# New method of immunotherapy delivery lowers pain in children with high-risk neuroblastoma

September 17 2015

In children with high-risk relapsed/refractory neuroblastoma, long-term infusion (LTI) of the antibody ch14.18/CHO (dinutuximab-beta; the European counterpart of dinutuximab) in combination with other drugs lowered neuropathic pain, a major side effect encountered with the current standard mode of short-term infusion (STI) of the drug, according to data from a phase I/II clinical trial presented at the CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference, held Sept. 16–19.

"Neuroblastoma is a childhood cancer with one of the highest death rates," said Holger N. Lode, MD, PhD, professor and chair of pediatrics at University Medicine Greifswald in Germany. "Treatment with an FDA-approved, neuroblastoma-specific monoclonal antibody, ch14.18, in combination with interleukin-2 and 13-cis-retinoic acid [13-cis-RA] has shown benefit for patients with this disease in the United States.

"In Europe, ch14.18 was remanufactured using CHO cells commissioned by SIOPEN, funded by European charities, and further developed by Apeiron Biologics. Dinutuximab-beta was first evaluated for safety in a phase I study, which confirmed the tolerability and showed activity when given as STI with a dosing regimen of 20 mg/m2 given by eight-hour infusions on five consecutive days; however, it is associated with severe neuropathic pain," Lode said.

The ch14.18 antibody targets GD2, which is a molecule abundantly expressed on neuroblastoma with limited to no expression on most healthy tissues except nerve fibers that signal pain. As a result, treatment with ch14.18 antibody is associated with induction of neuropathic pain, a significant side effect in these patients, Lode explained.

"A high amount of intravenous morphine is required to make STI tolerable for patients. Further, the rate of inflammatory side effects observed is substantial. We hypothesized that significant prolongation of the time of antibody infusion [LTI] will improve tolerability of the antibody while maintaining clinical activity and efficacy in high-risk neuroblastoma patients," Lode said.

"In our study, by changing the method of antibody delivery from STI to LTI, we observed an impressive reduction of on-target [pain] and off-target [inflammation] side effects, while maintaining effective drug levels over the entire treatment period, as assessed in a variety of bioassays, demonstrating the immune-modulatory effect of ch14.18/CHO and its potency to mediate destruction of neuroblastoma cells constantly over a period of six months," Lode said.

In two clinical trials, an ongoing SIOPEN phase II study (APN311-202) and a closed single-center program (APN311-303), Lode and colleagues enrolled 44 patients and 53 patients, respectively, with high-risk relapsed/refractory neuroblastoma. Patients received a total dose of 100 mg/m2 of ch14.18/CHO per cycle given as LTI continuously over 10 consecutive days. Five cycles were given in five-week intervals, and all patients also received interleukin-2 and oral 13-cis-RA.

The investigators evaluated treatment-related pain by three-time daily assessment of validated age-adapted pain scoring systems by parents and/or the medical team, and daily use of intravenous morphine was recorded for each patient in each cycle. The investigators compared their

observations of pain and adverse events from the LTI studies with the previously published data on neuroblastoma patients treated with STI of dinutuximab. Overall survival (OS) and progression-free survival (PFS) data from this study were compared with previously reported historical gold standard, which is a compilation of clinical trial data from comparable patients treated with modern-era front-line and relapse therapy.

Analysis of pain assessment scores and use of intravenous morphine indicated that LTI of ch14.18/CHO was associated with lowered pain, compared with data previously reported for children treated with STI. The investigators also observed lower frequencies of grade 3 or higher adverse events in the LTI group compared with the STI group, except for equal frequencies in vomiting, according to Lode.

After following the patients for a median of 2.9 years, one-year and four-year OS rates for patients treated with LTI in the SIOPEN cohort were about 94 percent and 61 percent, respectively, compared with about 56 percent and 14 percent, respectively, for those from the previous report.

After following the patients for a median of 2.8 years, one-year and four-year PFS rates for patients treated with LTI in the SIOPEN cohort were about 54 percent and 32 percent, respectively, compared with about 19 percent and 8 percent, respectively, for those from the previous report.

"This is a big step forward for children with neuroblastoma," Lode said. "The data provide an important baseline. They may have to be evaluated further in a randomized controlled clinical trial comparing STI and LTI." This would address the limitation of this study performed without a group treated with STI for direct comparison, Lode explained.

**More information:** "Anti-GD2 Antibody with GM-CSF, Interleukin-2, and Isotretinoin for Neuroblastoma." *N Engl J Med* 2010;

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