Combination external beam and internal radiation via $^{131}$I-CLR1404 in the treatment of head and neck squamous cell carcinoma xenografts.

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Introduction

Radiation is a central treatment modality for head and neck cancer (HNC). However, optimal outcome is commonly limited by the radiation tolerance of adjacent normal tissue structures. Radiation is sometimes valuable in the setting of locoregional tumor recurrence, however the risk of significant normal tissue toxicity is substantial with repeat irradiation and can have a profound adverse impact on patient quality of life. Although technical advances including intensity modulated radiotherapy (IMRT) can reduce normal tissue effects, the problem of repeat exposure of normal tissues to radiation is frequently limiting. The need to improve radiation response and precision within malignant tumors and enables internal delivery of radiation. This allows a combination of external and internal radiotherapy delivery with a goal of improving treatment outcome without enhanced normal tissue toxicities.

Therapeutic Outcome

Treatment of SCC22B tumor xenografts with XRT alone (blue), XRT and 7.4 MBq CLR1404 (dark red), or 2 x 3.7 MBq CLR1404 (bright red) (see treatment scheme).

Groups were randomized once an average tumor volume of 325 mm$^3$ was reached. Number of tumors per group was n = 16 (8 mice, bilateral tumors). Treatment was considered as failed when tumor volumes increased by 1.5-fold without subsequent regression below that threshold. Progression-free survival was defined by tumor volume increases < 1.5-fold, encompassing both tumor regression and volume stabilization.

Animals were monitored for 74 days after the start of treatment.

Conclusions

- Combined external beam radiation plus internal radiation via $^{131}$I-CLR1404 demonstrates superior tumor response over external beam radiation alone.
- PET-CT scans show a highly specific accumulation of $^{131}$I-CLR1404 in tumors of xenografted mice with relatively low dose accumulation in liver, heart, spine, and muscle.
- The mean dose delivered to the tumor by the administration of $^{131}$I-CLR1404 was approximately 30 Gy, with normal tissue receiving significantly lower doses.
- These data illustrate the relative tumor selectivity of CLR1404 PLE delivery as well as enhancement of tumor response with combined RT and $^{131}$I-CLR1404 treatment. De-intensification of external beam radiation dose, with attendant reduction in normal tissue toxicities so common in HNC patients, represents a central future objective to be tested in clinical trials with the ultimate goal of improving treatment outcome and quality of life for HNC patients.

Dose Estimation

Simulations were performed using the Monte Carlo (MC) code Geant4 version 9.4. Initial source distributions were sampled using activity distributions acquired by PET-CT scans. A total of 10 particles were simulated for each source to assure reasonable statistics. All simulations were run on a 16-node (64 Intel® Xeon™ 2.80 GHz processors) cluster.

A) Dose volume histograms calculated for the tumor and several important normal structures in an individual mouse carrying SCC-22B xenograft using image datasets taken at 4, 24, 48 and 72 hours post-injection.

B) Minimum, mean, and maximum dose per injected activity to a variety of normal structures.

C) Color wash of cumulative activity distribution and MC calculated absorbed dose distribution normalized per injected activity of $^{131}$I.

PET-CT Scan of mice carrying SCC-22B xenografts 72h after injection of $^{131}$I-CLR1404.

- A) PET scan reveals high tumor specificity with low background in the gastrointestinal system.
- B) Quantification of activity distribution shows minimal variance between the two animals.
- C) Quantification of activity distribution reveals moderate background doses within the liver and the heart (blood pool). Bone marrow and muscle showed low background levels.

Normal Tissue Distribution

- A) Activity concentration (Bq/ml).
- B) Animal distribution: Mouse A and Mouse B.
- C) Tumor to organ ratios.