Irinotecan for Relapsed Wilms Tumor in Pediatric Patients: SIOP Experience and Review of the Literature; A Report from the SIOP Renal Tumor Study Group (RTSG)

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Abbreviations key:

WT	Wilms tumor
HR	High-risk
IR	Intermediate-risk
CR	Complete response
PR	Partial response
SD	Stable disease
PD	Progressive disease
DA	Diffuse anaplasia
BT	Blastemal type
SIOP-RTSG	International Society of Pediatric Oncology - Renal Tumor Study Group

ABSTRACT

Background

While irinotecan has been studied in various pediatric solid tumors, its potential role in Wilms tumor (WT) is less clear. This retrospective descriptive study evaluates response and outcome of irinotecan treatment for different histological subtypes in relapsed WT.

Procedure

All participating countries were asked to identify patients with relapsed WT (0-18 years) who had been treated with irinotecan. Details on clinical characteristics, histological subtype, response, survival and toxicity were collected. A literature review was also performed.

Results

Sixteen patients were identified (median age 5 years, range 0-17) who had been treated with irinotecan, either as a single agent (N=1) or incorporated into multi-agent regimens (N=15). At initial diagnosis, the majority had advanced stage disease (stage III/ IV: N=11, stage V: N=1) and/or high-risk (HR) histology (HR diffuse anaplasia: N=4, HR blastemal-type: N=5). Among 14 evaluable patients, one complete response (CR) and two partial responses (PR) were observed in patients with initial intermediate-risk (IR) (CR and PR) and blastemal-type histology (PR). Two of the patients with CR/PR were still alive at last follow-up, both showing no evidence of disease. Among the 11 patients who had stable (N=4) or progressive (N=7) disease, one patient was alive after 22 months. Our results are consistent with previously published phase I/II studies on irinotecan in WT.

Conclusions

Some responses to irinotecan-containing regimens were registered in relapsed patients with initial IR or blastemal-type histology. Irinotecan may benefit a subset of patients with WT; however, more data are needed.

INTRODUCTION

Irinotecan has emerged as a promising agent in various pediatric solid tumors, especially for patients with relapsed, refractory or high-risk disease. This includes a subset of patients with relapsed Wilms tumor (WT) who have already received initial treatment with three or more drugs. For these patients survival rates range unsatisfactory between 10-50%, illustrating the need to explore novel agents like irinotecan.[1-3]

Irinotecan is a camptothecin compound which interferes with DNA replication and cell division. Its mechanism of action is similar to that of topotecan; by binding to the topoisomerase-I-DNA complex it prevents religation of cleaved DNA strands, ultimately leading to cell death. [4,5]

So far, no randomized studies on irinotecan have been performed in relapsed WT and limited information is available from preclinical and phase I/II studies. In the clinical setting, a protracted, lower-dose schedule is currently advised with daily administration of irinotecan for 5 consecutive days, with diarrhoea and abdominal pain as main dose-limiting toxicities.[4] Anti-tumor activity has been observed when irinotecan is used as a single agent or incorporated into various chemotherapeutic regimens.[6-20] Moreover, irinotecan combined with other chemotherapeutic agents is currently being studied in upfront treatment for metastatic diffuse anaplastic WT, a subset of patients with a poor prognosis.[20]

However, the benefits and harms of irinotecan in relapsed WT are still unclear and more data are needed to determine which patients may benefit from irinotecan treatment. In this study, we describe the response to irinotecan, either as a single agent or in combination chemotherapy, in patients with different histological subtypes of relapsed WT. We discuss these data in the context of a thorough literature review of all publications that assessed irinotecan for WT patients.

PATIENTS AND METHODS

Patients

The national coordinators of the International Society of Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) were asked to retrospectively identify children (0-18 years) in their countries, who had been diagnosed with relapsed WT and treated with irinotecan as part of their chemotherapeutic regimen. Local physicians reviewed the medical records for clinical characteristics, histology, stage at diagnosis, first-line treatment, number and type of relapse, salvage treatment schedule, toxicity, tumor response to irinotecan and outcome. Stage and histology at diagnosis were defined using SIOP criteria: high-risk (HR) tumors included those with diffuse anaplasia (DA) or blastemal-type (BT) histology after preoperative chemotherapy. Intermediate risk (IR) tumors were either stromal, epithelial, focal anaplasia, mixed or regressive histology.[21]

Definitions of response and toxicity

Irinotecan response was defined as the best observed response to irinotecan treatment and derived from the local centers' reports. The SIOP classifies response according to RECIST criteria as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD).[22] Response was evaluated through imaging studies based on respective volume change after at least one irinotecan-containing cycle. Toxicity data were retrieved from medical records and categorized into hematological, gastrointestinal, infection/febrile neutropenia or other, graded according to Common Terminology Criteria for Adverse Events (CTCAE).[23]

Literature search

A complete search of the Pubmed database was performed to identify all reports that describe pediatric WT patients treated with irinotecan, published until July 2016. Search criteria included synonyms for irinotecan, WT and pediatric. Reference lists were checked for missed articles.

RESULTS

Patient characteristics

Sixteen patients with relapsed WT treated with irinotecan either as a single agent or incorporated into different chemotherapeutic regimens between October 2004 and October 2015 were identified. Patient characteristics are depicted in **table 1**. Median age at relapse was five years (range 0-17 years), and median time between first tumor diagnosis and relapse was 10 months. Median follow-up after relapse was 10 months (range 2-26 months). The majority of patients had advanced-stage disease at diagnosis (stage I/II: N=4, stage III: N=4, stage IV: N=7). One patient had bilateral disease at diagnosis. Most relapses were metastatic (N=12), three patients presented with a local relapse and one patient had a combined local and metastatic relapse.

Histology at diagnosis was classified as IR in 7 patients and HR in 9 patients (HR-DA in four and HR-BT in 5 patients). In 9 cases, first-line treatment had consisted of a four-drug regimen containing cyclophosphamide/ifosfamide, carboplatin, etoposide and doxorubicin (CCED/ICED). Six patients had experienced multiple relapses; three patients had undergone prior high-dose chemotherapy with autologous stem cell rescue.

Irinotecan treatment

Most patients received five-day irinotecan cycles, with a median number of 2.5 cycles (range 1-12, number of cycles missing in 2 patients) (**table 2**). Dosing ranged between 11-50 mg/m^2/day (not reported in two patients). Only one patient received irinotecan as a single agent, while the others were treated with various irinotecan-containing regimens, including vincristine in 10 patients, temozolomide (with/without vincristine) in 5 patients and bevacizumab in two patients. For one patient, data on additional chemotherapy were missing.

In some patients, irinotecan was directly included in the relapse treatment, while in others it was started after alternative chemotherapeutic regimens had failed. Only one patient was recorded to have received a prior camptothecin (topotecan, patient #12 in table 2).

Response to irinotecan and survival

Response data were available for 14 patients. One patient reached complete response (CR) to irinotecan in combination with vincristine, partial response (PR) was demonstrated in two patients, stable disease (SD) in four patients and progressive disease (PD) in the remaining 7. Overall, three out of 14 patients were alive at last follow-up, ranging from 12 to 22 months, all without disease. Among the 11 patients who showed SD or PD, only one patient was alive without evidence of disease after 22 months.

Patients with IR-WT

The highest response rate was observed in patients with initial IR-histology (6 evaluable patients with 1 CR, 1 PR and 2 SD). Noteworthy, the two patients with CR/PR were both treated for their third relapse after initial stage II-III disease. The patient who reached CR had previously

received autologous stem cell rescue and was treated with an irinotecan-regimen (irinotecan dose 50mg/m^2/day) that contained vincristine. She was alive at last follow-up, showing no evidence of disease after 12 months. The patient with PR had received prior topotecan and received a similar dose of irinotecan, however combined with vincristine, temozolomide and bevacuzimab. After reaching PR, this patient developed PD and died of disease after 11 months. One of the patients with SD had an inactive rest lesion after local radiation therapy and high dose chemotherapy with autologous stem cell transplantation, and was alive without disease at last follow-up at 22 months.

Patients with HR-blastemal type WT

For four patients with HR-blastemal type histology response data were available. One reached PR after irinotecan, one had SD and the other two patients showed PD. The patient with PR was treated for a second relapse after initial stage III disease. She received vincristine and temozolomide in addition to irinotecan (irinotecan dose 50mg/m^2/day). After reaching PR, she underwent surgical resection of residual metastatic lung lesions and was alive showing no evidence of disease at 21 months.

Patients with HR-diffuse anaplasia WT

After treatment with irinotecan, only SD (N=1) or PD (N=3) was observed in the 4 patients with initial HR-diffuse anaplasia. All 4 patients died of disease within 10 months.

Toxicity

Data on toxicity were available for 10 patients. Hematological toxicity was reported in 5 patients (grade 3: N=4, grade 2: N=1). One patient had to discontinue irinotecan therapy after two cycles due to grade 4 febrile neutropenia with ICU admission. Four patients had gastrointestinal toxicity (grade 2 or 3). No toxicity-related deaths were reported and three patients experienced no toxicity at all.

Literature review

A Pubmed search retrieved 14 articles describing the administration of irinotecan to pediatric patients with WT, including phase I and II (pilot) trials, retrospective chart reviews and case series, summarized in **table 3**. No randomized trials were found.

Different irinotecan dosages and schedules of administration were used: irinotecan as a single agent in 5 studies [7,8,10,11,15], combined with temozolomide in 5 studies [9,14,16,18,19], with vincristine in 5 studies [14,18-20,24] and other combinations including carboplatin [12], cetuximab [13] or bevacizumab [18,19].

So far, three other studies have reported complete or partial responses to irinotecan in small numbers of patients with relapsed or refractory WT [10,16,19]. Only one of these studies specified stage and histology, retrospectively describing four patients with relapse after initial stage II-V favorable histology WT. Response to irinotecan, combined with vincristine, temozolomide and bevacuzimab, was observed in all four patients (CR: N=2, PR: N=2).[19]

A recent abstract by Daw et al., presented at the American Society of Clinical Oncology meeting, described 14 patients with newly diagnosed metastatic diffuse anaplastic WT, prospectively

treated with irinotecan and vincristine in a phase II trial.[20] In this setting, a partial response was observed in eleven patients (79%).

DISCUSSION

This multi-center retrospective descriptive study found that irinotecan can induce SD or PR in some patients with relapsed WT. This indicates that irinotecan may benefit a subset of WT patients. All responses were observed in patients with IR or HR-BT histology, but not in the four patients with HR-DA tumors. In addition, SD was observed in four patients (1 HR-DA, 1 HR-BT and 2 IR).

Currently, standard approaches for relapsed WT include cyclophosphamide, carboplatin, etoposide and doxorubicin for most patients, with/without ifosfamide, depending on prior treatment and initial tumor stage and histology.[1] A general principle in the treatment of recurrent WT is to add agents that have not been used in upfront treatment regimens, with the aim to reach PR and facilitate complete surgical resection or resolution of lesions after radiotherapy. For patients with initial HR-DA or HR-BT histology, or patients showing no response to salvage treatment, alternative therapies such as camptothecins are considered.[1,2,25]

Irinotecan has shown variable response rates in the heterogeneous group of studies that describe its use in pediatric solid tumors, including WT, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, osteosarcoma, hepatoblastoma and CNS tumors. These were mainly phase I and II studies and therefore aimed at dose-finding and toxicity. Since the first study by Furman et

al. in 1999, reported efficacy of irinotecan as a single agent has ranged from no response to response rates above 30%.[7,10,11,26-30] In our study, the majority of patients received irinotecan in combination with other chemotherapeutic drugs. Xenograft studies have shown that camptothecins can synergize with microtubule inhibitors such as vincristine, enhancing anti-tumor activity.[31] Clinical studies seem to support the theory that irinotecan is more effective when combined with other chemotherapeutic drugs like vincristine, temozolomide or bevacizumab, describing response rates up to 70% when these combinations are used.[9,13,17,32-35]

Only three other studies, aside from ours, have described complete or partial responses to irinotecan in small numbers of patients with relapsed or refractory WT.[10,16,19] Noteworthy, none of these studies were randomized and in some of the studies response may have been due to other agents that irinotecan was combined with. Moreover, none of these studies have compared irinotecan response in different histological subtypes of WT.

The only prospective study evaluating a camptothecin for relapsed WT is a phase II topotecan trial by Metzger et al., showing a 48% objective response rate (PR in 12/25 patients) to topotecan in multiply relapsed favorable histology WT and less responses in relapsed anaplastic WT (2/11 PR).[36] Similarly, a retrospective report on topotecan by Mavinkurve et al. observed more responses in patients with IR histology (2/14 CR, 1/14 PR) compared to those with HR histology (2/16 PR).[5] Remarkably, Daw et al. describe a response rate of 79% in DA-WT treated with irinotecan/vincristine in a window phase trial in newly diagnosed tumors, while in our study with relapsed patients, stable disease was the best observed response in DA-WT.[20] Preclinical studies have suggested that DA-WT can respond to irinotecan treatment.[6] We hypothesize that the lack

of response in DA-WT patients in our study may be due to a clonal evolution towards more resistant disease in the relapsed setting, however, the small number of treated patients does not allow for strong conclusions.

Irinotecan-related toxicity appears to be acceptable. In our study, grade 2-3 gastrointestinal and hematological toxicity were the most frequently reported, with only one case of grade 4 infection/febrile neutropenia requiring ICU admission. This is in line with previously published phase I and II trials on irinotecan in pediatric patients. In these studies, toxicity was generally well documented and neutropenia and diarrhoea were consistently reported as the most common toxicities, in most cases grade 1 or 2, with occasional cases of grade 3-4 toxicity.[7-19] Furthermore, cephalosporin prophylaxis has been described to effectively reduce irinotecan-associated diarrhoea in children.[37]

In conclusion, this study aimed to collect more data on the efficacy of irinotecan in the setting of recurrent WT, as we are aware of a progressive wider use of this drug outside controlled clinical trials or protocols. Our results, as well as the reviewed literature, suggest that irinotecan may contribute to survival in a subset of WT patients, showing some responses in relapsed patients with IR an HR-BT histology. Prospective data on irinotecan are warranted, as will be collected in the upcoming UMBRELLA SIOP-RTSG 2016 protocol in which irinotecan is advised for relapsed HR-WT patients who have failed treatment with more conventional drugs. Furthermore, studies on the use of irinotecan in upfront cases, rather than in the relapsed setting, are of interest since they may show higher response rates.

CONFLICT OF INTEREST STATEMENT

None declared.

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