Irinotecan in infants with MLL-rearranged relapsed or refractory acute lymphoblastic leukemia

Treatment Guideline

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Rationale

Infant ALL
Acute Lymphoblastic Leukemia (ALL) in infants (<1 year of age) remains one of the most aggressive types of childhood leukemia. The majority (~80%) of these patients carry leukemia-specific chromosomal translocations involving the MLL (or KMT2A) gene, which confer highly dismal prognoses with disease-free survival chances of only 30-40%.(1) Relapses occur early, 90% of all events will occur in the first 2 years after diagnosis in infant ALL, and survival after relapse is only 20%.(2) As current combination chemotherapeutic regimens fail to provoke favourable treatment outcomes, more adequate therapeutic strategies are urgently needed.

In vitro and in vivo studies of irinotecan in ALL
To expedite clinical transition of potentially effective therapeutics, we performed drug library screens, in order to identify promising agents effectively targeting MLL-rearranged infant ALL cells. This study revealed that the topoisomerase I inhibitor irinotecan highly efficiently eliminates MLL-rearranged infant ALL cells at extremely low nanomolar concentrations.(3) Subsequently we used xenograft mouse models of human MLL-rearranged infant ALL to assess the efficacy of Irinotecan against MLL-rearranged infant ALL in vivo. These studies demonstrated that Irinotecan completely blocks leukemia expansion and disease progression, and even induces complete remissions in mice with advanced stages of leukemia.(3)

In the PDx mouse model a dose of 40 mg/kg was used every second day. The response in the mouse models was shown after 2 weeks.

Irinotecan in pediatric cancers
Irinotecan is registered as single agent and combination therapy for the treatment of adult patients with advanced colorectal carcinoma. It has been used off-label in the treatment of solid tumours(4, 5) and brain tumours in children.(6) The COG used intensive multiagent therapy, including irinotecan in patients with rhabdomyosarcoma (5) Irinotecan is also used in the current relapsed rhabdomyosarcoma protocol (VIT-0910; ITCC025 study) in combination with vincristine + temozolomide. Both protocols included children < 1 year of age. Irinotecan is also used in children with recurrent low-grade glioma’s in combination with bevacizumab.(6) In conclusion, irinotecan has been used in pediatric solid and brain tumours, but not yet in infant ALL.

Toxicity of irinotecan
The intensity of the major toxicities of irinotecan (myelosuppression and diarrhea) are related to the exposure (AUC) to parent drug and metabolite SN-38. The most common non-hematologic grade 3 or higher toxicity is diarrhea (up to 20% of irinotecan-containing courses in the COG study). Two distinct patterns of diarrhea have been associated with irinotecan. First, early-onset diarrhea typically occurs within 4 hour of administration, and is associated with the “cholinergic syndrome”. It is readily reversible with atropine administration, and has not been dose-limiting. In contrast, late-onset diarrhea usually develops during the second week of therapy, and can be dose-limiting regardless of the irinotecan schedule. Cephalosporin prophylaxis is a safe and feasible way to help optimize use of irinotecan in children, and can improve both dose intensity and drug exposure.

Pharmacokinetics of irinotecan
Irinotecan must be converted by a carboxylesterase enzyme to the active metabolite SN-38 and is deactivated by Uridine diphosphate-Glucuronosyl Transferase 1A1 (UGT1A1) to inactive SN-38 glucuronide (SN-38G). Those who are homozygous for the UGT1A1*28 allele (Gilbert’s syndrome) are
at increased risk of haematological toxicity (grades 3 and 4), but have no increased risk of diarrhea. These patients should be administered the normally indicated irinotecan starting dose. More than 50% of an intravenously administered dose of irinotecan is excreted as unchanged drug, with 33% in the faeces mainly via the bile and 22% in urine.

The metabolic pathway is complex and include carboxylesterase, cytochrome P450 enzymes and glucuronosyl transferases:
- Hydrolysis by carboxylesterase into the active metabolite SN-38. SN-38 is mainly eliminated by glucuronidation (UGT1A1), and further by biliary and renal excretion. The SN-38 glucuronide is subsequently probably hydrolysed in the intestine.
- Cytochrome P450 3A enzymes-dependent oxidations resulting inactive APC (aminopentanoic acid derivate) and NPC (primary amine derivate).

Unchanged irinotecan is the major entity in plasma, followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity.

Figure 1. Metabolism of irinotecan. CES carboxylesterase, UGT 1A1 UDP-glucuronosyltransferase, CYP3A4 cytochrome P450 3A4 isozyme , APC 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxycamptothecin, NPC 7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin, SN-38 7-ethyl-10-hydroxy camptothecin, SN-38G glucuronidated SN-38.

Concomitant administration of irinotecan with a strong inhibitor (e.g. Ketoconazole) or inducer (e.g. Rifampicin, Carbamazepine, Phenobarbital, Phenytoin, St John's wort) of Cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided. Irinotecan clearance is decreased in patients with hyperbilirubinemia.

During the postnatal period, activity levels of CYP3A4 increase and reaches 30-40% of the adult levels by 1 months of age and adult levels by 1 year. UGT enzyme activity achieve 25% of the adult levels at 3 months, and adult levels by 6-30 months. Although the clinical relevance of this development in infants remains unclear.(7)

Because only relapsed/refractory patients will be treated, we expect most patients to be older than 1 year of age at time of relapse or refractory disease.

Evidently, this pre-clinical evidence clearly warrants use of Irinotecan in a clinical setting, in which irinotecan will be administered in a window prior to any (induction) treatment in R/R infant ALL.
**Patients**

Patients with 1\textsuperscript{st} relapse after hSCT or ≥ 2\textsuperscript{nd} relapsed or refractory MLL-rearranged infant ALL. Because patients should be diagnosed with relapsed or refractory infant ALL, patients might be older than 1 year of age at inclusion.

**Treatment**

![Treatment schedule](image)

Figure 2. Treatment schedule with a window period (green) prior to R/R therapy. The window can take 1-3 weeks depending on response.

Irinotecan is added as single agent, administered as a 1 daily infusion for 5 days (50 mg/m2/d, in 1 hr IV, day 1-5) in a window prior to any (induction) treatment.

**Dose adjustments** according to age are made as in the Interfant-06 protocol because of differences in drug metabolism in the first year of age. Children <6 months of age receive 2/3 of the calculated dose, 6-12 months of age: 3/4 of the calculated dose and children >12 months of age: full dose.

A second course of irinotecan can be considered in case of an adequate response with acceptable toxicity after the first course (figure 3). This course should start 3 weeks after the first dose of irinotecan. The same dosing schedule can be used.

**Response assessment**

At day 8 the response is assessed measured by absolute leukemic blast counts in peripheral blood. In case that a patient has stable or reduced blasts counts on day 8, one can wait another week for a second response assessment at day 15. This can be repeated for another week, with a response assessment at day 22. In case of progressive disease the patient should switch therapy at physician’s discretion.
Response is measured as absolute leukemic blast counts in peripheral blood (morphology and flowcytometry):

1. CR: Complete response (in peripheral blood): no leukemic blasts
2. PR: Partial response: any decrease in leukemic blasts, but leukemic blasts positive
3. SD: Stable disease: leukemic blast number stabilized
4. PD: Progressive disease: leukemic blasts increase

Response and Toxicity assessments

Prior to start of irinotecan (= day 1):
1. Blood counts and WBC differential (morphology and flowcytometry)
2. AST, AST, bilirubin(total and direct), GGT, urea, creatinine, sodium, potassium
3. Consider starting cephalosphorin as diarrhea prophylaxis (see supportive care)

During irinotecan(day 2-5):
1. Daily: Blood counts
2. Day 4: WBC differential
3. Day 4: AST, AST, bilirubin(total and direct), GGT, urea, creatinine, sodium, potassium
4. Tumorlysis lab according to institutional guidelines

Day 8
1. Response: Blood counts and WBC differential (morphology and flowcytometry) (blood counts and differentials twice weekly)
2. AST, AST, bilirubin(total and direct), GGT, urea, creatinine, sodium, potassium
Day 15 and 22

1. Response day 15 and day 22: Blood counts and WBC differential (morphology and flowcytometry)
   (blood counts and differentials twice weekly)
2. AST, AST, bilirubin (total and direct), GGT, urea, creatinine, sodium, potassium

Supportive care
Supportive care measures e.g. anti-emetics, tumor lysis syndrome, transfusions, infections and diarrhea will be implemented according to institutional guidelines. Diarrhea prophylaxes and treatment is described more extensively, but can also be implemented according to institutional guidelines as well.

Diarrhea
Prophylaxis: In the absence of any contraindications (ie known allergies), treatment with oral cefixime 8 mg/kg once a day as diarrhea prophylaxis is recommended and can be used until day 7. Also ceftibuten (Cedax) suspension (180 mg/5 ml), an oral third generation cephalosporin can be used, till 21 days after start of irinotecan (10 mg/kg/day in 2 doses).

Treatment
Patients with onset of diarrhea during the irinotecan infusion or during the first 8 hours following the completion of infusion should receive a dose of atropine 0.01-0.02 mg/kg IV. Early onset diarrhea is usually preceded by cholinergic symptoms like diaphoresis, flushing and abdominal cramping. Systematic prophylaxis is not recommended at the first cycle but is left to the physician’s judgment.

At the first sign of diarrhea starting > 8 hours after irinotecan administration, patients should begin intensive loperamide therapy. Each patient’s parent or legal guardian should be instructed to have anti-diarrheal medication readily available and begin treatment for diarrhea at the first episode of poorly formed or loose stools or earliest onset of bowel movements more frequent than normally expected for the patient. In addition, patients and family members should be instructed to contact their physician if any diarrhea occurs. Loperamide should be continued until a normal pattern of bowel movements returns.
Dehydration should be prevented and fluid and electrolytes intake should be guaranteed during the diarrhea episode.

Concomitant therapy
Concomitant administration of Irinotecan with an inhibitor (eg ketoconazole, itraconazole) or inducer (eg rifampicin, carbamazepine, phenobarbital, phenytoin, and St John’s wort) of the CYP 3A4 metabolic pathway may alter the metabolism of Irinotecan and should be avoided.
References