

Commentary

Acute neuropathic pain during antibody infusions as cancer therapy in children

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We present a topically focused piece on the subject of pain and anxiety implications of antibody infusions as part of cancer therapy in children, briefly describing our clinical and research experience as an illustration of the unique circumstance of pain and anxiety associated with antibody infusions.

Immunomodulating agents in the class of anti-GD2 antibody infusion therapy may be used in the treatment of neuroblastoma or melanoma in children. Treatment with anti-GD2 antibody is reserved for high risk neuroblastoma patients with advanced disease at the time of diagnosis, which represent nearly 40% of all neuroblastoma patients. Administration of these infusions can cause moderate to severe generalized neuropathic pain, prolonged over hours and repeated for several days, and may require IV opioid patient-controlled analgesia (PCA) with a basal infusion and boost option (Anghelescu, 2015). Anti-GD2 infusions cause an acute episode of neuropathic pain, with unique characteristics in the spectrum of neuropathic pain experiences, based on the high intensity and short duration of generalized pain, which parallels the duration of the antibody infusions (usually 8 hours). The mechanism of the acute neuropathic pain episode with antibody infusions is explained by the fact that GD2, a surface disialoganglioside present on neuroblastoma cells, is also expressed on peripheral nerves. Pain is believed to be a result of complement activation eliciting local neuronal activity, an on-target, off-

tumor effect of the anti-GD2 antibodies (Sorkin et al., 2010).

The pain associated with anti-GD2 therapy is similar to other neuropathic pain syndromes and is relatively opioid-resistant (Wallace et al., 1997); nevertheless, opioids are routinely utilized for pain control during anti-GD2 infusions. The use of opioids is supported in this setting based on their fast onset of action, while neuropathic pain specific interventions such as gabapentinoids or tricyclic antidepressants may require a few days to establish analgesic efficacy. Systemic anti-GD2 therapy-induced pain is characterized by mechanical allodynia without thermal hyperalgesia in animal models (Sorkin et al., 2002). Pharmacological treatment of the acute neuropathic pain episodes related to antibody infusions has been reported including IV opioid infusions, patient controlled analgesia with infusion and bolus doses (Anghelescu, 2015, and IV lidocaine infusions (Wallace et al., 1997). Lidocaine infusions have been shown to reduce opioid consumption during anti-GD2 antibody infusions and may help preserve NK cell activity by intrinsic sodium channel blocking activity and by reducing the exposure to opioids (Wallace et al., 1997).

In our pediatric oncology pain management experience, we observed that intravenous infusions with anti-GD2 antibodies for neuroblastoma or melanoma can trigger intense acute neuropathic pain episodes, as these patients often require high dose opioid therapy for the duration of the infusions. We published our experience in this area,

comparing two types of anti-GD2 antibody infusions (Angelescu, 2015). In our retrospective review, patients with neuroblastoma were treated at a single institution with ch14.18 or hu14.18K322A mAb, on the Children's Oncology Group (COG) protocol and ANBL0032 (NCT00026312) protocol, respectively. The ch14.18 mAb and hu14.18K322A protocols specified the use of opioids for premedication regimens for pain symptoms in the form of morphine, fentanyl, or hydromorphone. The ch14.18 mAb protocol specified a morphine loading dose of 50 mcg/kg prior to Ab administration, followed by 20-50 mcg/kg/hr continuously for 2 hours after completion of the Ab infusion, with additional doses and infusion rate escalation as needed. This model of opioid delivery was achieved by patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA), depending on the child's age and developmental level. The hu14.18K322A protocol specified morphine, hydromorphone, or fentanyl doses as needed at the discretion of the clinicians. Anxiolytic medications included lorazepam and midazolam.

In this study we analyzed the opioid requirements as IV morphine equivalent doses (mg/kg/day) and the anxiolytic medications required (mg/kg/day). In our series of 28 patients, ages 1.8 to 14.1 years (median age = 5.3 years) we found lower opioid and anxiolytic requirements for patients treated with hu14.18K322A than those treated with ch14.18 mAb; the differences in median opioid requirements reached statistical significance for days 3 and 4 and for the total doses over course 1. Anxiolytic requirements were higher in the group treated with ch14.18, but the difference was not statistically significant (Angelescu, 2015).

Under the circumstances of acute, intense pain and anxiety episodes related to antibody infusions, it may appear intuitive that the addition of psychological preparation and targeted intervention to the pharmacological interventions may be beneficial to reduce both pain and anxiety. Based on this hypothesis, we performed an analysis of the patient group described in the initial study (Angelescu, 2015), evaluating patients in two groups, one with exposure to psychology evaluation, counseling, and psychoeducation, and one without. Pain scores, opioid consumption and the anxiolytic

consumption concurrent with anti-GD2 antibody infusions were analyzed.

Of the 44 patients in the study, 33 (67%, median age = 7.4 years, range = 2.6-16.2) exclusively received pharmacological interventions for pain and anxiety, whereas 11 (33%, median age = 12.2, range = 4.4-20.9) were also exposed to psychological interventions for pain and anxiety. The differences between pain and anxiety outcome measures including 1) daily maximum pain scores; 2) mean (SD) daily opioid consumption (morphine equivalent doses, mg/kg/day); and 3) mean (SD) anxiolytic requirements (mg/kg/day) in the two groups were not statistically significantly different. Almost all daily compared values were slightly higher in the dual pharmacological and non-pharmacological intervention group than the pharmacological-only intervention group. Our results suggested that exposure to psychology evaluation, counseling, and psychoeducation did not appear to be associated with opioid use reduction and was in fact associated with non-significantly increased doses of anxiolytic. These findings may be indicative of referral bias, with patients with high anxiety or other psychological risk factors tending to be more likely to have referrals for psychology consultation.

Although our findings do not support that involvement of psychological interventions significantly reduce pain or anxiety, other studies suggest that non-pharmacological therapies for acute pediatric pain can help reduce perioperative anxiety and procedural pain (Brewer et al., 2006; Yip et al., 2009; Panella, 2016, Wren et al., 2019). Recently, use of hypnosis was found to reduce pain, postoperative opioid use, and duration of hospital stay amongst patients who underwent a Nuss procedure (Manworren et al., 2015) and shows pain benefit in pediatric oncology patients (Jibb et al., 2015). The role of virtual reality (VR) in acute pain and anxiety management is evolving, and promising results have been found with pediatric burn patients (Jeffs et al., 2014), sickle cell disease pain crises (Agrawal et al., 2019), and pediatric oncology patients (Gershon et al., 2004). Thus, the potential benefits of non-pharmacologic interventions such as hypnosis and immersive VR for pain and anxiety amongst anti-GD2 antibody infusion patients is an

avenue worth investigating. An immersive VR package that includes psychoeducation, anticipatory guidance, and distraction may be a suitable initial starting point. A prospective randomized controlled trial (RCT) comparing use of hypnosis to VR for management of acute pain and anxiety in anti-GD2 antibody infusions may help identify if either of these interventions significantly improve pain and anxiety during these infusions.

Despite the significant limitations of our study, we believe it may be informative for the pediatric

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pain management practitioners to be aware that the antibody infusions in the context of pediatric cancer merit attention for treatment of pain and anxiety with treatment strategies including both pharmacological and non-pharmacological interventions. Targeted psychological interventions may help reduce pain and anxiety related to antibody infusions. Prospective investigations may be able to elucidate the contribution of psychological interventions in addition to pain medication strategies to reduce pain and anxiety.

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