Original Article

Topotecan plus cyclophosphamide as maintenance chemotherapy for children with high-risk neuroblastoma in complete remission: short-term curative effects and toxicity

FENG Chen, TANG Suoqin*, WANG Jianwen, LIU Ying, YANG Guang

Department of Pediatrics, General Hospital of PLA, Beijing 100853, China

Abstract: Objective To evaluate chemotherapy-related toxicity and the short-term efficacy of topotecan and cyclophosphamide as maintenance chemotherapy for stage IV neuroblastoma in complete remission. Methods The clinical data of 16 children with stage IV neuroblastoma received 3 cycles of maintenance chemotherapy with topotecan (0.75 mg · m⁻² · day⁻¹, infused on days 0-4) and cyclophosphamide 250 mg · m⁻² · day⁻¹, infused on days 0-4). The two-year event-free survival after complete remission was recorded and the chemotherapy-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute. Results The most common chemotherapy-related toxicity was bone marrow suppression and suppressions of neutrophils, hemoglobin and platelets, which occurred in all the patients mostly of grade III and IV. All the patients experienced episodes of infections, which were controlled effectively with antibiotics. Impairment of gastrointestinal and liver functions in these cases was mostly mild (grade I and II) and recovered after corresponding treatments. None of the patients exhibited damages in the nervous system or the renal or cardiac functions. After complete remission, the two-year event-free survival rate of these patients was 68.75% (11/16). Conclusion Topotecan plus cyclophosphamide for maintenance chemotherapy can be effective and relative safe for stage IV neuroblastoma in complete remission, thus giving a chance to those patients who choose not to have stem cell transplantation. Key words: neuroblastoma; chemotherapy; topotecan; cyclophosphamide

INTRODUCTION

Neuroblastoma is the most common malignant tumor of the peripheral nervous system in childhood, responsible for 10% of children patients with tumors and 50% of tumor-related pediatric deaths. The prognosis is poor in children aged above 1 year old even following high-dose chemotherapy, radiotherapy and surgical therapy. Patients with unfavorable biological characteristics for neuroblastoma such as MYCN gene amplification often have poor outcomes, with a survival rate of only 20% to 35%. Combined use of high-dose chemotherapy, surgery, radiotherapy, transplantation of autologous hemopoietic stem cells from the peripheral blood and 13-cis retinoic acid biotherapy shows good prognosis in children patients with clinical stage IV neuroblastoma, and more favorable long-term prognosis may be obtained in children with complete remission before transplantation.

Some parents, though well aware of the benefits and necessity of autologous stem cell transplantation, are reluctant to accept the treatment for economic, psychological or other reasons. A phase II window has been completed in Pediatric Oncology Group (POG) for topotecan and cyclophosphamide in children with recurrent or refractory solid tumors. Our department, referring to the latest chemotherapeutic regimen for neuroblastoma proposed by Children's Oncology Group (COG), used topotecan combined with cyclophosphamide (CTX) as the maintenance regimen for treating such patients, in particular children with advanced neuroblastoma completely remitted following induction chemotherapy and surgical therapy. Here we report the related toxic and side effects and short-term efficacy of the therapeutic regimen in 16 children with stage IV neuroblastoma in complete remission.

PATIENTS AND METHODS

General data

Sixteen children with stage IV (International Neuroblastoma Staging System (INSS)) neuroblastoma established pathologically by fine needle aspiration biopsy or lymph node biopsy admitted in our department were recruited in this study, including 10 boys and 6 girls with the age of onset ranging from 1.8 to 7.5 years and disease course of 2 to 5 months. The primary sites were the abdomen in 14 patients and the posterior mediastinum in 2. Marrow metastasis occurred in 14 patients and multiple osseous metastases in 7. Following induction therapy and surgical therapy by reference to the A3973 regimen of COG, complete remission was
achieved and ascertained by re-examination with computed tomographic scanning, systemic bone scanning and bone marrow smear according to the therapeutic response evaluation criteria of neuroblastoma. The patients’ parents were repeatedly informed of the necessity of autologous stem cell transplantation but still wished for continued chemotherapy.

**Maintenance chemotherapeutic regimen**

Prior to therapeutic medication, routine blood test, liver and kidney function tests, myocardial enzyme test and ECG were carried out and confirmed normal. Topotecan 0.75 mg · m⁻² · day⁻¹ (0.025 mg · kg⁻¹ · day⁻¹ for patients with body weight <12 kg) and CTX 250 mg · m⁻² · day⁻¹ (8.33 mg · kg⁻¹ · day⁻¹ for those with body weight ≥12 kg) were given from days 0 to 4. Two venous accesses were created for intravenous infusion of hydration/alkalization solution (3000 ml · m⁻² · day⁻¹) over 24 h and topotecan over 1 h, respectively. Following continued intravenous administration of CTX for 4 h, drugs for protecting hepatic and cardiac functions were given. Recovery of bone marrow hematopoiesis was achieved in all cases without the occurrence of infections. The next course began 21 days after the initiation of chemotherapy, and a total of 3 courses were administered.

**Prevention of chemotherapeutic complications**

To prevent toxic and side effects of the drugs, mesna was given concomitantly with CTX administration at the total dose 160% that of CTX. Four doses were given at a 3-h interval and the initial dose was given prior to CTX. After completion of the administration of chemotherapeutic drugs, G-CSF 5 μg · kg⁻¹ · day⁻¹ was given to stimulate hematopoiesis for promoting bone marrow hematopoiesis recovery until an absolute neutrophil count (ANC) >1.5 × 10⁹/L was attained. For mucositis control, hydration and alkalization (3000 ml · m⁻² · day⁻¹) were well implemented, and measures were taken to control vomiting and protect the gastrointestinal mucosa. To control for potential infections, diet cleanness was ensured, and chemitrim was given to prevent pneumocystis carinii pneumonia; prophylactic antibiotics were given for an ANC below 1.0 × 10⁹/L or a body temperature exceeding 37.5 °C; meropenem was switched in the event of body temperature increase, and antibiotics were further replaced following drug sensitivity tests of pathogens. Other measures for controlling complications included fructose diphosphate sodium injection, cardiac, hepatic and renal function protection with ademetionine 1, 4-butanedisulfonate, hydration and alkalization solutions, and timely component blood transfusion in case of hemoglobin <60 g/L and platelets <20 × 10⁹/L.

**Treatment after maintenance chemotherapy**

Hematopoiesis recovered after the three courses of maintenance chemotherapy. Radiotherapy of the primary sites was delivered 15 times with a total dose of 20-30 Gy. After chemotherapy, 13-cis-retinoic acid (160 mg · m⁻² · day⁻¹, divided into two doses) was orally given for 14 days followed by resting for 14 days. The treatment lasted for 6 months in total. Follow-up observation was carried out after completion of the treatment.

**Criteria for evaluation of related toxic and side effects and short-term efficacy**

The related toxic and side effects were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) 3.0 of National Cancer Institute (NCI) and classified into 6 grades (0-5). The patients were evaluated after the treatment by ultrasound scan and clinical examinations every 3 months in the first year, and every 6 months in the next two years. The two-year disease-free survival rates of the children after complete remission were evaluated.

**Statistical analysis**

The data were presented as Mean±SD or percentages calculated using SPSS 13.0 software.

**RESULTS**

**Chemotherapy-related toxic and side effects**

Chemotherapy-related toxic and side effects are presented in Tab.1. The pre-operative chemotherapeutic regimen produced significant toxic effects on the bone marrow. Granulocyte toxicity reached grade IV in 100% of the patients; the accumulated incidence of grade III and IV toxicity of the erythroid cells and megakaryocytes was 100%. Agranulocytosis occurred 12.8 ± 2.7 days after the initiation of chemotherapy and lasted for 2.1 ± 1.5 days. Due to the deficiency of granulocytes, infections of different severities occurred in all the children but were controlled with active anti-infection treatment. In spite of intense antiemetic treatment, the incidence rate of such side reactions as vomiting and nausea related to the regimen was still as high as 100%, but the conditions were mostly mild (grade I and II). Following treatments for protecting cardiac, hepatic and renal functions, hepatic impairment (grade I or II) found in the majority of the cases recovered, and none of the cases exhibited renal, nervous or cardiac toxic or side effects.

**Short-term efficacy analysis**

All of the 16 children successfully completed the maintenance therapy and subsequent radiotherapy and tretinoin biotherapy, with a two-year disease-free survival of 68.75% (11/16). In the 5 patients with recurrence, 4 showed the primary site in the abdomen and 1 in the posterior mediastinum; marrow metastasis and multiple osseous metastases occurred in 4 cases and marrow metastasis in 1 case. The disease relapsed in the bone marrow of 3 patients at 10, 19 and 22 months after complete remission and in the bones of the other 2 patients at 16 and 21 months after complete remission.
DISCUSSION

Neuroblastoma is an extremely malignant tumor in infancy and childhood, composed histologically of undifferentiated sympathetoblasts. For children with this tumor in advanced stage in particular, transplantation of autologous hemopoietic stem cells from the peripheral blood following complete remission achieved by large-dose chemotherapy is crucial for good long-term prognosis. For those patients who choose not to have stem cell transplantation, maintenance chemotherapy following induction chemotherapy appears currently to be the last option. In our cases, the maintenance chemotherapeutic regimen with topotecan and CTX resulted in a two-year disease-free survival rate of 68.75%, but still, this regimen can not replace autologous hemopoietic stem cell transplantation. Such a high survival rate was ascribed to the complete remission of the patients before induction chemotherapy, local radiotherapy following maintenance chemotherapy and tretinoin biotherapy. Nevertheless, the long-term efficacy of this maintenance therapeutic regimen in children with stage IV neuroblastoma with complete remission following induction chemotherapy awaits further multicenter and large-sample-size studies.

The major drugs used for maintenance chemotherapeutic regimen are topotecan and CTX. Topotecan is a topoisomerase I inhibitor and a water-soluble semi-synthesized camptothecine anti-tumor agent. It works by specific binding to topoisomerase I in the replication prophase to hinder the enzyme from repairing broken ends of single strands, thereby causing destruction of DNA duplex structures and leading to death of the tumor cells. Topoisomerase I exists not only in cells in the dividing phase but also in quiescent tumors in the quiescent phase or generally resistant to chemotherapy agents. This drug has been used for treating refractory and recurrent solid tumors in children. CTX, as a cell cycle non-specific chemotherapeutic agent against malignant tumors including neuroblastoma in children. Combination of topotecan and CTX was intended for better controlling the progression of the primary disease. Three courses of chemotherapy can achieve the purpose of reducing tumor residue to the maximum extent possible, though local radiotherapy and tretinoin biotherapy are also indispensable.

This chemotherapeutic regimen can lead to serious bone marrow depression and gastrointestinal toxic and side effects. However, use of stimulating factors and active anti-infective therapy and heart, liver and kidney-protecting treatments can promote the tolerance of the children to this regimen. In our cases, the duration of agranulocytosis with this chemotherapeutic regimen was only 2.1±1.5 days, a result of application of the stimulating factors immediately following completion of the chemotherapy rather than after the occurrence of granulocytopenia to reduce the possibility of secondary infection. The primary side effect of CTX is hemorrhagic cystitis. In this chemotherapeutic regimen, the use of mesna and active large-dose hydration and alkalization minimized the risk of this complication.

We found that in children with stage IV neuroblastoma, the risk of tumor recurrence within a short term could not be eliminated with maintenance chemotherapy, radiotherapy and biotherapy following complete remission achieved by induction chemotherapy. Particularly, for patients with bone marrow metastasis and systemic multiple osseous metastases, higher topotecan and cyclophosphamide dosages could be used, and hemopoietic stem cell transplantation should be urged for high-quality long-term disease-free survival.

REFERENCES

472-80.