Irinotecan Plus Doxorubicin Hydrochloride Liposome for Relapsed or Refractory Wilms Tumor

Lian Zhang[1], Juan Wang[2], Lanying Guo[3], Yi Que[1], Feifei Sun[1], Jia Zhu[2], Su-Ying Lu[1], Junting Huang[2], Wu Liuhong[1], Ruiqing Cai[2], Zijun Zhen[1], Yizhuo Zhang[1], and Xiaofei Sun[4]

[1]Sun Yat-sen University Cancer Center
[2]Sun Yet-Sen University Cancer Center
[3]Fifth Affiliated Hospital of Guangzhou Medical College
[4]Sun Yet-Sen University

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Abstract

Purpose: The prognosis of the relapsed or refractory Wilms tumor (R/R WT) was dismal and new salvage chemotherapy was needed. This study aimed to evaluate the efficacy of the combination of irinotecan and doxorubicin hydrochloride liposome regimen (AI) for R/R WT. Methods: The present study enrolled the R/R WT who were treated with AI regimen at Sun Yat-Sen University Cancer Center from July 2018 to September 2020. The response was defined as the best observed response after the last two cycle and toxicity was evaluated. Result: Total of 16 patients with median age of 4.2 years (0.5 to 11 years) were enrolled, including 14 patients with relapsed disease and 2 patients with refractory disease. These patients received 1 to 8 courses (median 3 courses).14 patients were assessable for response: 2 complete response (CR), 5 partial response (PR), 2 stable disease (SD), 5 progression disease (PD). The objective response rate was 50% (2 CR, 5 PR) and the disease control rate was 64% (2 CR, 5 PR, and 2 SD). The median progression-free survival was 3.5 months (range 0.5-12 months), and the median survival duration was 8 months (range 1-28 months). Sixteen patients were assessable for toxicity, with most common grade 3 or 4 adverse events were alopecia (62%), leucopenia (40%), abdominal pain (38%), etc. No fatal adverse events have been observed. Conclusion: The AI regimen has positive efficacy with tolerated toxicity, it may provide an alternative option for the treatment of R/R WT.

Introduction

Wilms tumor is an embryonal tumor accounts for 90% childhood renal tumor[1,2]. Medical advances have been greatly improved in the survival rate for the children diagnosed as Wilms tumor in the past decades and exceed over than 85%, but these advances have done nothing with the relapsed or refractory type, and the result is still dismal. Conventional surgery, radiation therapy, and chemotherapy, such as the combination of actinomycin-D and vincristine and/or doxorubicin, are generally used as a standard therapy for Wilms tumor[3-6]. The salvage regimes, such as the alternating cycle of ICE (ifosfamide, carboplatin, etoposide) and CyCE (cyclophosphamide, carboplatin, etoposide), combined with targeted radiotherapy, has effective but transient response for the treatment of relapsed or refractory Wilms' tumor[7]. Limited options are remained to be selected for these types of patients due to the toxicity and side effects on bone marrow, the cardiac function, impaired function of liver and kidney[8-10].

Irinotecan, a topoisomerase I inhibitor, is semisynthetic analogue of the camptothecin with modest toxicity on myelosuppression, controllable non-hematologic side effect, and powerful effectivity against the pediatric solid tumor both in xenograft model and patients[11-14]. A phase I study of irinotecan in pediatric patients

recommended that the dose of irinotecan in phase II study was administered as a 60-min iv. infusion daily for 5 days, every 21 days[15]. Irinotecan combined with other chemotherapy agents (such as vincristine, temozolomide, bevacizumab) has been reported in the clinical application of pediatric solid cancer, including a subset of patients with relapsed Wilms tumor (WT)[3,5,16-19]. Results of the Children's Oncology Group AREN0321 Study showed that the overall response rate (ORR) of the VI regimen (irinotecan combined with vincristine) treated for newly diagnosed diffuse anaplastic Wilms tumor (DAWT) was 79%[20]. For the relapsed or refractory nephroblastoma, several retrospective clinical studies showed that the irinotecan-containing regimens have positive clinical efficacy, with tolerable toxicity[19,21-23]. Doxorubicin hydrochloride liposome was a novel formulation of doxorubicin encapsulated in polyethylene glycol-coated liposomes and was designed to enhance the efficacy and reduce the dose-limiting toxicities of conventional doxorubicin[24]. Research showed that the ORR of doxorubicin hydrochloride liposome alone for pediatric sarcoma was 37.5%[25]. Irinotecan and doxorubicin hydrochloride liposome had low nephrotoxicity, cardiotoxicity, and hematologic toxicity. However, it is still unclear that if patients benefited from irinotecan- Doxorubicin Hydrochloride Liposome regimen in the relapsed or refractory setting. In this study, we describe response and toxicity to irinotecan-liposomal doxorubicin hydrochloride regimens in a collection of patients with relapsed or refractory WT.

Materials and methods

Patients

From July 2018 to September 2020, 16 pediatric patients with relapsed and refractory Wilms' tumor who received doxorubicin hydrochloride liposome plus irinotecan regimen treated at Sun Yat-Sen University Cancer Center were collected and included in the analysis. The inclusion criteria include the following: (1) Patients with relapsed and refractory Wilms' tumor aged [?] 18 years; (2) Doxorubicin Hydrochloride Liposome plus irinotecan chemotherapy regimen; (3) The presence of evaluable target lesions; (4) Complete clinical data. Exclusion criteria was that Patients who had previously received chemotherapy with doxorubicin-containing liposomes or irinotecan regimens.

This study was approved by the Sun Yat-Sen University Cancer Center Ethics Committee.

Treatment Schedule

The frontline treatment of WT was according to the NWTS-5 protocol. Patients with relapsed or refractory WT received AI regimen until disease progression, unacceptable toxicities or patient withdrawal, but no more than 8 courses, and were evaluated efficacy every 2 cycles. AI regimen included doxorubicin hydrochloride liposome (40mg/m^2 per day, D1) and irinotecan (50mg/m^2 per day with 90-min infusion, d1-5), repeated every 3 weeks. Doxorubicin hydrochloride liposomes should be given anti-allergic pretreatment (including cimetidine, dexamethasone, diphenhydramine or phenadryl) half an hour before; atropine should be given half an hour before irinotecan to prevent choline syndrome. Written informed consent was obtained from all patients when they began treatment for AI regimen.

Stage and Pathology

Clinical stage was based on COG staging system. Initial pathology was according to the COG protocol and classified into favorable histology (FH) group and unfavorable histology (UFH) group. The FH group were classified into four subtypes: mesenchymal, epithelial, blastemal predominant, and mixed. The UFH group included diffuse anaplasia and focal anaplasia.

Efficacy and toxicity evaluation

Response was defined as the best observed response after at least one cycle of Doxorubicin Hydrochloride Liposome plus irinotecan regimen. According to the RECIST (Response Evaluation Criteria of Solid Tumors) standard for efficacy evaluation, it is divided into: complete response (CR), partial response (PR), stable (SD) and progression (PD). Progression Free Survival (PFS) is defined as the time from the start of the Doxorubicin Hydrochloride Liposome plus irinotecan regimen to the progression of the disease or the time of the last

follow-up. Overall Survival (OS) is defined as the time from the start of the Doxorubicin Hydrochloride Liposome plus irinotecan regimen to death or the last follow-up.

Toxicity assessment is based on the Common Terminology Criteria for Adverse Events (CTCAE 4.03).

Statistical Analysis

The SPSS software version 22.0 (IBM, Chicago, IL) was used for statistical analysis, and Kaplan-Meier method was used to calculate overall survival rate and progression-free survival rate.

Result

Patient characteristics

Total of 16 patients (male: female, 8:8) diagnosed as Wilms tumor were enrolled in this study, including 14 patients with relapsed disease and 2 patients with refractory disease, with median age of 4.2 years (0.5 to 11 years) at relapsed or refractory disease and median time of 17.5months (7 to 108 months) between tumor diagnosis and relapse or refractory. Most of patients had advanced-stage disease at diagnosis (stage II: N = 4, stage III: N = 6, stage IV: N = 5), and one patient had bilateral disease at diagnosis. Histology of all the patients at diagnosis was classified as FH group. These patients received 1 to 8 courses (median 3 courses) of AI regimen. All the patients received pretreated with chemotherapy, 9 patients with 2^{nd} line and 5 patients with 3^{rd} or more lines of pretreated chemotherapy regimen. The accumulative doses of doxorubicin were $150/m^2$ to $400mg/m^2$ (median $250mg/m^2$) (Table 1).

Response

The duration from the initial treatment of AI regimen to subsequent PD was 0.5 to 12 months (median, 3.5months).

Prior to the treatment of AI regimen, the 16 enrolled patients had either progression at local site(N=2) or metastasis (N=9, all the metastasis sites were lung) or both of local site and metastasis (N=5). Following several courses of this regimen, 14 patients were assessable for response: 2 CR, 5 PR, 2 SD, 5 PD (Table 2). Overall, 7 out of 14 patients (50%) were alive at last follow-up, ranging from 2.6 to 32.4 months.

Both of two patients achieved CR were alive at last follow-up (Patient# 6 who reached CR after 6 courses of AI regimen showed tumor relapse after 5 months, then received other salvage chemotherapy including topotecan and cyclophosphamide, and alive with disease for 28.8 months at last follow-up; patient #12 achieved CR after 8 cycles of AI regimen and alive at last follow-up, showing no evidence of disease for 9.2 months). Of 5 patients achieved PR (received 4 to 6 courses of AI regimen), 4 patients achieved CR after further clinical management(patients #3 and patient# 5 received surgery and radiation of pulmonary lesions, patients#13 and patient #14 received whole lung radiation), and 1 patient (patient#8) achieved PR after 4 courses of AI regimen but PD after 6 courses and then received other salvage therapy. Both of two patients achieved SD (2 to 3 courses) changed to further salvage chemotherapy regimen but died of tumor progression at last follow-up. Of 5 patients reached PR after AI regimen, 3 patients alive without disease, 1 patient alive with disease and 1 patient died of disease at last follow-up. Both of two patients achieved SD after AI regimen died of disease at last follow-up. Of the five patients achieved PD, patient #7 were performed to remove of the lung lesions and then received radiation of the whole lung and alive at last follow-up for 3.7 months, the other four patients (patient#1, patient #9, patient #10, patient #11) died of disease progression at last follow-up.

The disease control rate (DCR) was 64% (2 CR, 5 PR, and 2 SD), and the objective response rate (ORR) was 50% (2 CR, 5 PR). The median progression-free survival was 3.5 months (range 0.5-12 months), and the median survival duration was 8 months (range 1-28 months) (Figure 1 and table 3).

Toxicity

Total of 16 patients were systemically assessed for the toxicities (Table 4). No fatal adverse events and renal toxicity have been observed, and modest adverse effect can be administered at outpatient service.

The commonly grade 3 or 4 toxicity-related events were diarrhea (23%), abdominal pain (38%), alopecia (62%), and leucopenia (40%). Grade 1 to 2 vomiting and nausea was easily administered. Generally, grade 3 or 4 diarrhea was manageable if the antidiarrhea medications were routinely used. In this study, 11 patients received Pegylated Recombinant Human Granulocyte Colony Stimulating Factor (PEG-rhG-CSF) for Injection and most patients had mild myelosuppression or febrile neutropenia. Modest hepatic (13%) and cardiac (7%) toxicity has been observed. Several nonspecific symptoms, including mucositis and fatigue, are occurred, and readily managed. None of the patients delayed chemotherapy because of the toxic and side effects of chemotherapy.

Discussion

In recent years, a number of retrospective studies have shown that irinotecan-containing regimens have a certain effect in recurrent Wilms tumor, but most of them are retrospective studies, the number of enrolled subject is small, and the combination of irinotecan and chemotherapy drugs is notuniform[19,21-23]。A SIOP retrospective study showed that 14 patients with evaluable relapsed Wilms tumor who received Irinotecan-containing regimens (including VCR, TMZ, bevacizumab, ect.) had an ORR of 21.4%, and the effective rate was not high[23]. Anthracyclines are effective chemotherapeutics for patients with Wilms' tumor. Concerns about the cardiotoxicity of anthracyclines have restricted the dose of anthracyclines. Studies revealed that doxorubicin-induced HF occurs in 3% to 5% with 400 mg/m^2[27].Cumulative doses of doxorubicin in patients with Wilms tumor in COG and SIOP studies were no more than 250 mg/m^2[20,28].Doxorubicin hydrochloride liposome is a novel formulation of doxorubicin encapsulated in polyethylene glycol-coated liposome and its PK are markedly different from those of doxorubicin. Study showed that patients exposed to relatively high cumulative doses, 540–840 mg/m^2, did not have evidence of acute congestive heart failure, which suggests that doxorubicin hydrochloride liposome might be less cardiotoxic than doxorubicin[29]. Doxorubicin hydrochloride liposome may become a potentially effective chemotherapeutic drug for children with relapsed and refractory Wilms tumor. Alternating the doxorubicin hydrochloride liposome to conventional anthracycline may improve the prognosis of the relapsed or refractory WT patients. Irinotecan combined with doxorubicin hydrochloride liposome may become an effective rescue chemotherapy for relapsed and refractory Wilms tumor. Study showed that the maximum tolerated dose of doxorubicin hydrochloride liposome administered every 4 weeks to pediatric patients was 60 mg/m^2 [25].According to our experience in doxorubicin hydrochloride liposome, in this study we accepted the regimen of doxorubicin hydrochloride liposome as 40mg /m^2 for 1 single day treatment.

In this study, among the 14 evaluable patients, 2 patients achieved CR and 5 achieved PR after AI regimen chemotherapy, and the ORR of the AI regimen was 50%, indicating that the AI regimen was effective for relapsed and refractory Wilms' tumor. However, the SIOP study showed that irinotecan-containing regimens had poor efficacy in relapsed Wilms tumor, with an ORR of 21.4%[23]. The curative effect of this study on patients with relapsed and refractory Wilms tumor is better than that of SIOP clinical research. The reason may be that the curative effect of irinotecan combined with doxorubicin hydrochloride liposome is better than other Irinotecan-containing regimens (such as VCR, TMZ, Bevacizumab, etc.).

The COG AREN0321 clinical study showed that irinotecan combined with VCR showed good efficacy in newly treated DA WT patients[20]. The SIOP clinical study enrolled 14 patients with evaluable efficacy, 8 patients were first relapse, and 9 patients had HR histological type, including 4 diffuse anaplasia (DA) WT and 5 blastemal type (BT). The ORR of IR and HR WT patients was 33.3% and 11.1%, respectively. The results of SIOP study indicate that the relapsed HR WT patients was not sensitive to the irinotecan-containing salvage regimens. In the present study, none of the patient was diagnosed as HR WT. If AI regimen is effective for HR WT need to be further explored.

In this study, 2 CR patients achieved longer survival after AI regimen chemotherapy; 4 out of 5 PR patients who achieved CR after further clinical management (surgery or radiotherapy) survived at the last follow-up, the response to the AI regimen can converted into survival benefit; 5 PD patients had poor survival, most of them were died within 2 years and needed to find a new therapeutic strategy.

In this study, the median number of treatment courses for patients receiving AI regimen was 3 (1 to 8 courses), and the median cumulative dose of doxorubicin hydrochloride liposome was 120 mg/m2 (40-240 mg/m2). 7 patients had mild abnormalities in the electrocardiogram, but none of the patients had severe cardiotoxicity (such as heart failure, arrhythmia, etc.). Because of the short follow-up time, long time was needed to follow up the long-term cardiotoxicity. In the study, most patients relapsed more than 2 times and received high-intensity chemotherapy in the past, and concerning that the AI regimen may cause severe bone marrow suppression, all patients were given long-acting granulocyte stimulating factor to prevent neutropenia. The most common grade 3 and 4 side effects observed in this study including alopecia (62%), leucopenia (40%), abdominal pain (38%), diarrhea (23%), Mucositis (16%). None of the patients delayed treatment due to toxicity. Studies have shown that the dose-limiting toxicity of doxorubicin hydrochloride liposome is mucositis. The incidence of mucositis in this study is not high, suggesting that doxorubicin hydrochloride liposome 40mg/m^2 is safe for relapsed and refractory Wilms tumor[25]. Whether increasing the dose of doxorubicin hydrochloride liposome can further improve the efficacy is worthy to explore.

Of note, this is the first time to report this therapeutic regimen to combine these two agents. In this study, we noted the adverse effect are commonly self-limited and easily controllable with routinely intervention, and this therapeutic regimen was generally continued without delayed therapy. Still, we acknowledge some limitations are existed. As a single-arm study, the comparison could not be performed because this study is lack of control group, it may arise selection bias as non-randomized design. Furthermore, limited sample sizes were enrolled in this study. However, all patients with manageable adverse effects could continue the therapeutic regimen without delay of therapy, and this study provided valuable experience for the treatment of relapsed or refractory Wilms' tumor.

In conclusion, the combination regimen of irinotecan and doxorubicin hydrochloride liposome indicates promising efficacy for relapsed or refractory WT patients with tolerable toxicities, especially for FH group WT. Prospective clinical trial is warranted.

Contributions

Lian Zhang, Juan Wang, Lanying Guo, Yizhuo Zhang and Xiaofei Sun designed the study, Lian Zhang, Juan Wang performed the analysis and drafted the manuscript; Yi Que, Feifei Sun, Jia Zhu, Suying Lu, Junting Huang, Liuhong Wu, Ruiqing Cai, Zijun Zhen revised the manuscript.

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Disclosure statement

The authors declare no conflicts of interest.

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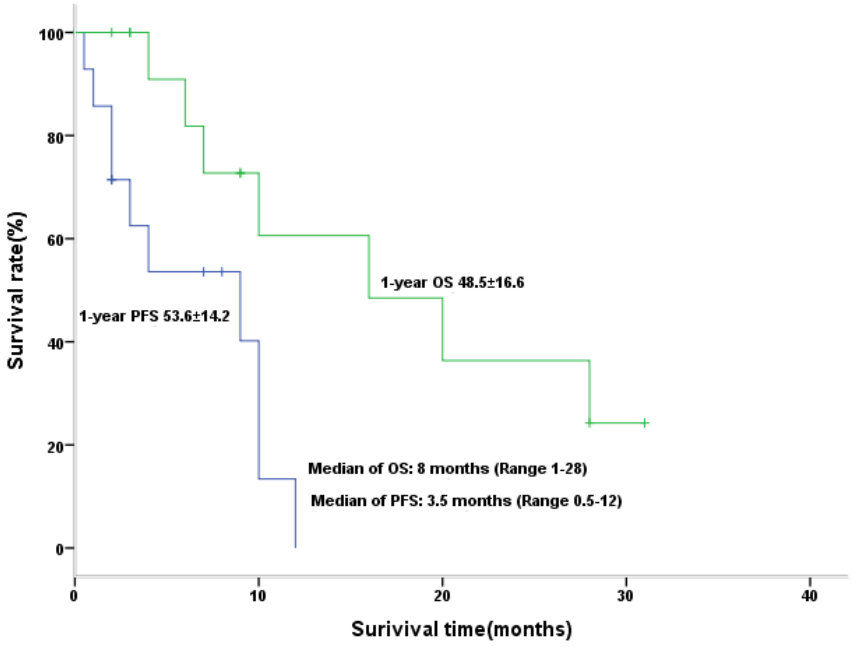
Figure legend

Figure 1 . Kaplan-Meier graph for progression-free survival and overall survival in patients with efficacy assessment (n=14)



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