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Clinical trial

Phase 1/2 study of a WT1 peptide-dosing emulsion in pediatric patients with recurrent/refractory diffuse intrinsic pontine glioma, glioblastoma, or anaplastic astrocytoma

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Highlights

- The prognosis of pediatric high-grade gliomas including DIPG is dismal.
- Conventional therapies eventually become ineffective for the tumors.
- A phase 1/2 study of a novel WT1 peptide vaccine was conducted.
- The vaccine was well tolerated and apparently induced WT1-specific immune responses.
- The vaccine suggestively warrants its clinical development.

Abstract

Background

The prognosis of pediatric patients with diffuse intrinsic pontine glioma (DIPG), glioblastoma, or anaplastic astrocytomas (AAs) is dismal. This first-in-child phase 1/2 study examined the safety and efficacy of a Wilms' tumor gene 1 (*WT1*) peptide vaccine, along with the associations of delayed-type hypersensitivity (DTH) and cytotoxic T lymphocyte (CTL) frequency/count with clinical outcomes.

Methods

Patients (<20 years) were intradermally injected with the vaccine.

Results

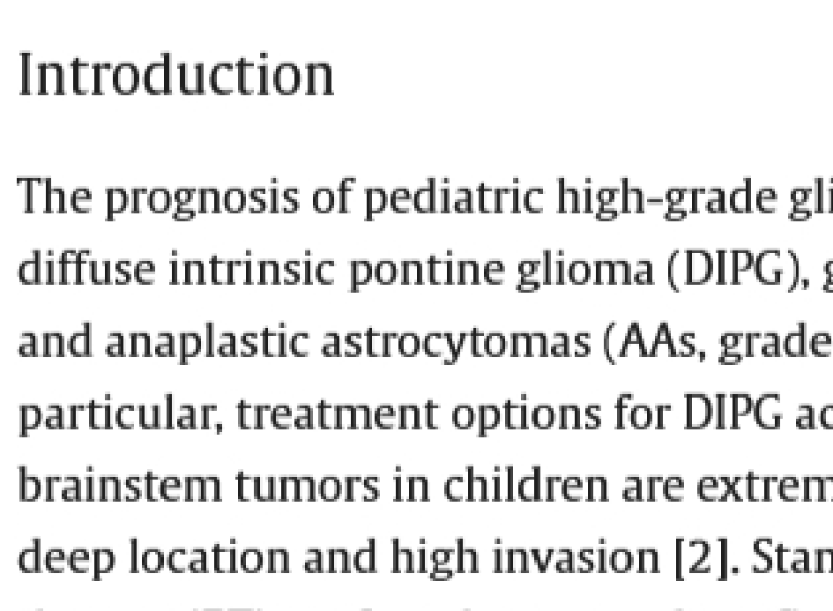
Among all patients (N = 18; median age: 8.9 years), 11, 5, and 2 had DIPG, glioblastoma, and AAs, respectively. In Phase 1 (n = 4), 3.5 mg was determined for use in Phase 2 (n = 14) because no dose-limiting toxicities occurred. In Phases 1 and 2, injection site reactions (n = 14, 77.8%) were the most common adverse events. All and DIPG patients showed the 9-month overall survival (OS) rates—the primary endpoint—of 44.4% (90% confidence interval (CI) [24.4–65.9]) and 27.3% [7.9–56.4], respectively. The vaccine was not effective statistically because the lower limit of the 90% CI for the primary efficacy endpoint in DIPG patients did not exceed its prespecified threshold—20%. Median OS was 5.4 months for DIPG. Among all patients, median OS was significantly longer (p = 0.024) for WT1-specific immune responders (9.9 months [6.0–33.4]) presenting increased CTL frequency/count and/or being positive for DTH than for nonresponders (4.9 months [2.2–16.5]).

Conclusions

The vaccine was not effective statistically but was well tolerated and appeared to have induced WT1-specific immune responses, suggesting improved survival in WT1-specific immune responders among DIPG patients and warranting its further development.

ClinicalTrials.gov Identifier: NCT02750891

Graphical Abstract



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Introduction

The prognosis of pediatric high-grade gliomas (HGGs) including diffuse intrinsic pontine glioma (DIPG), glioblastoma (grade IV), and anaplastic astrocytomas (AAs, grade III) is dismal [1]. In particular, treatment options for DIPG accounting for 80% of brainstem tumors in children are extremely limited due to its deep location and high invasion [2]. Standardized radiation therapy (RT) confers short-term benefits for DIPG, with a median overall survival (OS) of less than 1 year (8–11 months) [3].

Wilms' tumor gene 1 (*WT1*)—which is overexpressed in HGGs including DIPG [4], [5], [6]—is an oncogene that regulates cell proliferation and apoptosis [7], [8] and promotes angiogenesis and tumor progression [7], [9], [10]. We focused on WT1, which was ranked first among 75 cancer antigens [11] and which was reported to be the most promising cancer antigen [12] and a stem cell antigen [13] and to allow immunotherapeutic targeting for cancer stem cell antigens [14]. A WT1 killer (WT1-K) peptide vaccine provided an encouraging clinical evolution in a pediatric patient with relapsed diffuse midline glioma [4]. We initiated to develop a WT1-K peptide vaccine in around 2010. WT1-K showed efficacy for newly diagnosed glioblastoma [15] and recurrent glioblastoma multiforme [16] in adults. Furthermore, WT1 HLA class I and II peptide vaccines showed efficacy for recurrent malignant glioblastoma in adults [17]. These clinical findings drove us to develop a WT1 peptide vaccine as the Ombipepimut-S [WT1-K and -helper (H) peptides]-Dosing Emulsion (ODE) for pediatric patients with a target brain tumor.

An *in vivo* study of ODE in mice [18] demonstrated the following: 1) ODE can promote both WT1-specific killer and helper T cell-mediated immune responses against WT1-positive tumors; 2) WT1-K peptide comprises HLA class I epitopes that pulse WT1-specific CD8⁺ cytotoxic T cells (CTLs) only; 3) WT1-H peptide comprises an HLA class II epitope and increases CTL frequency and count; and 4) CTLs induced with ODE are capable of functioning even within an immunosuppressive tumor microenvironment. The safety of ODE was confirmed in a phase 1 study in adult patients with advanced malignancies [19] and a phase 1/2 study in adult patients with myelodysplastic syndromes [20]. We conducted the present study to examine the safety and efficacy of ODE for pediatric patients with DIPG, glioblastoma, or AA, along with the associations of potential biomarkers [delayed-type hypersensitivity (DTH)] and WT1-specific CTL frequency and count] with patient prognosis.

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Section snippets

Study population, inclusion criteria, and exclusion criteria

Pediatric patients were recruited through referral. Their clinicopathological data were collected by an independent third party contracted by the sponsor (Sumitomo Pharma Co., Ltd.). Eligible patients met all of the inclusion criteria, the key criteria of which are shown as follows: 1) a diagnosis of DIPG including brain stem tumors confirmed by magnetic resonance imaging (MRI) and clinical course [note: histological, cytological, and molecular examinations were not mandatory in Japan at the …

Patients

Patients were enrolled (April 2016–April 2017) and studied (April 2016–January 2020). Of 18 patients enrolled at six study sites, 11 (61.1%) had DIPG, 5 had histologically confirmed glioblastoma, and 2 had histologically confirmed AA (Table 1). All patients, about whom pseudoprogression was ruled out as described above, had a recurrent/refractory primary disease. Median age at the time of enrollment was 8.9 years (2.8–18.7 years), and almost all (n = 17, 94.4%) patients were male. The …

Discussion

This first-in-child phase 1/2 clinical trial, which assessed the safety and efficacy of ODE for pediatric patients with recurrent/refractory DIPG, glioblastoma, or AA, showed the favorable clinical outcomes of cancer immunotherapy with ODE in all of studied patients: 1 PR and 3 SD in DIPG patients, 2 SD in glioblastoma patients, and 1 SD in AA patients. At study completion, notably, 1 immune responder each with DIPG, glioblastoma, and AA survived for more than 20 months after study initiation.

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Data availability

Data are available upon reasonable request to the corresponding author. …

CRediT authorship contribution statement

Y. Hashii: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft , Review & editing. **H. Fujisaki:** Investigation, Review & editing. **H. Goto:** Data curation, Investigation, Writing – review & editing. **K. Horibe:** Conceptualization, Data curation, Investigation, Writing – review & editing. **K. Sugiyama:** Data curation, Investigation, Writing – review & editing. **T. Yanagisawa:** Data curation, Investigation, Writing – review & editing. **J. Hara:** Conceptualization, Data …

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used bioRender [created in BioRender. Hashii, Y. (2026)] to generate the graphic abstract. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article. …

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Yoshiko Hashii reports administrative support, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Sumitomo Pharma Co Ltd. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Hiroyuki …

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