OPTIMIZING A COMBINATION RADIO-IMMUNOTHERAPY REGIMEN IN A PRECLINICAL MODEL OF TREATMENT-RESISTANT, HIGH-RISK NEUROBLASTOMA


Background Neuroblastoma (NBL), a cancer derived from neural crest precursor cells, is the most common extra-cranial solid tumor in children, with a median age of diagnosis of 22 months. Patients diagnosed with NBL are segmented into prognostic categories with ~50% categorized as high-risk (HR). Of these patients, ~40% are refractory to, or relapse following, initial treatment; there are currently no effective treatment options for these patients once they have failed salvage therapy of chemotherapy combined with αGD2 therapy (dinutuximab). Our group has previously published work developing a combination adaptive and innate immunotherapy regimen, “CAIR”, to treat a murine model of treatment-resistant, HR-NBL. 1,2 CAIR utilizes αGD2 immunocytokine (hu14.18-IL2), radiotherapy (RT), αCD40, CpG, and αCTLA4 but questions remain about the relative contribution of each component. In this study, we tested if our model of HR-NBL is resistant to salvage therapy of temozolomide and irinotecan (TEM+IRI) and if components of our effective CAIR therapy can be removed, in order to determine their necessity.

Methods To establish 9464D-GD2 as a model for treatment-resistant, HR-NBL, tumor-bearing mice were treated with TEM+IRI and/or hu14.18-IL2. To establish the necessity of each component of CAIR, mice bearing 9464D-GD2 tumors were treated with CAIR (12Gy RT, αCD40, αCTLA4, CpG, and hu14.18-IL2) or variations of CAIR subtracting one component.

Results Salvage therapy of TEM+IRI and/or hu14.18-IL2 extended the survival of mice (p<0.03) but did not result in 9464D-GD2 tumor cures. Adding RT (12Gy, SARRP) improved survival (p<0.0001), but not more than RT alone (p=0.29), and still did not cure tumors.

Removing RT or hu14.18-IL2 from CAIR dramatically shortened survival (p<0.0001) and yielded few tumor cures (1/16, 0/16 versus 13/30). Conversely, removing αCD40, αCTLA4, or CpG did not alter survival (p=0.81, p=0.85, p=0.70) relative to CAIR, and resulted in similar rates of tumor cures (8/16, 9/21, 7/16 versus 13/30). Removing two of the "expendable" components (αCD40, αCTLA4, CpG) generally reduced efficacy, with only CAIR subtracting CpG and αCTLA4 (RT, hu14.18-IL2, and αCD40) curing a similar number of mice as CAIR (3/16 versus 13/30, survival p=0.12).

Conclusions Here we demonstrate that 9464D-GD2 tumors behave similarly to human HR-NBLs that fail to be cured by salvage therapy. In contrast, these tumors can be cured by both CAIR therapy and by several versions of a reduced CAIR therapy (CAIR subtracting αCD40, αCTLA4, or CpG). We are now exploring the role of each component of CAIR in anti-tumor immune responses in this immunologically cold model.

REFERENCES

Ethics Approval The study was approved by the University of Wisconsin’s School of Medicine and Public Health Institutional Animal Care and Use Committee (IACUC), protocol: M005984.