Imatinib mesylate treatment for platelet-derived growth factor receptor alfa-positive choroid plexus carcinoma

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Abstract

We herein report a female child with choroid plexus carcinoma treated with standard dose of imatinib at disease recurrence. This patient failed initial twice-surgical resections, central nervous system (CNS) irradiation, and adjuvant chemotherapies and high-dose thiotepa and melphalan with auto peripheral blood stem cell rescue. Finally, imatinib treatment was undergone as a palliative setting, however the tumor did not reduce and the patient died of tumor bleedings. We consider that the reasons for the failure are as follows: i) adequate CNS level of imatinib were not obtained because of the blood brain barrier, ii) the lack of platelet-derived growth factor receptor beta expression in our case may have a crucial role.

Introduction

Among childhood brain tumors, choroid plexus carcinomas (CPCs) are rare and have a dismal prognosis.[1] Recently, Nupponen *et al.*[2] reported that CPC cells express platelet-derived growth factor receptor (PDGFR) alfa or beta, and Koos *et al.*[3] revealed that imatinib mesylate (Gleevec™), a tyrosine kinase inhibitor, suppresses choroid plexus cell proliferation in a dose-dependent manner by blocking the PDGFR beta signaling pathway. Herein, we report the case of a PDGFR alfa-positive CPC that showed no response to imatinib mesylate.

Case Report

A 28-month-old girl with fever and seizures was brought to our hospital. Brain computed tomography revealed a large tumor accompanied with bleeding in the right lateral ventricle. After twice operations, the tumor, which was pathologically diagnosed as CPC, was almost completely (over 95%) removed. She was subsequently administered chemotherapy with vincristine, cisplatin, cyclophosphamide, and etoposide (the VCCE[4] regimen). Following 5 courses of VCCE, X-ray irradiation was performed (18 Gy to the whole brain and spine; boost of 32 Gy to the scar of the resected tumor). Despite all these treatments, the tumor recurred in the third ventricle and spine after 6 months. Afterwards, salvage chemotherapy with adriamycin, cyclophosphamide, carboplatin, etoposide, and methotrexate (the ACCEM[5] regimen) was initiated. After completion of 6 courses of ACCEM, high-dose chemotherapy with thiotepa and melpharan along with auto-peripheral blood stem cell transplantation (autoPBSCT) was administered. However, 4 months after autoPBSCT, the cerebrospinal fluid (CSF) was positive for CPC cells, and the mass had recurred at the third ventricular profunda. Therefore, imatinib mesylate (Gleevec™, 400 mg/(m^2·day) peroraly) alone was administered as palliative treatment. However, tumor progression did not stall. The patient finally died at the age of 62 months because of acute renal failure due to

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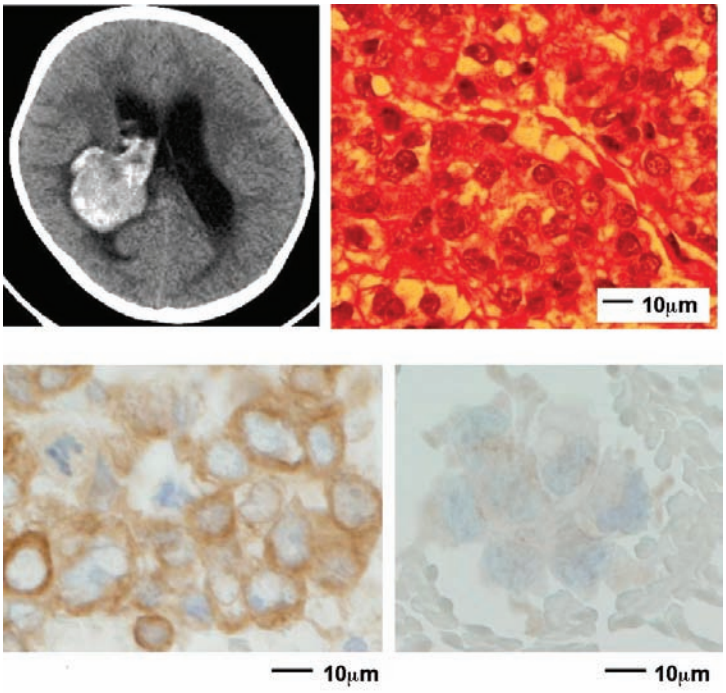

Figure 1. Upper left panel: The brain computed tomography scan at first manifestation. Upper right panel: The H-E staining of tumor section at diagnosis. Lower panels: Immunohistochemical staining of platelet derived growth factor receptor (PDGFR) alfa (lower left panel: tumor section at diagnosis; lower right panel: cerebrospinal fluid at disease recurrence). Comparison of the histological findings of the tumor samples obtained during the first operation and the cytological findings of the cerebrospinal fluid samples obtained at 4 months after auto-peripheral blood stem cell transplantation revealed that the choroid plexus carcinoma (CPC) cells had continued to express PDGFR alfa at the same rate (nearly 30% of all CPC cells were positively stained), while both samples were negative for PDGFR beta expression.

hemorrhagic shock caused by bleeding from the mass in the third ventricle. The CSF levels of imatinib were not gauged.

Discussion

The PDGF and PDGFR system plays a role in cell growth and angiogenesis in some tumors.[6,7] It is known that PDGFR signaling is blocked by imatinib (Gleevec™; a tyrosine kinase inhibitor with high specificity for PDGFR) as well as c-kit, and c-abl.[8] Some trials are being conducted on the use of imatinib in the treatment of pediatric neoplasms such as solid tumors[9] and malignant gliomas.[10] Furthermore, it was recently reported that CPC cells express PDGFR alfa and beta,[2] and that PDGFR beta expression is attenuated by imatinib in Z310, which is one of immortalized choroid plexus epithelial cell lines expressing PDGFR beta.[3] We consider the following assumptions as the causes of failure: i) imatinib could not penetrate adequately into the CSF because of the blood brain barrier (Baruchel *et al*.[11] reported that CSF levels of imatinib was less than 5% of those of plasma levels); ii) the CPC cells in our case did not respond to imatinib probably because the CPC cells lacked PDGFR beta expression. However, the expression of PDGFR alfa in our case is presumed to play an essential role in the tumor regrowth, since this phenotype have retained even after potent treatments including with anticancer drugs, irradiation, and the auto PBSCT.

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