PREDICTING INDIVIDUAL RADIATION SENSITIVITY: WHERE NEXT?

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PREDICTING RADIATION SENSITIVITY

1. Adverse effects after radiation therapy.
2. Implications for the victims of a large-scale rad-nuc ‘event’.

XRT ADVERSE EVENTS AS END-POINTS: A MOVING TARGET

- Toxicity observed with ‘traditional’ radiotherapy techniques.
- Impact of chemotherapy.
- Impact of new technologies (IMRT, SRT, etc.).
- Impact of novel ‘targeted’ agents.

ADVERSE EVENTS AS END-POINTS FOR RADIATION SENSITIVITY

- Early versus Late events.
- Unacceptable events (blindness, paralysis, fistula, etc.).
- Grade 3-4 events: Less common but generally unequivocal.
- Grade 1-2 events: More common but ‘noisy’.
- Second Malignant Neoplasms.

IMRT

- Can decrease the volume of normal tissue receiving high doses while *markedly increasing* the volume of normal tissue receiving low doses.
- Utilization in the US has skyrocketed in recent years.
- Important to follow these patients prospectively using candidate biomarkers.

Novel ‘targeted’ agents

- Targeted agents may act as potent radiation modifiers.
- Early clinical studies, however, pose considerable technical and ethical challenges.
- Developing assays of ‘radiation effects’ is crucial (*applicable in-vitro, in-vivo and clinically*) with implications for radiotherapy and rad-nuc events.
- Image-based assays most attractive.

COMBINING TARGETED AGENTS AND RADIATION

TUMOR

- **Conduct baseline assays.**
- **Administer XRT to lesion #1.**
  - ***Study markers of XRT effects in lesion #1.***
- **Administer the drug.**
  - ***Study markers of drug effects.***
- **Administer XRT to lesion #2 (** hours later).**
  - ***Study markers of XRT effects in lesion #2.***

NORMAL TISSUES

- **Conduct baseline assays.**
- **Administer XRT to lesion #1.**
  - ***Study markers of XRT effects in normal tissues near lesion #1.***
- **Administer the drug.**
  - ***Study markers of drug effects.***
- **Administer XRT to lesion #2 (** hours later).**
  - ***Study markers of XRT effects in normal tissues near lesion #2.***

TOTAL BODY IRRADIATION

- Employed for hematological and non-hematological malignancies, life-threatening abnormalities in the hematopoietic cells, and replacing crucial enzymes in patients with metabolic storage diseases.
- Rather crude techniques of RT are employed for TBI; much confusion exists about what is the target vs OAR, and how much radiation should be administered to which tissues and when?

TOTAL BODY IRRADIATION

- Biodefense Advance Research & Development Authority (BARDA), BAA-BARDA-08-08: “Therapies for Hematopoietic Syndrome, Bone Marrow Stromal Cell Loss and Vascular Injury Resulting From Acute Exposure to Ionizing Radiation”.

TOTAL BODY IRRADIATION

- Depletion of host Treg and Myeloid-Derived Suppressor cells.
- Removal of host NK, CD4+ and CD8+ cells.
- Gut irradiation alters host-microbe homeostasis (translocation of gut microbes to the mesenteric lymph nodes, with systemic liberation of bacterial-derived toll-like receptor agonists) thereby
  - Activating the innate immune system (evidenced by an increase in the splenic dendritic cells).
  - Fueling surviving and reconstituting CD4 cells to develop into Th17-like cells (increase the antitumor reactivity of adoptively transferred T cells).

SUMMARY-1

- Studies from the 1990s in a variety of common cancers provide an excellent snapshot of the toxicity encountered after ‘traditional’ radiotherapy alone and radiotherapy plus chemotherapy.

SUMMARY-2

- Increasing use of new technology (e.g. IMRT) and ‘targeted’ agents may modify the patterns of toxicity which should be prospectively monitored.

SUMMARY-3

- Lessons learned from victims of rad-nuc events may be very helpful for radiotherapy patients and vice-versa.