A Curative Approach to Central Nervous System Metastases of Neuroblastoma


Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical College, New York, NY

Abstract

Background: Neuroblastomas metastatic to the central nervous system (CNS NB) are associated with significant mortality. Median survival for patients with CNS NB is ~6 months. Intracranial compartmental radioimmunotherapy (cRIT) with radiolabeled monoclonal antibody (mAb) is a promising treatment option for CNS disease. 131I-8H9 targeting tumor cell-surface glycoprotein B7-H3 offers a therapeutic strategy. We analyzed overall survival of patients with CNS NB treated with intraventricular 131I-8H9 (cRIT) at Memorial Sloan Kettering Cancer Center (MSK) since 2003.

Methods: After radiographic/ pathological confirmation of CNS NB, all assessment of adequate CSF flow, cRIT eligible patients underwent treatment on an IRB-approved protocol with either iodine-124 or iodine-131 iodine-labeled murine IgG1 monoclonal antibody (mAb) targeting tumor cell-surface glycoprotein B7-H3. Studies included post-cRIT treatments and systemic immunotherapy (group 1). Data are presented as overall survival after detection of CNS metastasis.

Results: Among 105 patients with CNS NB were evaluated; 80 patients (76%) were treated (57 group 1, 23 historic). CNS disease is associated with significant mortality (median survival < 6 months, < 10% survival at 36 months). Intraventricular (8H9) cRIT administration involved a 2 mCi tracer of 124I- or 131I-8H9 with nuclear imaging and IFU-guided intraventricular injection (cRIT). Group 1 (n = 57): 19 (33%) had prior intracranial disease. Median overall survival > 50 months; nearly 50% survive at least 36 months. 131I-8H9 cRIT offers a therapeutic strategy for intracranial disease. Disease surveillance included serial MR brain/spine, MIBG, CT, and bone marrow evaluation.

Conclusions: 131I-8H9 cRIT has clinical utility to treat B7-H3+ CNS/LM tumors. Long-term follow-up of subjects for survival and disease recurrence continues at MSK. 131I-8H9 cRIT is a promising treatment option for patients with CNS NB.

Background

Central Nervous System and Lymphoproliferative (CNS-LM) Neoplasms

- There is a medical need for targeted innovative therapies to treat CNS-LM metastases.
- CNS-LM tumors are associated with significant mortality.
- Histologic tumor subtypes vary (~15%-20% of patients with CNS-LM).
- Medial survival <10 months even with surgical resection.
- CNS is difficult to treat and represents a sanctuary site for metastatic cancer.
- Common approved treatment strategies may include:
  - Surgical debulking
  - Radiation therapy
  - Combination chemotherapy

B7-H3+ and B7-H2- Non-Hodgkin’s Lymphoma (B7-H3+ NHL)

- Immunohistochemical expression of B7-H3 is restricted to the cell membranes of certain solid tumors, but is limited in normal tissues.
- The B7s are specific for 4-H1G3 and recognize the antigen on tumors of disease lineage.
- 8H9 retains its immunoreactive properties for specific targeting of tumors.
- ~10%-15% suppress tumor growth in mice with established xenografts.

Methods

After radiographic/patological confirmation of CNS NB, patients were treated on an approved protocol with 124I-cRIT or 131I-cRIT (Fig. 1) according to the following treatment regimens:

- Group 1 (n = 57): 131I-8H9 cRIT eligible patients underwent CNS salvage regimen (Table 1). Median overall survival >50 months; nearly 50% survive at least 36 months.
- Group 2 (n = 23): Patients were treated with full salvage non-regimen therapies with 131I-cRIT.

Results

Table 2. Summary of Survival: 131I-8H9 and Historically-treated CNS NB Patients

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Historic Patients</th>
<th>131I-8H9 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>52 (68%)</td>
<td>42 (53%)</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>5.5 m (1.1–8.7 m)</td>
<td>5 m (4-5 cycles)</td>
</tr>
<tr>
<td>Overall survival rate</td>
<td>5 (95% CI)</td>
<td>5.5 (4-5 cycles)</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>5 m (1.1–8.7 m)</td>
<td>5 m (4-5 cycles)</td>
</tr>
<tr>
<td>Overall survival rate</td>
<td>5 (95% CI)</td>
<td>5.5 (4-5 cycles)</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>5 m (1.1–8.7 m)</td>
<td>5 m (4-5 cycles)</td>
</tr>
<tr>
<td>Overall survival rate</td>
<td>5 (95% CI)</td>
<td>5.5 (4-5 cycles)</td>
</tr>
</tbody>
</table>

Conclusions

- 131I-8H9 cRIT has clinical utility to treat B7-H3+ CNS tumors.
- 131I-8H9 cRIT has median overall survival 106 months, nearly 50% survival at 36 months.
- 131I-8H9 cRIT produces objective measurable evidence of efficacy in pediatric patients with CNS NB.
- Long-term follow-up of subjects for survival and disease recurrence continues at MSK. 131I-8H9 cRIT is a promising treatment option for patients with CNS NB.