RESEARCH ARTICLE

Clinical Study on Carboplatin for Treating Pediatric Patients with Wilms Tumors

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Abstract

This analysis was conducted to evaluate the efficacy and safety of carboplatin based chemotherapy in treating pediatric patients with Wilms tumors. Methods: Clinical studies evaluating the efficacy and safety of carboplatin based regimens on response and safety for pediatric patients with Wilms tumors were identified using a predefined search strategy. Pooled response rates (RRs) of treatment were calculated. Results: In carboplatin based regimens, 4 clinical studies which including 127 patients with advanced Wilms tumors were considered eligible for inclusion. With this carboplatin based chemotherapy, 2 clinical studies included carboplatin, ifosfamide and etoposide. Systemic analysis suggested that, in all patients, the pooled PR was 64.5% (82/127) in carboplatin based regimens. Thrombocytopenia and leukocytopenia were the main side effects. No grade III or IV renal or liver toxicity was observed. No treatment related death occurred with carboplatin based treatment. Conclusion: This systemic analysis suggests that carboplatine based regimens are associated with a reasonable response rate and accepted toxicities for treating pediatric patients with Wilms tumors.

Keywords: Carboplatine - Wilms tumor - toxicity

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Introduction

Combined treatment for patients with Wilms´ tumor (WT) is an important factor contributing to the improvement of prognosis (Pritchard-Jones et al., 2003; Kalapurakal et al., 2004). It was reported that the response rate of children with relapsed or resistant WT to a combination of carboplatin, ifosfamide, and etoposide, at the maximal tolerated dose of 635 mg/m^2 for carboplatin, is associated with a CR rate of 32% and a total response rate of 63% (Kung et al., 1993; Kung et al., 1995). In the field of cancer chemotherapy including in the treatment of WT, carboplatin is a common choice (Akkuzu et al., 2013; Bag et al., 2013; Butthongkomvong et al., 2013; Fu et al., 2013; 2013; Khemapech et al., 2013; Kucukoztas et al., 2013; Natukula et al., 2013; Oranratanaphan et al., 2013; Ozdemir et al., 2013; Zhang et al., 2013; Pitakkarnkul et al., 2013). It was reported that carboplatin, at a dose of 550 mg/m^2 every 3 weeks, as a single drug resulted in a response rate of 53% in children with relapsed WT (de Camargo et al., 1994). Other agents, e.g., etoposide and ifosfamide also demonstrated activity (Tournade et al., 1988; Pein et al., 1993; de Camargo et al., 1994), a response rate of 50% to ifosfamide (3 gm/m^2 over 2 days, every 2 weeks) in children with relapsed WT was also reported (Tournade et al., 1988). The use of etoposide (200 mg/m^2/day for 5 days) as a single agent in relapsed WT was previous reported in a response rate of 42% (Pein et al., 1993). However, the role of carboplatin in treating patients with WT has not been systemically investigated.

According to this background, we hypothesize that carboplatin originated regimen could be established as an optimal schedule for treating pediatric patients with WT.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (carboplatin) and (Wilms tumor). All clinical studies evaluating the impact of carboplatin on the response or survival and side effects for WT published in English prior to Jun 1st of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with cyclophosphamide or etoposide; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic and/or locally advanced WT, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age< 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

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Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors; the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 68 papers relevant to the search words by the end of June, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (de Camargo et al., 1994; Zoubek et al., 1995; Abu-Ghosh et al., 2002; Kung et al., 1995) when carboplatin was used as single or in combination of chemotherapy. These studies had been carried out in Brazil, European countries, and the United States. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

Characteristics of carboplatin as a single agent of chemotherapy, studies included are presented as short-term outcomes: the response rate of de Camargo et al. was 53.3% (8/15), of Zoubek et al. (1995) was 77.8% (7/9). When carboplatin was used in combination with ifosfamide and etoposide, 2 studies included in this study are presented and the short-term outcomes suggested that the response rate of Abu-Ghosh et al. was 81.8%, of Kung et al. was 63%.Totally, 127 patients were enrolled and 82 patients achieved CR or PR, the pooled response rate thus was 64.5% (82/127) in carboplatin based regimens.

Thrombocytopenia and leukocytopenia were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in carboplatin based treatment.

Discussion

In previous studies, investigators have reported good response rates of carboplatin in treating patients with relapsed WT (Marina et al., 1994; Marina et al., 1994). But, it remains to be determined whether the higher doses of chemotherapy containing carboplatin could be compared with that of lower doses and what combination should be considered. Especially, consideration should be focused on the minimal instead of maximal dose needed to cure WT (O'Dwyer et al., 1985; Grundy et al., 1989). The use of two agents combination regimen containing carboplatin and vp-16 in treating patients with refractory or relapsed WT for two courses achieved a response rate of 73% (Pein et al., 1994). However, only 31% of patients remain disease-free and in CR at a median of 40 months of follow-up. Further, three-agent regimens containing carboplatin, e.g. the use of ICE for patients in this setting is associated with a response rate of 71% (Kung et al., 1993; Kung et al., 1995). The use of high-dose chemotherapy followed by autologous stem cell transplantation may be effective in salvaging patients with relapsed WT and poor prognostic features. A 3-year disease-free survival and overall survival of 50 ± 17% and 60 ± 18%, respectively, were reported after high-dose chemotherapy and autologous stem cell transplantation in a group of patients with high-risk relapsed WT transplanted in post-relapse CR or PR (Pein et al., 1998). It was reported that carboplatin, at a dose of 550 mg/m^2 every 3 weeks, as a single drug resulted in a response rate of 53% in children with relapsed WT (de Camargo et al., 1994). When the dose of chemotherapy is increased toxicities are invariably increased. Usually, hematopoietic toxicity is the major factor limiting the use of more dose-intensive chemotherapy regimens for children with recurrent/relapsed WT. The incidence of grade III/IV neutropenia was 81% for patients treated with ifosfamide/etoposide (ifosfamide at 2000 mg/m^2/day for 3 days, etoposide at 100 mg/m^2/day for 3 days) and the incidence of grade III/IV thrombocytopenia was 25.5% (Kung et al., 1993). Similarly, Miser et al. reported a high incidence of grade III/IV neutropenia (96% of cycles) following the ifosfamide/etoposide combination and a lower incidence of thrombocytopenia (20-30%) (Miser et al., 1987; Miser et al., 1993). The carboplatin/etoposide combination could result in a 92% incidence of grade III/IV neutropenia, and a higher incidence of grade IV thrombocytopenia when compared with ifosfamide/etoposide regimens (Pein et al., 1994). The combination of ICE therapy in pediatric patients is reported to bear a similar grade III/IV neutropenia (83-84%) as reported by both POG and CCG (Kung et al., 1993; Kung et al., 1995; Cairo et al., 2001). Grade III/IV thrombocytopenia was 59 and 84% in both POG and CCG study groups, respectively. Thus, consideration should be fully paid to the condition of patients.

In previous, it was identified that subgroups of relapsed WT patients with poor prognostic had features, e.g., unfavorable histology, abdominal recurrence with previous radiation therapy, advanced disease stage, early recurrence (<12 months) and previous three-drug therapy (Grundy et al., 1989). Recently Pein et al. reported the results of a multivariate analysis of eight adverse prognostic factors in children with relapsed WT and showed a significant effect on 3-year survival of unfavorable histology, early recurrence ≤6 months, multiple organ recurrence and lymph node involvement at recurrence (Pein et al., 1999). The use of ICE chemotherapy in previous study resulted in a high response rate of 82% with long-term overall and progression-free survival (63.6 ± 14.5%) of all the patients who attained a CR initially or subsequently, either following further chemotherapy, radiotherapy, or high-dose chemotherapy and PBSC transplantation. The dose-intensive therapy allows patients with high-risk disease and poor prognostic features to enter into a CR or a PR with the probability of further therapy with newer therapeutic agents and/or novel therapeutic approaches (i.e. high-dose chemotherapy followed by PBSC transplantation). Although both patients with unfavorable histology had a poor outcome a larger number of patients with unfavorable histology are needed to better evaluate the efficacy of ICE in this subgroup. In

comparison, Tannous et al. recently reported the results of an intergroup CCG and POG trial of a retrieval study in children with relapsed WT (Tannous et al., 2000). High-risk patients were treated with chemotherapy regimens containing carboplatin (1 gm/m^2)/etoposide (300 mg/m^2) and cyclophosphamide (2200 mg/m^2)/etoposide (500 mg/m^2) during induction and maintenance in addition to local radiotherapy and surgery. CR was seen in 42% of patients and PR in 36% following two cycles of induction therapy (overall response rate 78%). Patients in CR after surgery were treated with maintenance chemotherapy cycles of alternating cyclophosphamide/etoposide and carboplatin/etoposide. The reported event-free survival and survival in this group of patients was 59 and 64%, respectively. These results suggested that patients with different risk factors should be treated with different regimens.

Our study suggested that when carboplatin was used in combination with ifosfamide and etoposide, 2 studies included in this study are presented and the short-term outcomes suggested that the response rate of Abu-Ghosh et al. was 81.8%, of Kung et al. was 63%.Totally, 127 patients were enrolled and 82 patients achieved CR or PR, the pooled response rate thus was 64.5% (82/127) in carboplatin based regimens. Thrombocytopenia and leukocytopenia were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in carboplatin based treatment. Thus, we recommend that patients with low risk factors should be treated with single carboplatin or carboplatin combined with another agent, e.g., etoposide or ifosfamide; patients with high risk factors and good tolerability could be treated with carboplatin combined with other two agents.

In conclusion, this systemic analysis suggests that carboplatine based regimens are associated with reasonable response rate and accepted toxicities for treating pediatric patients with Wilms tumor.

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