Interleukin-13 Targeting for the Treatment of Malignant Peripheral Nerve Sheath Tumors

Oliver Daniel Mrowczynski MS; Russell Payne MD; A. B. Madhankumar; Alexandre Bourcier BS; Christine Y Mau MD; Vagisha Ravi; Becky Slagle-Webb; Kimberly Harbaugh MD; Elias Boulos Rizk MD; James R. Connor
[Institution]

Click To Add Logo

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) are soft tissue sarcomas that arise from peripheral nerves. A target of MPNSTs is the receptor for interleukin-13 (IL-13R). IL-13R has an a1 and a2 subtype, and activation of a1 leads to apoptosis. MPNSTs have increased expression of the a2 subtype, IL-13Ra2. IL-13Ra2 is an oncogene that acts as a decoy receptor which has a higher affinity for IL-13, allowing cancer to evade death by binding and sequestering all of the IL-13 thus inhibiting a1 activation. MPNSTs are currently treated with surgical resection, sometimes requiring complete limb amputation, as well as chemoradiation, all of which demonstrate limited effectiveness, and highlight the necessity for novel therapies. The goal of this study was to demonstrate the effectiveness of intratumoral IL-13 targeted pseudomonas exotoxin (GB-13) and IL-13 targeted liposomal doxorubicin (IL13-Lip-Dox) for MPNST treatment. The upregulated IL-13Ra2 on MPNSTs provides a unique opportunity for utilizing these therapies to precisely target MPNSTs and cause tumor cell death.

Methods

We interrogate the effectiveness of

Results

GB-13 and IL13-Lip-Dox treatment caused significant MPNST cell death in vitro. Both treatments led to a significant decrease in tumor progression in vivo. Immunohistochemical analysis showed increased necrosis, decreased Ki67, and increased cleaved caspase-3. The specific targeting of IL-13Ra2 also lead to a decreased side effect profile due to IL-13Ra2 not being expressed in normal tissues.

Conclusions

The current MPNST treatment paradigm is composed of 3-prongs: surgery, chemotherapy, and radiation, all of which have been demonstrated to be unsatisfactory. This lays the groundwork for the change of this paradigm and subsequently optimal patient outcomes by the addition of a 4th prong, intratumoral treatment with GB-13 as well as enhancing the chemotherapeutic arm with targeted liposomal therapy.

Learning Objectives

By the conclusion of this session, participants should be able to 1) Understand the devastating prognosis of MPNST and the necessity for novel treatment modalities, 2) Identify IL-13Ra2 as a novel therapeutic target in MPNSTs that can be effectively utilized for treatment, 3) Become familiar with a novel intratumoral treatment strategy that when performed with GB-13 provided significant decrease in tumor burden in vivo.

References

1. Farid M, Demicco EG, Garcia R, et al. Malignant peripheral nerve sheath tumors. Oncologist. 2014;19(2):193-201. doi:10.1634/theoncologist.2013-0328.

2. Trojanowski JQ, Kleinman GM, Proppe KH. Malignant tumors of nerve sheath origin. Cancer. 1980;46(5):1202-1212. doi:10.1002/1097-0142(19800901)46:5<1202::AID-CNCR2820460521>3.0.CO;2-5.

3. Cichowski K, Jacks T. NF1 Tumor Suppressor Gene Function. Cell. 2001;104(4):593-604. doi:10.1016/S0092-8674(01)00245-8.

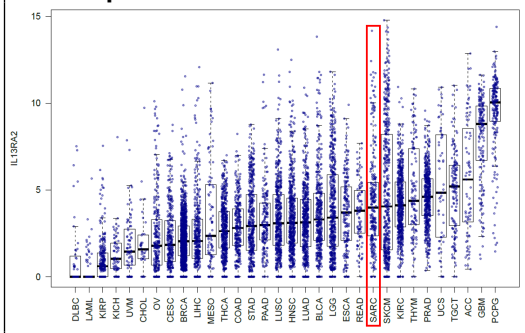
4. Widemann BC. Current status of sporadic and neurofibromatosis type 1-associated malignant peripheral nerve sheath tumors. Curr Oncol Rep. 2009;11(4):322-328.

5. Ng VY, Scharschmidt TJ, Mayerson JL, Fisher JL. Incidence and survival in sarcoma in the United States: a focus on musculoskeletal lesions. Anticancer Res. 2013;33(6):2597-2604.

6. Stucky C-CH, Johnson KN, Gray RJ, et al. Malignant peripheral nerve sheath tumors (MPNST): the Mayo Clinic experience. Ann Surg Oncol. 2012;19(3):878-885. doi:10.1245/s10434-011-1978-7.

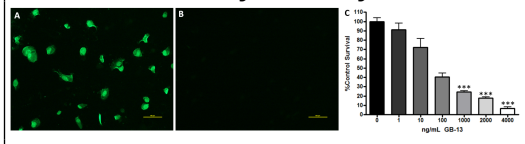
7. Kolberg M, Høland M, Agesen TH, et al. Survival meta-analyses for >1800 malignant peripheral nerve sheath tumor patients with and without

Figure 1. IL-13 receptor alpha 2 expression in TCGA database



IL13R2 analysis from the TCGA database showing MPNSTs which are in the “SARC” category of sarcomas are in the top 10 of highest IL13R2 expression in all tumor types.

Figure 2. IL-13R2 expression and in vitro cytotoxicity



(A) MPNST cells with IL-13R2 antibody incubation. (B) MPNST cells incubated without primary IL-13R2 antibody, but with secondary antibody to control for IL-13R2 antibody specificity. (C) In vitro cytotoxicity analysis showing that increasing GB-13 concentration causes enhanced MPNST cell death.

Figure 3. Schematic of our intratumoral treatment strategy.