Diffuse midline glioma H3 K27-altered Immunotherapy

Abstract

Diffuse midline glioma H3 K27-altered, a rare and aggressive brain tumor primarily affecting children and young adults, presents a significant clinical challenge. This article delves into the promising potential of immunotherapy as an emerging treatment approach for this specific subtype of glioma. The H3 K27M mutation, responsible for altering the tumor's epigenetics and reducing its responsiveness to standard treatments, necessitates innovative therapeutic strategies.

Immunotherapy aims to harness the patient's immune system to recognize and combat cancer cells, including those harboring H3 K27M mutations. Key immunotherapy strategies explored in this context include checkpoint inhibitors, peptide vaccines, and chimeric antigen receptor (CAR) T-cell therapy.

Furthermore, the article provides an overview of the INTERCEPT H3 clinical trial, an open-label, multicenter initiative that combines H3K27M-vac with radiotherapy and atezolizumab to evaluate safety, tolerability, and immunogenicity. The trial focuses on adult patients with newly diagnosed H3K27M-mutant diffuse midline gliomas.

The discussion also highlights the importance of safety and immunogenicity assessment within the trial, emphasizing its potential impact on treating this challenging disease. Additionally, the article explores the utilization of GD2-CAR T cell therapy and the significance of personalized treatment based on comprehensive molecular profiling.

In conclusion, the investigation of immunotherapy and clinical trials such as INTERCEPT H3 presents a promising avenue for improving the prognosis and treatment of Diffuse midline glioma H3 K27-altered. The innovative approaches discussed in this article offer hope for addressing the unique challenges posed by this rare and aggressive brain tumor.

Introduction

Immunotherapy is an emerging and promising area of research for the treatment of various types of cancer, including diffuse midline glioma with H3 K27-alterations. However, the use of immunotherapy in treating these gliomas is still in the experimental stage, and clinical trials are ongoing to better understand its potential efficacy.

The H3 K27M mutation results in changes in the epigenetics of the tumor, making it less responsive to standard treatments. Immunotherapy aims to harness the patient's immune system to recognize and attack cancer cells, including those with H3 K27M mutations. There are a few immunotherapy approaches being explored for these gliomas:

Checkpoint Inhibitors: Checkpoint inhibitors are drugs that block certain proteins (checkpoint proteins) that prevent immune cells from attacking cancer cells. Clinical trials are evaluating the use of checkpoint inhibitors like pembrolizumab and nivolumab in patients with H3 K27M-mutant gliomas.

Peptide Vaccines: Researchers are working on developing vaccines that target the specific H3 K27M mutation. These vaccines aim to stimulate the immune system to recognize and attack tumor cells with this mutation.

Chimeric Antigen Receptor (CAR) T-Cell Therapy: CAR T-cell therapy involves modifying a patient's T cells to express receptors that specifically target cancer cells. This approach has shown promise in other types of cancer and is being investigated for H3 K27M-mutant gliomas.

It's important to note that the effectiveness of immunotherapy in treating diffuse midline glioma with H3 K27-alterations is still being studied, and results from clinical trials are awaited to determine its safety and efficacy. Additionally, the suitability of immunotherapy as a treatment option for individual patients may depend on several factors, including the tumor's specific genetic profile, the patient's overall health, and the stage of the disease.

If you or a loved one is considering immunotherapy for this condition, it's important to consult with a healthcare team that specializes in neuro-oncology and participate in clinical trials when appropriate. Clinical trials offer access to cutting-edge treatments and can contribute to the advancement of knowledge about this rare and challenging type of cancer. Always discuss treatment options and potential risks with your medical team to make informed decisions about your care.

INTERCEPT H3 is an open-label, single-arm study, multicenter national phase 1 trial to assess the safety, tolerability and immunogenicity of H3K27M-vaccine in combination with standard radiotherapy and the immune checkpoint inhibitor atezolizumab (ATE). 15 adult patients with newly diagnosed K27M-mutant histone-3.1 (H3.1K27M) or histone-3.3 (H3.3K27M) DMG will be enrolled in this trial. The 27mer peptide vaccine H3K27M-vac will be administered concomitantly to standard radiotherapy (RT) followed by combinatorial treatment with the programmed death-ligand 1 (PD-L1) targeting antibody ATE. The first three vaccines will be administered bi-weekly (q2w) followed by a dose at the beginning of recovery after RT and six-weekly administrations of doses 5 to 11 thereafter. In a safety lead-in, the first three patients (pts. 1-3) will be enrolled sequentially.

Perspective: H3K27M-vac is a neoepitope targeting long peptide vaccine derived from the clonal driver mutation H3K27M in DMG. The INTERCEPT H3 trial aims at demonstrating (1) safety and (2) immunogenicity of repeated fixed dose vaccinations of H3K27M-vac administered with RT and ATE in adult patients with newly diagnosed H3K27M-mutant DMG.

Trial registration: NCT04808245 [1)].

The INTERCEPT H3 trial represents a significant step in the ongoing exploration of immunotherapy for DMG patients. The strategy of targeting the H3K27M mutation using H3K27M-vac and ATE is innovative and promises new insights into the management of this devastating disease. While the trial's design and small sample size pose limitations, its emphasis on safety and immunogenicity is crucial for a novel approach to treating H3K27M-mutant DMG. Future results from this trial may inform further research and potentially pave the way for a more effective and personalized treatment strategy for DMG patients. This trial underscores the importance of innovative approaches in the fight against rare and aggressive brain tumors.

GD2-CAR T cell therapy

see GD2-CAR T cell therapy

Systemic administration of chemotherapeutic agents is often hindered by the blood brain barrier (BBB), and even drugs that successfully cross the barrier may suffer from unpredictable distributions. The challenge in treating this deadly disease relies on effective delivery of a therapeutic agent to the bulk tumor as well as infiltrating cells. Therefore, methods that can enhance drug delivery to the brain are of great interest. Convection-enhanced delivery (CED) is a strategy that bypasses the BBB entirely and enhances drug distribution by applying hydraulic pressure to deliver agents directly and evenly into a target region. This technique reliably distributes infusate homogenously through the interstitial space of the target region and achieves high local drug concentrations in the brain. Moreover, recent studies have also shown that continuous delivery of drug over an extended period of time is safe, feasible, and more efficacious than standard single session CED. Therefore, CED represents a promising technique for treating midline tumors with the H3K27M mutation [2)].

Based on the molecular heterogeneity observed in this tumor type, personalized treatment is considered to substantially improve therapeutic options. Therefore, clinical evidence for therapy, guided by comprehensive molecular profiling, is urgently required. In this study, we analyzed feasibility and clinical outcomes in a cohort of 12 H3K27M glioma cases treated at two centers. Patients were subjected to personalized treatment either at primary diagnosis or disease progression and received backbone therapy including focal irradiation. Molecular analyses included whole-exome sequencing of tumor and germline DNA, RNA-sequencing, and transcriptomic profiling. Patients were monitored with regular clinical as well as radiological follow-up. In one case, liquid biopsy of cerebrospinal fluid (CSF) was used. Analyses could be completed in 83% (10/12) and subsequent personalized treatment for one or more additional pharmacological therapies could be recommended in 90% (9/10). Personalized treatment included inhibition of the PI3K/AKT/mTOR pathway (3/9), MAPK signaling (2/9), immunotherapy (2/9), receptor tyrosine kinase inhibition (2/9), and retinoic receptor agonist (1/9). The overall response rate within the cohort was 78% (7/9) including one complete remission, three partial responses, and three stable diseases. Sustained responses lasting for 28 to 150 weeks were observed for cases with PIK3CA mutations treated with either miltefosine or everolimus and additional treatment with trametinib/dabrafenib in a case with BRAFV600E mutation. Immune checkpoint inhibitor treatment of a case with increased tumor mutational burden (TMB) resulted in complete remission lasting 40 weeks. Median time to progression was 29 weeks. Median overall survival (OS) in the personalized treatment cohort was 16.5 months. Last, we compared OS to a control cohort (n = 9) showing a median OS of 17.5 months. No significant difference between the cohorts could be detected, but long-term survivors (>2 years) were only present in the personalized treatment cohort. Taken together, we present the first evidence of clinical efficacy and an improved patient outcome through a personalized approach at least in selected cases of H3K27M glioma [3)].

Findings suggest that targeting PLK1 with small-molecule inhibitors, in combination with radiation therapy, will hold a novel strategy in the treatment of Diffuse intrinsic pontine glioma (DIPG) that warrants further investigation [4)].

1)

Grassl N, Sahm K, Süße H, Poschke I, Bunse L, Bunse T, Boschert T, Mildenberger I, Rupp AK, Ewinger MP, Lanz LM, Denk M, Tabatabai G, Ronellenfitsch MW, Herrlinger U, Glas M, Krex D, Vajkoczy P, Wick A, Harting I, Sahm F, von Deimling A, Bendszus M, Wick W, Platten M. INTERCEPT H3: a multicenter phase I peptide vaccine trial for the treatment of H3-mutated diffuse midline gliomas. Neurol Res Pract. 2023 Oct 19;5(1):55. doi: 10.1186/s42466-023-00282-4. PMID: 37853454.

2)

Himes BT, Zhang L, Daniels DJ. Treatment Strategies in Diffuse Midline Gliomas With the H3K27M Mutation: The Role of Convection-Enhanced Delivery in Overcoming Anatomic Challenges. Front Oncol. 2019 Feb 8;9:31. doi: 10.3389/fonc.2019.00031. PMID: 30800634; PMCID: PMC6375835.

3)

Gojo J, Pavelka Z, Zapletalova D, Schmook MT, Mayr L, Madlener S, Kyr M, Vejmelkova K, Smrcka M, Czech T, Dorfer C, Skotakova J, Azizi AA, Chocholous M, Reisinger D, Lastovicka D, Valik D, Haberler C, Peyrl A, Noskova H, Pál K, Jezova M, Veselska R, Kozakova S, Slaby O, Slavc I, Sterba J. Personalized Treatment of H3K27M-Mutant Pediatric Diffuse Gliomas Provides Improved Therapeutic Opportunities. Front Oncol. 2020 Jan 10;9:1436. doi: 10.3389/fonc.2019.01436. PMID: 31998633; PMCID: PMC6965319.

4)

Amani V, Prince EW, Alimova I, Balakrishnan I, Birks D, Donson AM, Harris P, Levy JM, Handler M, Foreman NK, Venkataraman S, Vibhakar R. Polo-like Kinase 1 as a potential therapeutic target in Diffuse Intrinsic Pontine Glioma. BMC Cancer. 2016 Aug 18;16:647. doi: 10.1186/s12885-016-2690-6. PubMed PMID: 27538997.