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Purpose/Objective(s): Radiation therapy is commonly used for treatment of patients with intrathoracic malignancies, such as lung cancer, esophageal cancer, and lymphoma. Radiation-Induced Heart Disease (RIHD) is a major source of morbidity and mortality in patients receiving thoracic radiation. Therefore, there is an acute need for development of non-invasive approaches for detection of RIHD at a stage that offers potential for early intervention and reversibility. Cardiac mitochondrial dysfunction is a hallmark of radiation-induced cardiac injury. During aerobic respiration, pyruvate enters the tricarboxylic acid cycle and is metabolized into bicarbonate in mitochondria. We hypothesized that radiation-induced mitochondrial dysfunction results in decreased conversion of pyruvate to bicarbonate in the mitochondria and increased conversion to lactate in cytosol. We sought to non-invasively assess radiation-induced changes in mitochondrial myocardial metabolism by tracking the fate of hyperpolarized (HP) C-13 pyruvate utilization using Magnetic Resonance Spectroscopy (MRS).
Materials/Methods: Sprague-Dawley rats (n = 10) underwent baseline echocardiography and HP C-13 pyruvate MRS. Rats in the cardiac radiation group (n = 5) underwent image-guided cardiac radiation with cone-beam CT, to a total dose of 40 Gy in 5 fractions. All rats underwent repeat echocardiography and hyperpolarized C-13 pyruvate MRS one week later.
Results: For the first time, we have demonstrated feasibility of employing HP C-13 pyruvate MRS for detecting radiation-induced myocardial mitochondrial metabolic changes in a pre-clinical rat model. In the cardiac radiation group, C-13 pyruvate MRS demonstrated a statistically significant decrease in cardiac bicarbonate-to-lactate ratio compared to pre-radiation baseline ($P = 0.02$, one-tailed paired t-test), suggesting increased metabolism of pyruvate into lactate in the cytoplasm (at the expense of metabolism into bicarbonate in the mitochondria) due to mitochondrial dysfunction. No significant decrease in this ratio was observed in the non-irradiated, age matched controls ($P = 0.90$). No significant changes in left ventricular ejection fraction or global longitudinal strain were observed in either the cardiac irradiation or control group of rats at this time point.
Conclusion: Radiation-induced myocardial mitochondrial dysfunction is an early event and can be detected **in vivo** by hyperpolarized C-13 pyruvate MRS within 1 week after radiation, and prior to onset of echocardiographic changes. Due to its non-invasive nature, this technology has the potential to serve as a platform for building radiation-focused cardio-oncology programs for early detection and mitigation of radiation-induced cardiac injury in hundreds of thousands of patients receiving thoracic radiation annually.

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Radiotherapy Bridging in Patients With R/R High-Grade Lymphoma Receiving CD19 CAR-T in the UK

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Purpose/Objective(s): Radiotherapy (RT) has potential synergistic effects with CD19 CAR-T but is not yet widely used as bridging therapy for lymphoma. Comprehensive outcome data of RT bridged patients are limited, and selection criteria for RT bridging and optimal dose / fractionation are unknown. We hypothesized that RT is a safe, well tolerated and effective bridging to CAR-T even in patients with advanced stage and high-risk features. We analyzed details of RT bridging in a prospective national CAR-T cohort, examining patient, disease and treatment factors which may affect outcome of RT bridging.
Materials/Methods: We analyzed consecutive patients with r/r high-grade lymphoma who had leukapheresis for axicabtagene ciloleucel (axi-cel) or tisagenlecleucel (tisa-cel) between Dec 2018 - Nov 2020 in 10 UK centers and received RT bridging.
Results: Of 371 leukapheresed patients, 76 (21%) received RT bridging (61 RT alone, 15 combined modality treatment (CMT)). Median age was 58 years. 65% had **de novo** diffuse large B-cell lymphoma, 7% primary mediastinal B-cell, and 28% transformed lymphoma. 64 were infused (50 axi-cel, 14 tisa-cel), with a median turnaround time of 44 days from apheresis to infusion. 12/75 (16%) patients did not proceed to CAR-T infusion (6 progressive disease (PD), 4 deaths (not related to RT), 1 manufacturing failure, 1 CR after bridging). The dropout rates were 11%, 33% & 22% for RT, CMT and chemotherapy-bridged patients respectively ($P = 0.086$). Disease characteristics were similar in RT & CMT groups; the majority had advanced stage (71% and 86%), 34% & 43% bulky disease, 59% & 73% extranodal involvement, 55% & 57% were primary refractory to R-CHOP, 75% & 67% had SD/PD as best response to last treatment, 18% & 13% had prior autologous transplant, and 31% & 33% had double/triple hit or -expression. In-field response in 53 cases bridged with RT alone (doses 20 − 40Gy) was 85% (11/14) for early stage (3 CR) and 63% (22/35) for advanced stage. Details of the radiation techniques and RT-related toxicities will be provided at the meeting. The ongoing overall response rate at 3 months post infusion was 63% (50% CR). With a median follow-up of 11.5 months, the median time to progression has not been reached. The 6- & 12-months event-free survival was 60% (95% CI: 47-71) and 58% (95% CI: 45 -69), respectively, with no significant difference between RT and CMT. The median overall survival (OS) was 17.8 months (95% CI: 8.9-NR), with 6- & 12-months OS rates of 77% (95% CI: 64 − 86) and 65% (95% CI: 50-76). Post CAR-T toxicity was favorable, with 7/64 (11%) experiencing G3/4 cytokine release syndrome, 8/64 (13%) G3/4 neurotoxicity. Treatment-related mortality was 4.6%.
Conclusion: RT is a safe and effective bridging therapy prior to CD19 CART in lymphoma. In this large prospective real world national cohort with high proportion of advanced stage and high-risk features, RT bridging was given successfully with low dropout rate and excellent survival outcomes.

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