Irinotecan dose schedule for the treatment of Ewing sarcoma

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Abstract

Background: Irinotecan and temozolmide achieve objective responses in patients with Ewing sarcoma which recurrences after initial therapy. Optional dose schedules have not been defined. Procedure: We reviewed published series of patients treated with irinotecan and temozolomide for Ewing sarcoma which recurred after initial therapy. We compared objective response rates for patients who received 5 day irinotecan treatment schedules to response rates for patients who achieved 10 day irinotecan treatment schedules. Results: Among 94 patients treated with a 10 day irinotecan schedule there were 48 objective responses (51%). Among 218 patients treated with a 5 day irinotecan schedule there were 65 responses (30%). Conclusion: When we use irinotecan to treat Ewing sarcoma we should administer 10 days of treatment.

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The combination of irinotecan and temozolomide has demonstrated activity in the treatment of recurrent Ewing sarcoma. The initial preclinical development of this combination therapy was carried out at the St. Jude Children's Research Hospital (SJCRH). The investigators examined a variety of doses and dose schedules for the two agents.[1] They reported that schedules which called for 10 days of irinotecan demonstrated greater activity than schedules which utilized shorter durations of administration. Investigators from SJCRH reported the results of a phase I evaluation of irinotecan and temozolomide.[2] This manuscript included a statement confirming their evaluation of alternative schedules: "Among all the schedules investigated, the schedule of daily administration for five consecutive days for two consecutive weeks [(qd $\cdot$ 5) $\cdot$ 2] has shown to be the most effective one".

European investigators have performed a prospective trial of four chemotherapy regimens for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES).[3] The rEECur trial was designed as a "pick the winner" strategy to compare four systemic therapy regimens: high dose ifosfamide, cyclophosphamide/topotecan, irinotecan/temozolomide, and gemcitabine/docetaxel. At the time of the second interim analysis, the investigators concluded that the combination of irinotecan and temozolomide was inferior to two of the other regimens. The study design called for the administration of irinotecan for five days in each cycle in combination with temozolomide.

There are multiple reports of the clinical efficacy of irinotecan and temozolomide in the treatment of recurrent Ewing sarcoma (Table 1).[3-15] The majority of these reports are retrospective analyses of clinical experience. Of the 12 published reports only 4 were prospective phase 1 trials. The Salah study is difficult to analyze.[15] 53 patients participated in the study but only 43 were evaluable for objective response. Of the 53 patients, 47 received irinotecan in a 5 day schedule and 6 received irinotecan in a 10 day schedule. The authors did not report the breakdown of responses by treatment regimen. For the purpose of analysis an arbitrary assignment of responses was made by assigning responses in proportionately to the use of regimens. Of 12 objective responses observed in 43 evaluable patients, for the purpose of the analysis one of 5 who received the 10 day schedule was assumed to have achieved an objective response and 11 0f 38 patients who received the 5 days schedule were assumed to have achieved an objective response. The Kurucu study reported an overall objective response rate of 55% (11 of 20 patients) but did not break down responses as CR or PR.[12]

The majority of patients in these reports were accrued in the context of retrospective reviews. In prospective clinical trials the timing of follow up evaluations is prespecified. The lack of prespecified follow up in retrospective reviews makes comparison of event free or progression free survival problematic. This is less of a problem for the evaluation of objective responses. All of the reports utilized objective response as the primary study outcome and objective response rate is the basis of the present analysis.

The Children's Oncology Group performed a prospective randomized trial comparing a 5 day and a 10 day irinotecan schedule and observed no difference between the two treatment regimens,[16] This report does not conflict with the present analysis for two reasons. First, that study was limited to patients with rhabdomyosarcoma and cannot be assumed to be relevant to the treatment of Ewing sarcoma. Second, that study utilized vincristine and irinotecan; no temozolomide was administered with the irinotecan in that study.

Despite these limitations, the number of reported patients is large. In aggregate there were 312 patients. Among them there were 111 patients with objective responses. The response rates reported with a 10 day irinotecan schedule were higher than those reported with a 5 day irinotecan schedule. Among 94 patients

treated with a 10 day irinotecan schedule there were 48 objective responses (51%)(Table 2). Among 218 patients treated with a 5 day irinotecan schedule there were 65 responses (30%).

Since 2013 we have conducted a prospective phase II clinical trial evaluating the addition of cycles of irinotecan and temozolomide added to cycles of cyclophosphamide, doxorubicin and vincristine and cycles of ifosfamide and etoposide for the treatment of newly diagnosed Ewing sarcoma (NCI NCT01864109). All cycles administer irinotecan 20 mg/m2/day x 10 days and temozolomide 100 mg/m2/day x 5 days. Protocol guidelines specify the administration of a second generation cephalosporin beginning two days prior to administration of irinotecan and continuing through the cycle.[17] Guidelines also specify administration of activated charcoal on each day of administration of irinotecan. Adverse events are recorded by research nurses at the completion of each cycle of therapy. As of May, 2022, we have administered 384 cycles of this combination. We have observed the following frequency of adverse events grade 3 or higher: febrile neutropenia 0%, vomiting <1%, diarrhea <1%. This compares favorably to the frequency of adverse events grade 3 or higher reported for the irinotecan temozolomide arm of the ReECur study: febrile neutropenia 8%, vomiting 10%, diarrhea 24%.

These data suggest that, in the absence of definitive evidence that shorter schedules of irinotecan are as effective as longer schedules, when we employ irinotecan in the treatment of Ewing sarcoma we should utilize the longer administration schedule. It suggests that the investigators of the rEECur trial might consider an additional comparison arm utilizing a 10 day irinotecan schedule for patients with recurrent/refractory Ewing sarcoma.

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