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LETTER TO THE EDITOR

Is cytokine-release syndrome the cause of rituximab treatment-related infusion reactions in children with nephrotic syndrome? Impact of anti-rituximab antibodies

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Dear Editor,

We read with great interest the article titled "Infusion reactions associated with rituximab treatment for childhood-onset complicated nephrotic syndrome" by Kamei et al. In a retrospective study on 309 rituximab (RTX) infusions in 159 patients with complicated nephrotic syndrome (NS), an infusion reaction (IR) was observed with 165 (53.4%) infusions [1]. Furthermore, CD20 cell counts before the initiation of RTX were found to be significantly higher in patients with IR than in those without IR (276 vs 197/mm^3, $P < 0.05$), and sore throat and cough resembling an upper respiratory tract infection were the most common symptoms of IR events (66%). These observations led them to speculate that the release of cytokines and chemokines during B-cell destruction due to RTX infusion (the cytokine-release syndrome) was the most likely cause of IR events. Unfortunately, serum cytokine and chemokine levels before and after RTX infusions were not measured in their study. Furthermore, although we have previously reported in *Pediatric Nephrology* that severe IR developed just after the initiation of fourth infusion in an RTX-resistant NS child with anti-rituximab antibodies (ARA) [2], they did not discuss the potential involvement of ARA in the pathogenesis of IR.

On the basis of our experience at a single center, we would like to comment on the impact of ARA on the development of severe IR in children with steroid-dependent NS (SDNS). Between July 2007 and March 2017, we retrospectively reviewed the records of 66 patients (42 boys; mean age, 10.7 years; total 160 RTX infusions) with SDNS who had initially received a single infusion of RTX at the Saitama Children's Medical Center. IR occurred with 80 (50%) infusions, and respiratory symptoms, such as sore throat and mild dyspnea, occurred most frequently in 52 (61%) of all 85 IR events. Severe IR, requiring interruption of RTX infusion and pharmacological treatment with steroids and antihistamines, occurred with only five infusions, most of which (80%) developed during the subsequent administrations (at the time of second, third, fourth, and fifth RTX infusions). Median time of IR onset was 90 min, and IR was observed within 3 h in 73 (92%) infusions. In total, 39 (59%) patients received additional RTX treatment, and the incidence of IR was not significantly different among the subsequent administrations of RTX; the incidence was 52% at first (34/66), 51% at second (20/39), 45% at third (9/20), 47% at fourth (8/17), and 50% at fifth or later (9/18) RTX infusions. We compared patient characteristics at the time of RTX infusion between IR-positive (+) and IR-negative (−) groups (80 vs 80 infusions). There were no significant differences between the groups regarding clinical characteristics such as gender, age at RTX infusion, number of RTX infusions, prednisolone dose or use of immunosuppressive agents at RTX initiation, and serum IgE levels. The CD20 cell count in the lymphocytes before the initiation of RTX was significantly higher in the IR (+) group than in the IR (−) group (426 vs 303/mm^3, $P < 0.05$). However, there was no significant difference in the serum median levels of cytokines (before and after RTX infusion), such as interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TNF-α), and interferon-gamma between the two groups. Serum ARA levels, measured using electrochemiluminescence immunoassay, markedly increased from 58 to 4469 ng/mL (before and 7 days after RTX infusion) in one patient with severe IR at fourth RTX infusion. Despite maintenance therapy with immunosuppressive agents after RTX infusion, early relapse of NS (< 12 month after RTX infusion) occurred in all three patients with severe IR.

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Contrary to the results reported in adult patients with B cell chronic lymphocytic leukemia (CLL), we did not find IR to be more frequently observed at first infusion and associated with elevated serum levels of cytokines, such as IL-6 and TNF-α. This discrepancy may be related to the marked difference in the B cell population in NS and CLL because peripheral B cell count in children with NS was highly significantly lower than that in adults with CLL (approximately 1/100). Conversely, we observed that most severe IR occurred in the subsequent RTX administrations and high ARA levels developed in one of two patients for whom data were available. Similar to our observations, Ann et al. described the development of ARA in two Korean children with complicated NS who experienced severe IR at third RTX infusion [3]. In addition, the frequency of development of ARA was reported to be high in patients with autoimmune diseases than in those with B cell malignancies and may be associated with early relapse of NS due to early recovery of B cells. Thus, we recommend that serum ARA levels should be measured before initiation of subsequent RTX administrations, particularly in RTX-resistant patients with severe IR. Furthermore, we propose the use of more humanized anti-CD20 monoclonal antibodies, such as ofatumumab, as an alternative for such RTX-resistant patients due to ARA development.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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