 Radiation therapy biomarkers – Clinical applications

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The discovery of X-rays in 1895 gave birth to the major treatment facility for cancer, the radiation therapy (RT). About 60% of cancer patients in the world are being treated with RT either as a single treatment modality or in combination with surgery and / or chemotherapy. In the earlier half of 20th century the ionizing radiation for cancer treatment was delivered through orthovoltage X-rays (200 – 500kV), the skin dose was higher and poor dose penetration. Further innovations in the form of cobalt-60 and linear accelerator mega voltage therapy overcome the hurdles and were able to treat deep seated tumors. The treatment is generally fractionated and the doser per fraction (or per day) is 2 Gray (Gy). It usually takes about 4 to 7 weeks to complete a course of curative RT. This fractionation was based on four R's of Radiation biology, Repair, Repopulation, Redistribution and Reoxygenation. This favored the tolerance of normal tissue and sensitization of tumor tissue to radiation during curative RT. The unit of radiation is Gray(Gy). A dose of 1Gy produces approximately 105 ionization events per cell, causing about 1000 single strand DNA breaks and 40 double strand DNA breaks (DSBs) per nucleus. The majority of the DSBs are repaired by the cell. The DSBs initiate a long chain of cellular responses which if not repaired can result in a lethal event. Many downstream effects including cell cycle checkpoint activation, stimulation of stress-response genes, induction of DNA response gene and apoptotic genes get activated. In addition to DNA strand break cell membrane damage can also lead to cell death. When high single fraction doses of more than 8Gy is delivered it can lead to microvascular disruption and cell death. Modification of radiation responses at cellular level in vitro experiments and also in-vivo use of molecules and drugs during radiation has been attempted. DNA damage sensor is MRN complex, which activates ATR proteins leading to phosphorylation of chromatin protein, Histone H2AX. This is detectable with fluorescent microscopy and has become a marker for DSB repair in clinical setting. Many components of the DNA-DSB repair pathways have been investigated as therapeutic targets. Homologous recombination is one pathway for repair which can be inhibited by targeting RAD-51 protein. Poly ADP-ribose polymerase (PARP) is involved in DNA repair, activates other proteins like XRCC1, which is a base excision repair protein. Inhibition of PARP in BRCA defective cells produces additional cell kill called synthetic lethality. This phenomenon is being evaluated in radiotherapy and chemotherapy trials. Apoptotic cell death occurs following activation of cell surface death receptors like TNF. Intra cellular signaling pathway, like EGFR pathway, has been modified by drugs like Cetuximab and Nimotuzumab which sensitizes the cells to radiation. Tumor hypoxia is a biomarker of radiation resistance. Presence of adequate molecular oxygen in the cell increases radiation-induced cell kill by three fold. Tumors are hypoxic and carbonic anhydrate IX. Osteopontin are some markers of hypoxia. Clinical studies to overcome hypoxia have been done using oxygen modifiers like hyperbaric oxygen, Carbogennicotinamide, Tirapamazine and Nitroimidazole. The only compound which has been found to be clinically useful is Nimorazole in head & neck cancer. Anti-angiogenic therapy and genetherapy along with immuno-modulation have been attempted during radiation to enhance the effect. Small vessel radiation damage initiates inflammation and leads to fibrosis. Overproduction of TGFβ molecule has been identified as a factor for fibrosis occurrence, especially pulmonary fibrosis. Keratinocyte growth factor has been studied to reduce late radiation lung effects and oral mucositis. Gene expression signature studies identified a group of ten genes, (AR, c Jun, STAT1, PKC, Re1A, cABL, SUMO1, CDK1, HDAC1 & IRFI) that are associated with radio-sensitivity in rectal, esophageal, head & neck, and breast cancer treated with radiotherapy or chemoradiotherapy. The molecular approaches to sensitize the tumor to radiation and protect the normal tissues is expected to play a major role in oncology management in future.

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