group of Radiotherapy and Medical Physical, Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogotá, Colombia); MOLANO, Mónica (Microbiology and Infection Diseases, The Royal Women's Hospital, Melbourne, Australia); MAGNÉ, Nicolas (Department of Radiation Oncology, Institut de cancérologie de la Loire-Lucien Neuwirth, Radiobiologie Cellulaire et Moléculaire, France); GAMBOA, Oscar (Unit Group of Analysis,Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogotá, Colombia); CARRILLO, Schyrly (National Cancer Institute)

Presenter: MORENO-ACOSTA, Pablo (Research Group in Radiobiology Clinical, Molecular and Cellular, National Cancer Institute, Bogota, Colombia)

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