Biomarkers of Radiation Response – Review of the Literature

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Abstract

Radiation is a commonly used treatment modality with both curative and palliative intents in the context of cancer management. However, radiotherapy does not result in homogenous patient response, with some patients receiving limited benefit. Inflammation is a hallmark of radiation therapy and an increase of various pro-inflammatory cytokines, enzymes, and blood biomarkers occurs after radiation therapy. However, increased inflammation may result in variable outcomes in patients after radiation therapy. Certain inflammatory markers are associated with increased survival, decreased local recurrence and better QOL, while other inflammatory markers are associated with poorer outcomes. Many pro-inflammatory genes are implicated in the prognosis of patients after radiation therapy.

Objective

The present selective review was conducted to summarize the literature that has previously investigated biomarkers of radiation response. The clinical utility of biomarkers for predicting response to treatment is significant and may assist with personalization of cancer care and appropriate resource allocation.

Materials & Methods

A literature search was conducted on Medline and Embase databases using keywords including “inflammation”, “cancer”, “radiation”, “neoplasm” “cancer” “pain” “biological marker”, “allele”, and “genomics”. Results were limited to studies conducted in humans and the English language. The search generated a total of 5,480 results that were independently screened by 2 authors (MC, AF) first by title, then abstract, and subsequently full text using eligibility and ineligibility criteria. Figure 1 provides an overview of the screening process. If a disagreement arose on whether an article should be included, discussion ensued until a consensus could be reached. If a consensus was not reached a third author (LR) was consulted.

Results

Author (year)	Notes	Biomarker	Results
Barrett (2014)	19 genes (52 SNPs) previously associated with radiation-induced toxicities were analyzed in 280 patients treated with curative radiation or chemoradiation for NSCLC to assess their correlation with overall survival	IL-1a	IL1-α SNP was significantly associated with overall survival (HR: 0.58, 95%CI 0.35-0.96, p = 0.03) Number of minor allele variation copies correlated with improved overall survival but higher risk of pneumonitis
Schoenfeld (2013)	3 SNPs within the RNASEL gene were correlated to the development of lethal prostate cancer or biochemical recurrence in 434 early-stage prostate cancer patients who received radiotherapy	RNASEL gene Variants: rs12757998 rs486907 rs627928	The rs12757998 variant was significantly associated with decreased risk of the composite endpoint (HR:0.65; 95% CI:0.45-0.94; p = 0.02) and also biochemical recurrence alone (HR: 0.60; 95% CI: 0.40 – 0.89; p = 0.01)
Bortolin (2014)	Correlated plasma levels of circulating inflammatory cytokines with local recurrence (LR) and distant failure (DF) rates in 22 early-stage NSCLC patients treated with stereotactic body radiation therapy (SBRT)	Cytokines: IL-1β IL-1ra IL-2 IL-4 IL-5 IL-6 IL-10 IL-12(p40) IL-13 IL-15 IL-17 INF-γ TNF-α Chemokines: IL-8 MIP-1α MIP-1β Growth factors: IL-7 EGF FGF-2 TGF-α VEGF	LR was significantly associated with EGF, IL-10, and IL-1β levels at baseline ($p < 0.05$) DF was significantly associated with EGF, IL-4, IL-15, IL-12, IL-1b, IL-1ra, INF-[redacted] and VEGF levels at baseline ($p < 0.05$) Baseline levels of IL-1ra, IL-12, IL-10, IL-17, INF-[redacted] and FGF-2 were increased in NSCLC patients compared to healthy controls
Yu (2015)	Analysed 9 miRNA levels from blood samples of 24 esophageal squamous cell carcinoma (ESCC) patients prior to, during, and following radiotherapy; these were correlated with radiographic response to radiation as well as 3-year overall survival	miR-21 miR-16 miR-126 miR-223 miR-375 miR-22 miR-148b miR-185 miR-221	miR-16 levels following radiotherapy were significantly higher in patients with good treatment outcomes versus poor treatment outcomes (p = 0.038, fold change = 2.85) A 2-fold or higher increase in miR-16 levels was a significant prognostic factor for overall survival in multivariate analysis (HR = 0.263, 95% CI = 0 .093-0.745, p = 0 .012)

Discussion

- miRNA has garnered interest as a potential biomarker for predictors of radiation response due to: differential miRNA profiles before and after radiation therapy, and being non-invasive and cost-effective prognostic tool
- miRNA have been implicated in many different cellular metabolic and signaling pathways within cells
- Increase in inflammatory biomarkers was not found to be correlated with either poor or good response/outcomes in patients being treated with radiotherapy
- Increased counts of plasma biomarkers such as NLR, ANC, WBC were prognostic for worse overall survival within cancer patients

Conclusion

- Medical professionals and researchers should continue to explore and research the relationship between inflammatory pathways, certain genetic variants and the outcome of patients receiving radiation therapy
- More research into the use of miRNA profiles should be conducted as they have the potential to be a cost-effective, non-invasive and also dynamic way of predicting and monitoring radiation response in terminally ill cancer patients

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