Omburtamab

- Determination of the Intralesional Distribution of Theranostic (124)I-Omburtamab Convection-Enhanced Delivery in Treatment of Diffuse Intrinsic Pontine Glioma
- Theranostic Intratumoral Convection-Enhanced Delivery of (124)I-Omburtamab in Patients with Diffuse Intrinsic Pontine Glioma: Pharmacokinetics and Lesion Dosimetry
- Outcomes of intraventricular 131-I-omburtamab and external beam radiotherapy in patients with recurrent medulloblastoma and ependymoma
- Phase 1 study of intraventricular (131)I-omburtamab targeting B7H3 (CD276)-expressing CNS malignancies
- Repeat convection-enhanced delivery for diffuse intrinsic pontine glioma

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Omburtamab is a murine monoclonal antibody that targets the B7-H3 antigen (CD276), which is overexpressed on a variety of pediatric and adult solid tumors, including neuroblastoma, medulloblastoma, ependymoma, and Diffuse Intrinsic Pontine Glioma (DIPG). It has gained attention as a promising therapeutic tool due to its ability to selectively bind to cancer cells, making it suitable for both diagnostic imaging and targeted radioimmunotherapy.

Key Characteristics

Target: B7-H3 (CD276) is a cell surface glycoprotein that is highly expressed in many tumors but exhibits limited expression in normal tissues. This makes it a good target for antibody-based therapies. Radiolabeling: Omburtamab can be labeled with radioactive isotopes, such as Iodine-124 (124I) for imaging purposes or Iodine-131 (131I) for therapeutic use. When radiolabeled, omburtamab delivers targeted radiation directly to cancer cells.

Applications

: Radioimmunotherapy:

131I-omburtamab is used for radioimmunotherapy in conditions like neuroblastoma and leptomeningeal metastases. When injected into the cerebrospinal fluid (CSF) or directly into tumors, it delivers radiation to the tumor site while sparing healthy tissue. It has been evaluated in phase I/II clinical trials and has shown encouraging results in prolonging survival and reducing tumor burden in pediatric cancer patients. Theranostics:

As a theranostic agent, omburtamab can be used for both therapeutic and diagnostic purposes. 124I-omburtamab is employed in imaging studies to evaluate the distribution of the antibody within the tumor and estimate radiation doses for therapy. This allows clinicians to visualize and tailor treatment with precision. Diffuse Intrinsic Pontine Glioma (DIPG):

Omburtamab has been studied as part of a novel approach for DIPG, using convection-enhanced delivery (CED) to inject the radiolabeled antibody directly into the brainstem tumor. This method ensures a higher concentration of the drug at the tumor site, offering a promising new treatment

avenue for this devastating disease. Clinical Trials and Research: Omburtamab is being studied in various clinical trials, particularly for pediatric cancers. It has shown potential in difficult-to-treat cancers, such as recurrent medulloblastoma, ependymoma, and neuroblastoma, improving outcomes in some patients who have exhausted other therapeutic options. Additionally, its use in radioimmunotherapy has demonstrated a favorable safety profile, with manageable toxicities primarily related to hematologic effects.

Omburtamab represents an important step forward in targeted cancer therapy, providing a means to deliver potent radiotherapy with precision, minimizing damage to surrounding healthy tissues.

Pandit-Taskar et al. conducted a pilot, first-in-human study using 124I-omburtamab imaging and theranostics as a therapeutic approach using a localized convection-enhanced delivery (CED) technique for administering radiolabeled antibody. They report the detailed pharmacokinetics and dosimetry results of intratumoral delivery of 124I-omburtamab. Forty-five DIPG patients who received 9.0-370.7 MBq of 124I-omburtamab intratumorally via CED underwent serial brain and whole-body PET/CT imaging at 3-5 time points after injection within 4, 24-48, 72-96, 120-144, and 168-240 h from the end of infusion. Serial blood samples were obtained for kinetic analysis. Whole-body, blood, lesion, and normal-tissue activities were measured, kinetic parameters (uptake and clearance half-life times) estimated, and radiation-absorbed doses calculated using the OLINDA software program. All patients showed prominent activity within the lesion that was retained over several days and was detectable up to the last time point of imaging, with a mean 124I residence time in the lesion of 24.9 h and dose equivalent of 353 ± 181 mSv/MBq. Whole-body doses were low, with a dose equivalent of 0.69 ± 0.28 mSv/MBq. Systemic distribution and activities in normal organs and blood were low. The radiation dose to blood was very low, with a mean value of 0.27 ± 0.21 mGy/MBq. Whole-body clearance was monoexponential with a mean biologic half-life of 62.7 h and an effective half-life of 37.9 h. Blood clearance was biexponential, with a mean biologic half-life of 22.2 h for the rapid α phase and 155 h for the slower β phase. Conclusion: Intratumoral CED of 124I-omburtamab is a novel theranostics approach in DIPG. It allows for the delivery of high radiation doses to the DIPG lesions, with high lesion activities low systemic activities, and high tumor-to-normal-tissue ratios and achieving a wide safety margin. Imaging of the actual therapeutic administration of 124I-omburtamab allows for direct estimation of the therapeutic lesion and normal-tissue-absorbed doses [1)].

Intraventricular compartmental radioimmunotherapy (cRIT) with 131-I-omburtamab is a potential therapy for recurrent primary brain tumors that can seed the thecal space. These patients often previously received external beam radiotherapy (EBRT) to a portion or full craniospinal axis (CSI) as part of upfront therapy. Little is known regarding outcomes after re-irradiation as part of multimodality therapy including cRIT. This study evaluates predictors of response, patterns of failure, and radiologic events after cRIT.

Methods: Patients with recurrent medulloblastoma or ependymoma who received 131-I-omburtamab on a prospective clinical trial were included. Extent of disease at cRIT initiation (no evidence of disease [NED] vs measurable disease [MD]) was assessed as associated with progression-free (PFS) and overall survival (OS) by Kaplan-Meier analysis.

Results: All 27 patients (20 medulloblastoma, 7 ependymoma) had EBRT preceding cRIT: most (22, 81%) included CSI (median dose 2340 cGy, boost to 5400 cGy). Twelve (44%) also received EBRT at relapse as bridging to cRIT. There were no cases of radionecrosis. At cRIT initiation, 11 (55%)

medulloblastoma and 3 (43%) ependymoma patients were NED, associated with improved PFS (p = 0.002) and OS (p = 0.048) in medulloblastoma. Most relapses were multifocal. With a medium follow-up of 3.0 years (95% confidence interval, 1.8-7.4), 6 patients remain alive with NED.

Conclusion: For patients with medulloblastoma, remission at time of cRIT was associated with significantly improved survival outcomes. Relapses are often multifocal, particularly in the setting of measurable disease at cRIT initiation. EBRT is a promising tool to achieve NED status at cRIT initiation, with no cases of radiation necrosis [2)].

The cell surface glycoprotein B7H3 is expressed on a range of solid tumors with a restricted expression on normal tissues. We hypothesized that compartmental radioimmunotherapy (cRIT) with the anti-B7H3 murine monoclonal antibody omburtamab injected intraventricularly could safely target CNS malignancies.

Patients and methods: We conducted a phase I trial of intraventricular 131I-omburtamab using a standard 3 + 3 design. Eligibility criteria included adequate cerebrospinal fluid (CSF) flow, no major organ toxicity, and for patients > dose level 6, availability of autologous stem cells. Patients initially received 74 MBq radioiodinated omburtamab to evaluate dosimetry and biodistribution followed by therapeutic 131I-omburtamab dose-escalated from 370 to 2960 MBq. Patients were monitored clinically and biochemically for toxicity graded using CTCAEv 3.0. Dosimetry was evaluated using serial CSF and blood sampling, and serial PET or gamma-camera scans. Patients could receive a second cycle in the absence of grade 3/4 non-hematologic toxicity or progressive disease.

Results: Thirty-eight patients received 100 radioiodinated omburtamab injections. Diagnoses included metastatic neuroblastoma (n = 16) and other B7H3-expressing solid tumors (n = 22). Thirty-five patients received at least 1 cycle of treatment with both dosimetry and therapy doses. Acute toxicities included < grade 4 self-limited headache, vomiting or fever, and biochemical abnormalities. Grade 3/4 thrombocytopenia was the most common hematologic toxicity. Recommended phase 2 dose was 1850 MBq/injection. The median radiation dose to the CSF and blood by sampling was 1.01 and 0.04 mGy/MBq, respectively, showing a consistently high therapeutic advantage for CSF. Major organ exposure was well below maximum tolerated levels. In patients developing antidrug antibodies, blood clearance, and therefore therapeutic index, was significantly increased. In patients receiving cRIT for neuroblastoma, survival was markedly increased (median PFS 7.5 years) compared to historical data.

Conclusions: cRIT with 131I-omburtamab is safe, has favorable dosimetry and may have a therapeutic benefit as adjuvant therapy for B7-H3-expressing leptomeningeal metastases [3)].

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report on the safety and experience in a group of pediatric patients who received sequential CED into the brainstem for the treatment of diffuse intrinsic pontine glioma.

Methods: Patients in this study were enrolled in a phase I single-center clinical trial using 124I-8H9 monoclonal antibody (124I-omburtamab) administered by CED (clinicaltrials.gov identifier NCT01502917). A retrospective chart and imaging review were used to assess demographic data, CED infusion data, and postoperative neurological and surgical outcomes. MRI scans were analyzed using iPlan Flow software for volumetric measurements. Target and catheter coordinates as well as radial, depth, and absolute error in MRI space were calculated with the ClearPoint imaging software.

Results: Seven patients underwent 2 or more sequential CED infusions. No patients experienced Clinical Terminology Criteria for Adverse Events grade 3 or greater deficits. One patient had a persistent grade 2 cranial nerve deficit after a second infusion. No patient experienced hemorrhage or stroke postoperatively. There was a statistically significant decrease in radial error ($p = 0.005$) and absolute tip error ($p = 0.008$) for the second infusion compared with the initial infusion. Sequential infusions did not result in significantly different distribution capacities between the first and second infusions (volume of distribution determined by the PET signal/volume of infusion ratio [mean ± SD]: 2.66 ± 0.35 vs 2.42 ± 0.75; $p = 0.45$).

Conclusions: This series demonstrates the ability to safely perform sequential CED infusions into the pediatric brainstem. Past treatments did not negatively influence the procedural workflow, technical application of the targeting interface, or distribution capacity. This limited experience provides a foundation for using repeat CED for oncological purposes [4].

Conclusion

In conclusion, the use of radiolabeled antibodies like 124I-omburtamab in the treatment of Diffuse Intrinsic Pontine Glioma (DIPG) represents a promising theranostic approach, particularly when delivered via intratumoral convection-enhanced delivery (CED). This technique allows for the precise targeting of DIPG lesions with high radiation doses while minimizing systemic exposure and preserving normal tissue. The safety and efficacy of this approach have been demonstrated, with favorable pharmacokinetics, high tumor-to-normal-tissue radiation ratios, and promising clinical outcomes. Additionally, compartmental radioimmunotherapy (cRIT) using 131I-omburtamab has shown therapeutic potential in recurrent CNS malignancies, with improved survival in patients achieving no evidence of disease (NED) status. These advances in radiolabeled antibody therapies offer a significant step forward in the management of aggressive pediatric tumors like DIPG, although further studies are required to optimize treatment protocols and expand their therapeutic reach.

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