Immunotherapy for Advanced Pediatric Rhabdomyosarcoma: **A Promising Future or Distant Dream?**

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Evaluating the Current Landscape and Future Directions

1. Understand the current challenges and poor prognosis of advanced RMS.
2. Review the backbone of current standard-of-care treatment.
3. Evaluate key clinical trial data on immunotherapy in advanced RMS.
4. Explore novel therapeutic approaches and ongoing research.
5. Discuss the future potential and hurdles of immunotherapy in this disease.

Rhabdomyosarcoma: A Primer

- Most common soft tissue sarcoma in children. Two major subtypes:
  - ① Embryonal (ERMS): More common, better prognosis.
  - ② Alveolar (ARMS): Less common, often metastatic, poorer prognosis; driven by **PAX/FOXO1 fusion oncogene**.

- Fact: RMS accounts for approximately 3-4% of all childhood cancers.

Skapek SX et al. Rhabdomyosarcoma. Nat Rev Dis Primers. 2019

The Challenge of Advanced Disease:
"Advanced" disease includes metastatic and recurrent/refractory RMS

- Localized disease: >70% 5-year survival.
- Metastatic disease: <30% 5-year survival (often 20-30%).
- Recurrent disease: <20% 5-year survival; prognosis is dismal.

Oberlin O et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. J Clin Oncol. 2008.

Why is Advanced RMS So Difficult to Treat?

- **Biological Aggressiveness:** Alveolar RMS is highly proliferative and invasive.
- **Therapeutic Resistance:** Intrinsic and acquired resistance to chemo/radiation.
- **Tumor Heterogeneity:** Diverse cell populations within the tumor.
- **"Cold" Tumor Microenvironment (TME):** Typically low in tumor-infiltrating lymphocytes (TILs), making immune engagement hard.
- Fact: The presence of the PAX-FOXO1 fusion gene is a key marker of high risk and is associated with a distinct, aggressive biology.

Williamson D, et al. Fusion gene-negative alveolar rhabdomyosarcoma is clinically and molecularly indistinguishable from embryonal rhabdomyosarcoma. J Clin Oncol. 2010.

The Current Backbone of Treatment

Multimodal therapy is the cornerstone:

- Chemotherapy: Remains the gold standard for upfront treatment, including for metastatic disease.
- Local Control:
  - Surgery: Complete resection if feasible.
  - Radiation Therapy: Essential for local control, especially for unresectable or metastatic sites.

Weiss AR, et al. Histology and fusion status in rhabdomyosarcoma: A pooled analysis of clinical trials from the Children's Oncology Group (COG). J Clin Oncol. 2019.

Limitations of Current Therapy

- **High Toxicity:** Significant acute and long-term side effects (cardiotoxicity, infertility, secondary malignancies).
- **Therapeutic Plateau:** Intensifying chemotherapy has not yielded significant survival gains in decades.
- **Treatment Failure:** Most patients with advanced disease will relapse, with few salvage options.

"This plateau necessitates novel approaches like immunotherapy"

The Rationale for Immunotherapy

The immune system can be harnessed to specifically target and kill cancer cells, potentially offering:

- ❖ High specificity.
- ❖ Durable, long-term memory.
- ❖ A different toxicity profile than chemotherapy.
- ❖ Key Modalities: *Checkpoint inhibitors, CAR T-cells, Antibody-Drug Conjugates (ADCs), Cancer Vaccines.*

The "Cold" Tumor Problem:

A major hurdle for immunotherapy in RMS

"Cold" TME characteristics:

- Low mutational burden (few neoantigens for immune cells to recognize).
- Low PD-L1 expression.
- Sparse Tumor-Infiltrating Lymphocytes (TILs).
- Immunosuppressive cells (Tregs, MDSCs).
- **Fact: Only ~15% of RMS samples show significant PD-L1 expression.**

Davis KL, et al. Comprehensive analysis of tumour immune microenvironment in paediatric rhabdomyosarcoma. J Clin Oncol. 2018.

Clinical Trials:

Checkpoint Inhibitors: ipilimumab, nivolumab, pembrolizumab

- Monoclonal antibodies: block inhibitory pathways used by tumors to invade immune
- Trial: SARC028 (Phase II)
- Agent: ***Pembrolizumab*** (anti-PD-1)
- Results: Limited activity in RMS. No objective responses in 12 RMS patients. Demonstrated the challenge of single-agent CPI in "cold" sarcomas.

Tawbi HA, et al. *Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028):...* Lancet Oncol. 2017.

Clinical Trials:

Checkpoint Inhibitors: atezolizumab, durvalumab

- Monoclonal antibodies: block inhibitory pathways used by tumors to invade immune
- Trial: NCT03719430
- Agent: Atezolizumab (anti-PD-L 1)
- Most of current trials are a combination therapy with chemotherapy

Clinical Trials:

Targeted antibody-drug conjugates (TADCs):

- Monoclonal antibodies binds tumor antigen and create a killing complex
- rial: ADVL1621 (Phase II)
- Agent: ***Dinutuximab*** (anti-GD2 monoclonal antibody) + chemotherapy.
- Rationale: GD2 is highly expressed on RMS cells.
- Results: Promising activity. 4/17 patients with refractory RMS achieved a complete response (CR).

Navid F, et al. Phase II Trial of Dinutuximab with Chemotherapy in Children with Newly Diagnosed High-Risk Metastatic Rhabdomyosarcoma. J Clin Oncol. 2021.

Clinical Trials:

CAR T-Cell Therapy

- Trial: Early-phase trials (e.g., NCI, CHOP)
- Targets: HER2, GD2, B7-H3, EGFR.
- Results: Early data shows some evidence of disease stability and regression in a subset of patients. Challenges include target heterogeneity, antigen escape, and the immunosuppressive TME.

Heitzeneder S, et al. *GPC2-CAR T cells tuned for low antigen density mediate potent activity against neuroblastoma without toxicity.* Cancer Cell. 2022. (Highlights CAR T work on targets also relevant to RMS).

Novel Work and Future Directions

Novel Target: B7-H3 (CD276)

- B7-H3 is a widely expressed immune checkpoint molecule on many solid tumors, including RMS.
- Antibody-Drug Conjugates (ADCs): **Omburtamab** (linked to a radioactive isotope).
- CAR T-Cells: B7-H3 directed CAR T-cells are in early clinical development.
- **Fact: B7-H3 is expressed in >90% of RMS tumor samples which is opposed to GD2 or PD-L1 in practice.**

Majzner RG, et al. *CAR T Cells Targeting B7-H3, a Pan-Cancer Antigen, Demonstrate Potent Preclinical Activity Against Pediatric Solid Tumors and Brain Tumors.* Clin Cancer Res. 2019.

Novel Work and Future Directions

Novel Target: GD2

- Content: Not just for neuroblastoma. GD2 is consistently expressed in RMS.
- Approaches:
- ADCs/GD2 CAR T-Cells: As mentioned.
- Immunocytokine: **Naxitamab** (humanized anti-GD2 antibody).
- Ongoing Trial: **Studies evaluating naxitamab in combination with chemotherapy in RMS.**

Novel Work and Future Directions

Liquid biopsies & diagnostics

- The role of circulating tumor DNA (ctDNA) in monitoring disease and guiding therapy.

Targeting the Fusion Oncogene

- **The PAX3/7-FOXO1 fusion is a prime target. It is a "neoantigen" unique to cancer cells.**

Approaches:

- Vaccines: Peptide vaccines designed to elicit a T-cell response against the fusion protein.
- T-cell Receptor (TCR) Therapy: Engineering T-cells to recognize and kill cells presenting the fusion peptide.

"This represents a highly specific, tumor-exclusive strategy"

Combining Modalities: The Key to Success?

The future likely lies in rational combinations to turn "cold" tumors "hot."

Examples:

- Immunotherapy + Radiation (abscopal effect).
- Immunotherapy + Chemotherapy (chemotherapy can cause immunogenic cell death).
- ADC + Checkpoint Inhibitor.
- CAR T-cells + checkpoint inhibitors.
- **Fact: The DARPA trial is a basket study testing the combination of atezolizumab (anti-PD-L1) with standard VAC chemotherapy in newly diagnosed metastatic RMS.**

Answering the Title Question

- ✓**A Distant Dream? For single-agent, off-the-shelf immunotherapy like checkpoint inhibitors, the current reality is disappointing.**

- ✓A Promising Future? Absolutely. For targeted immunotherapies (ADCs, CAR-T, fusion-directed therapies) used in rational combinations, the future is incredibly promising. It is a future of personalized medicine.

Current Mainstay

- **Aggressive Multi-Agent Chemotherapy remains the foundational, non-surgical backbone of treatment for advanced RMS.**
- Evolving Role (The Future):
- **Immunotherapy is not yet a standard first-line treatment.**
- Its current role is primarily in clinical trials and as salvage therapy for refractory disease.
- The goal of ongoing research is to successfully integrate effective immunotherapies with backbone chemotherapy to improve outcomes, aiming to eventually reduce chemotherapy intensity and its associated long-term toxicities.

Thank you