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A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors

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ABSTRACT

Lymphopenia is a common accompaniment of multimodal cancer therapy. As the most radiosensitive cells of the hematopoietic system, lymphocytes residing within or circulating through a radiation portal are frequently depleted by radiation therapy. The recognition that radiation-induced reduction of circulating lymphocyte counts and eventual lymphocyte infiltration of tumors have a tangible impact on overall survival outcomes has revived the interest in understanding the causes of treatment-associated lymphopenia and developing strategies to predict, prevent and ameliorate this well-documented phenomenon. In this systematic review, we have performed a comprehensive search of the literature to elucidate the studies that document a correlation between radiation-associated lymphopenia and survival outcomes in solid malignancies. We also summarize potential unifying paradigms that account for radiation-induced lymphopenia across studies and lay the groundwork for attempting to explain and/or counter this phenomenon.

1. Introduction

Radiation therapy (RT), a frequently utilized therapeutic modality in cancer therapy, strives to achieve an optimal balance between creating sufficient tumor cell death to reduce the likelihood of cancer recurrence and avoiding too much cell injury in normal tissues to cause unacceptable or hazardous side effects. This therapeutic ratio is factored into the careful tailoring of radiation treatment regimens specifically for each clinical scenario encountered. In general, however, accepted clinical treatment regimens finely tune the total radiation dose, radiation volume, and radiation dose per fraction so as to exploit the difference between tumor and normal tissues in terms of proliferation capacity of cells, intrinsic repair capability of tissue to overcome radiation injury, and oxygenation of tissue. While every effort is made to spare radiation injury to normal tissues, over the course of nearly a century of radiation treatments a lot has been learned about tissue injury. This tissue injury is cataloged as acute, subacute or chronic injury based on the temporal relation between administration of radiation and onset of symptoms or signs (Hall and Giaccia, 2006). Radiation injury to the hematopoietic system can manifest as an acute side effect due to depletion of progenitor cells or as chronic injury due to alterations in vasculature and fibrosis in lymphoid organs like bone marrow, thymus and spleen (Mauch et al., 1995; Weinmann et al., 2001a). The predominant hematological toxicities studied so far have been neutropenia, anemia and thrombocytopenia since their clinical manifestation is fairly self-evident in terms of increased incidence of opportunistic infections, bleeding and fatigue or reduction in exercise capacity (Ray-Coquard et al., 2003).

Lymphopenia is a common side effect of chemotherapy and drugs like steroids which are used in cancer patients. From the standpoint of RT-induced lymphopenia, it is well known that lymphocytes are the most radiosensitive cells amongst the erythroid, myeloid and lymphoid lineage. Lymphocyte LD_{50} (lethal dose required to reduce the surviving fraction of lymphocytes by 50%) is 2 Gy and LD_{90} (lethal dose required to reduce the surviving fraction of lymphocytes by 90%) is 3 Gy (Nakamura et al., 1990). Yovino et al. mathematically modeled radiation dose to circulating lymphocytes (CL) in patients undergoing conventional fractionated brain radiotherapy for high grade gliomas. They found that after 30 fractions of 2 Gy RT, the mean dose to CL was 2.2 Gy and 99% of CL received $\geq$0.5 Gy (Yovino et al., 2013). The impact of RT on reducing CL counts has been known for decades (Meyer, 1970; Newman et al., 1987; Petrini et al., 1977). Yet its potential association with tumor control and overall survival outcomes remained largely unexplored until recently. The recognition that the immune system

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plays a vital role in tumor surveillance and the advent of immunotherapy has renewed the focus on preserving a pool of functioning lymphocytes in the circulation. Reduced pretreatment lymphocyte counts and reduced lymphocyte infiltration in pathologically resected specimens have been associated with poor disease-free survival (DFS) and overall survival (OS) in breast, rectal, glioblastoma multiforme, non-small cell lung cancer and other tumors (Chen et al., 2016; Kitayama et al., 2011; Lohr et al., 2011; Hiraoka et al., 2006). Given that CL are the cells that eventually infiltrate tumors, it seems reasonable to assume that their depletion might contribute to suboptimal treatment outcomes.

RT acts as a double-edged sword on the immune system. It has an immunostimulatory effect via increased release of tumor associated antigens (TAA), radiation-induced neoantigens, increased expression of heat shock proteins (HSP), release of high mobility group box protein (HMBG) and recruitment of effector cells into the tumor microenvironment. But it also has an immunosuppressive effect by increasing expression of MHC class molecules, upregulating programmed death domain ligand-1 (PDL-1), cytotoxic T lymphocyte antigen-4 (CTLA-4), and depletion of CL and lymphoid progenitor cells in primary and secondary lymphoid organs (Formenti and Demaria, 2009). The mechanistic underpinnings of the interplay between the immunostimulatory effects and the immunosuppressive effects of RT and its impact on DFS and OS remains to be understood. We planned this systematic review to enumerate, evaluate and summarize lessons learned from the clinical studies in solid malignancies that have reported an association between RT-associated lymphopenia and survival.

2. Materials and methods

2.1. Literature search

The PubMed (National Institutes of Health), Embase (Elsevier), and Cochrane Central (Cochrane collaboration) databases were searched with the key words – radiation; cancer; lymphopenia and survival. The MESH and Emtree terms used with the various Boolean combinations have been attached in the Supplementary file. The search spanned the duration from the inception of each database up to April 17, 2017. The search was performed on April 18, 2017.

2.1.1. Non database search methods

Conference proceedings from American Society of Radiation Oncology (ASTRO), European Society of Therapeutic Radiation Oncology (ESTRO), European Society of Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO) for the timeframe 2000–2017 were conducted to identify additional articles. The search did not have a language filter. BP and SM independently searched the databases and conference proceedings with application of search terms for the relevant articles and any disagreements were resolved by mutual discussion. SK was the point person for resolving any disagreement in the inclusion of studies. BP, SM, and SK are trained radiation oncologists with knowledge of search protocols and previous experience in performing systematic reviews.

2.2. Eligibility criteria for articles

The following eligibility criteria were used for inclusion and exclusion of articles.

2.2.1. Inclusion criteria

(i) A prospective/retrospective clinical study of solid malignancies in humans, (ii) Radiation was an integral part of treatment – neoadjuvant, definitive or adjuvant, and (iii) Documented treatment-related lymphopenia and its impact on survival.

2.2.2. Exclusion criteria

(i) Hematological malignancies (ii) Preclinical in vitro and in vivo studies, (iii) Lymphopenia outcomes not correlated with survival outcomes, (iv) Whole body/hemi-body irradiation, (v) Reports only on pretreatment lymphopenia, lymphocytes in pathological specimens, lymphocyte association with chemotherapy or surgery alone, (vi) Radioactive isotope treatment, and (vii) Studies reporting outcomes in HIV positive patients or immunodeficiency states.

2.3. Article review

A systematic approach was followed by authors (BP, SM) for reviewing the eligibility of articles. The articles from the initial search of the electronic databases were imported into reference manager software. An independent review of the abstracts and full paper articles was done by BP and SM. The duplicates were removed and the titles of articles were evaluated. Abstracts found to be relevant to the topic of interest were shortlisted. Then the full length paper of the shortlisted articles were assessed for the eligibility criteria. The articles that reported RT an integral part of treatment and correlated CL counts with survival outcomes were shortlisted for final qualitative systematic review. The included study references were cross-searched for additional studies. The search strategy has been depicted in the PRISMA flow diagram (Fig. 1).

2.4. Common terminologies used

Absolute lymphocyte count (ALC) and total lymphocyte count (TLC) have been used interchangeably.

Grades of lymphopenia – Common Terminology Criteria for Adverse Events (CTCAE) Grade 1: < 1000–800/mm^3, Grade 2: < 800–500/mm^3, Grade 3: < 500–200/mm^3, Grade 4: < 200 cells/mm^3.

3. Results

Electronic search of PubMed, Embase and Cochrane Central resulted in 4296 abstracts. Non-database search of conference proceedings and cross-reference search of included studies resulted in three and one new studies, respectively. After removal of duplicates, 3591 abstracts were assessed. 49 articles were found to be relevant to the research question. The full length articles of 49 studies were assessed and 20 studies (17 full length articles, 3 articles from conference proceedings) were found to fit the inclusion criteria. Table 1 depicts the studies included in this systematic review. Among 20 studies, only one study on brain tumor was a prospective cohort study, the remaining 19 articles were retrospective studies. Notable exclusions were – lymphopenia after palliative radiation of bone metastasis, brain metastasis in breast cancer, stereotactic body radiotherapy in spine metastasis; lymphopenia in pediatric patients without documentation of survival outcomes and in seven articles data was presented as abstracts in conferences and full data was published separately as a journal article. Since varying median lymphocyte counts were used for survival outcomes, a quantitative meta-analysis was not possible. Furthermore, studies had wide variability in the timing of lymphopenia determination, pooled effect estimates across multiple disease sites would ignore the differences in total radiation dose and fractionation, entire datasets were unavailable in reports published only as abstracts and there is wide variability in the quality of evidence between retrospective and prospective studies. All of these features contributed to our decision to perform a qualitative review illustrating the association between radiation-associated lymphopenia and survival outcomes grouped by tumor subsites.

4. Brain tumors

Three articles reported the correlation between RT-associated lymphopenia and survival outcomes in brain tumors. Grossman et al.