

**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.

1 **INTRODUCTION**

2

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

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

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

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

24 **PATIENTS AND METHODS**

25

26 **Patients**

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

37

38 **Definitions of response and toxicity**

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

46

47 **Literature search**

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

51

52 **RESULTS**

53

54 **Patient characteristics**

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

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

68

69

70 **Irinotecan treatment**

71 Most patients received five-day irinotecan cycles, with a median number of 2.5 cycles (range 1-  
72 12, number of cycles missing in 2 patients) (**table 2**). Dosing ranged between 11-50 mg/m<sup>2</sup>/day  
73 (not reported in two patients). Only one patient received irinotecan as a single agent, while the  
74 others were treated with various irinotecan-containing regimens, including vincristine in 10  
75 patients, temozolomide (with/without vincristine) in 5 patients and bevacizumab in two patients.  
76 For one patient, data on additional chemotherapy were missing.

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

80

81 **Response to irinotecan and survival**

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

88

89 *Patients with IR-WT*

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

93 received autologous stem cell rescue and was treated with an irinotecan-regimen (irinotecan dose  
94 50mg/m<sup>2</sup>/day) that contained vincristine. She was alive at last follow-up, showing no evidence of  
95 disease after 12 months. The patient with PR had received prior topotecan and received a similar  
96 dose of irinotecan, however combined with vincristine, temozolomide and bevacuzimab. After  
97 reaching PR, this patient developed PD and died of disease after 11 months. One of the patients  
98 with SD had an inactive rest lesion after local radiation therapy and high dose chemotherapy  
99 with autologous stem cell transplantation, and was alive without disease at last follow-up at 22  
100 months.

101

102 *Patients with HR-blastemal type WT*

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

109

110 *Patients with HR-diffuse anaplasia WT*

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

113

114

115

116 **Toxicity**

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

122  
123 **Literature review**

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

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

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

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

138 treated with irinotecan and vincristine in a phase II trial.<sup>20</sup> In this setting, a partial response was  
139 observed in eleven patients (79%).

140

## 141 **DISCUSSION**

142

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

148

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

156

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

161 al. in 1999, reported efficacy of irinotecan as a single agent has ranged from no response to  
162 response rates above 30%.<sup>7,10,11,26-30</sup> In our study, the majority of patients received irinotecan in  
163 combination with other chemotherapeutic drugs. Xenograft studies have shown that  
164 camptothecins can synergize with microtubule inhibitors such as vincristine, enhancing anti-  
165 tumor activity.<sup>31</sup> Clinical studies seem to support the theory that irinotecan is more effective  
166 when combined with other chemotherapeutic drugs like vincristine, temozolomide or  
167 bevacizumab, describing response rates up to 70% when these combinations are used.<sup>9,13,17,32-35</sup>  
168  
169 Only three other studies, aside from ours, have described complete or partial responses to  
170 irinotecan in small numbers of patients with relapsed or refractory WT.<sup>10,16,19</sup> Noteworthy, none  
171 of these studies were randomized and in some of the studies response may have been due to  
172 other agents that irinotecan was combined with. Moreover, none of these studies have compared  
173 irinotecan response in different histological subtypes of WT.

174  
175 The only prospective study evaluating a camptothecin for relapsed WT is a phase II topotecan  
176 trial by Metzger et al., showing a 48% objective response rate (PR in 12/25 patients) to topotecan  
177 in multiply relapsed favorable histology WT and less responses in relapsed anaplastic WT (2/11  
178 PR).<sup>36</sup> Similarly, a retrospective report on topotecan by Mavinkurve et al. observed more  
179 responses in patients with IR histology (2/14 CR, 1/14 PR) compared to those with HR histology  
180 (2/16 PR).<sup>5</sup> Remarkably, Daw et al. describe a response rate of 79% in DA-WT treated with  
181 irinotecan/vincristine in a window phase trial in newly diagnosed tumors, while in our study with  
182 relapsed patients, stable disease was the best observed response in DA-WT.<sup>20</sup> Preclinical studies  
183 have suggested that DA-WT can respond to irinotecan treatment.<sup>6</sup> We hypothesize that the lack

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

187  
188 Irinotecan-related toxicity appears to be acceptable. In our study, grade 2-3 gastrointestinal and  
189 hematological toxicity were the most frequently reported, with only one case of grade 4  
190 infection/febrile neutropenia requiring ICU admission. This is in line with previously published  
191 phase I and II trials on irinotecan in pediatric patients. In these studies, toxicity was generally  
192 well documented and neutropenia and diarrhoea were consistently reported as the most common  
193 toxicities, in most cases grade 1 or 2, with occasional cases of grade 3-4 toxicity.<sup>7-19</sup>  
194 Furthermore, cephalosporin prophylaxis has been described to effectively reduce irinotecan-  
195 associated diarrhoea in children.<sup>37</sup>

196  
197 In conclusion, this study aimed to collect more data on the efficacy of irinotecan in the setting of  
198 recurrent WT, as we are aware of a progressive wider use of this drug outside controlled clinical  
199 trials or protocols. Our results, as well as the reviewed literature, suggest that irinotecan may  
200 contribute to survival in a subset of WT patients, showing some responses in relapsed patients  
201 with IR an HR-BT histology. Prospective data on irinotecan are warranted, as will be collected in  
202 the upcoming UMBRELLA SIOP-RTSG 2016 protocol in which irinotecan is advised for  
203 relapsed HR-WT patients who have failed treatment with more conventional drugs. Furthermore,  
204 studies on the use of irinotecan in upfront cases, rather than in the relapsed setting, are of interest  
205 since they may show higher response rates.

## CONFLICT OF INTEREST STATEMENT

None declared.

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