Single-Agent Rituximab for Primary CNS Lymphoma During Pregnancy As a Bridge to Definitive Management

Case Report

A 30-year-old female at 22 weeks gestation with her third child presented in February 2008 with a 10-day history of episodic imbalance with left-sided tonic-clonic activity without loss of consciousness. The episodes were followed by a progressive frontal headache. Initial exam was unremarkable, but a noncontrast magnetic resonance imaging (MRI) of the head demonstrated a large region of T2 hyperintensity in the white matter extending from the anterior right lateral ventricle to the right frontal lobe. A second region of T2 hyperintensity with mild mass effect extended from the superior-posterior right ventricle to the right frontal lobe (Fig 1A). As the evaluation was ongoing, the patient developed new weakness of the left arm and leg. A biopsy of the right frontal lobe demonstrated a CD20-positive diffuse large B-cell lymphoma that was Epstein-Barr virus negative (Figs 2A and 2B).

Dexamethasone 4 mg three times daily was initiated after biopsy at week 24, but the patient developed progressive weakness after 4 days. Exam demonstrated 1 of 5 (with 5 being normal) strength of the left hip and knee flexors, 2 of 5 of the left lower extremity dorsiflexors and plantar flexors, and 2 of 5 of the left deltoids. She was unable to ambulate. It was clear that there was tumor progression despite steroids and that alternative therapy for her primary CNS lymphoma (PCNSL) was urgently needed. A comprehensive multidisciplinary discussion was held with the patient and her family regarding the risks and potential benefits of high-dose methotrexate to her and the 25-week-old fetus. The patient was offered the choice of terminating pregnancy or proceeding with treatment for her PCNSL. Ultimately, the patient elected to continue the pregnancy and attempt to control her disease with the anti-CD20 monoclonal antibody rituximab as the fetus matured to viability. The plan was to initiate high-dose chemotherapy with methotrexate (HD-MTX) if there was any evidence of progression or even lack of response to rituximab.

Rituximab 375 mg/m² was initiated at week 25, and dexamethasone 4 mg three times daily was continued. Within 12 hours, the weakness in her left upper extremity had resolved, and the weakness in

Fig 1.

Fig 2.

her left lower extremity had improved. She began to ambulate with the use of a walker. A total of four once-weekly doses of rituximab were administered, with the fourth dose occurring at 28 weeks gestation. Her neurologic deficits resolved within 10 days of the first dose. Dexamethasone was tapered from 4 mg three times daily to 2 mg three times daily. A noncontrast MRI of the head was repeated at 30 weeks gestation and demonstrated improvement (Fig 1B). A vaginal delivery was attempted at 31 weeks gestation but was converted to a cesarean section as a result of breech presentation and was performed without

complications. After birth, the patient's dexamethasone was then decreased to 2 mg twice daily.

The mother recovered well and was dismissed 72 hours post partum. One week later, she developed low-grade headaches and right-sided sensory symptoms. An MRI demonstrated progression of a lesion in the right frontal lobe as well as new lesions with associated edema in both frontal lobes (Fig 1C). Dexamethasone was then increased to 4 mg twice daily, and on postpartum day 10, HD-MTX at 8 g/m² was initiated. HD-MTX was administered every 2 weeks for six

Fig 3.

cycles. Dexamethasone was discontinued after the fourth cycle. MRI after two and six cycles demonstrated a partial response and complete remission, respectively (Fig 1D). Because of the patient's age and high risk of recurrence, she proceeded with high-dose chemotherapy (BEAM) with autologous peripheral blood stem-cell transplantation as consolidation. At the completion of her conditioning and stem cell infusion, she was dismissed from the hospital and completed the remainder of her course as an outpatient. Neutrophil engraftment was achieved on post-transplantation day 13. She developed a rash consistent with varicella zoster at post-transplantation day 65 but otherwise did not experience infectious complications. An MRI at day 100 demonstrated a continued complete response.

At the time of birth, the daughter had Apgar scores of 7 and 8. Birth weight was 1,260 g, and height was 36.5 cm. Several hours after birth, the newborn had persistent apnea necessitating mechanical ventilation. She required minimal support for 48 hours. Hydrocortisone was administered at physiologic doses given her prolonged prenatal exposure to corticosteroids and was gradually weaned over 3 weeks. Two days after delivery, T- and B-cell lymphocyte subsets were assessed. At that time, a single CD19-positive B lymphocyte per microliter was demonstrated. T cells were within normal limits. Immunoglobulin (Ig) M was undetectable, and IgA and IgG levels were within normal limits for age at day 4. Despite the near absence of B cells, there were no infectious complications throughout the neonatal period.

Parenteral nutrition was utilized briefly and was tapered over 1 week. At the time of hospital dismissal, 8 weeks after birth, the child was feeding well. At 10 weeks of age, CD19 B cells remained undetectable; IgA, IgM, and IgG levels were all severely depressed. Once-monthly intravenous immunoglobulin at 1.5 g/kg was then initiated. At 4 months of age, immunoglobulins and B cells had normalized and monthly intravenous immunoglobulin was discontinued. Reconstitution was confirmed 1 month later, at which time routine 2-month immunizations (with the exception of live virus vaccines) were administered. At 7 months of age, the child was exposed to varicella. Despite no clinical evidence of infection, she was hospitalized for 2 days for intravenous acyclovir. She did not progress to active varicella infection and completed a 7-day course of oral acyclovir.

As of October 12, 2012, our patient remains in a complete remission, more than 4.5 years after diagnosis. Her ovarian function has resumed, and she has experienced complete recovery of her neurologic deficits. Her daughter is now 4 years of age and is healthy. She has achieved all of her developmental milestones at the appropriate ages and is within the normal range on growth charts for height and weight.

Discussion

This 30-year-old woman with presenting symptoms at 22 weeks and a diagnosis of primary CNS lymphoma at 24 weeks gestation presented a clinical dilemma. Although methotrexate is a well-known teratogen and abortifacient during the first trimester, it has been reported to likely be safe in the second and third trimesters.¹⁻⁹ To our knowledge, however, there have been no reports to date demonstrating the risks to the fetus of the methotrexate doses ($3.5\text{--}8\text{ g/m}^2$) that are used in PCNSL regimens that are recognized as the standard of care. In addition, only one series in the literature has reviewed the use of rituximab in pregnancy; however, this was based on reporting of patients receiving rituximab who became pregnant despite counseling

to avoid pregnancy. Despite the limitations, there did not appear to be any significant increase in adverse outcomes.¹⁰

Although the use of rituximab has been demonstrated to improve survival in other B-Cell lymphomas, it has not yet been firmly established in PCNSLs. Small phase II studies have demonstrated promising results; however, this has not been confirmed in a randomized trial.¹¹⁻¹³ While the penetration of rituximab into the cerebrospinal fluid has been demonstrated to be limited by the blood-brain barrier to a level of less than 1% to 2% of that in serum; it has been proposed that any disruption of the blood-brain barrier may lead to greater rituximab penetration.¹⁴

A single study has reported a significant disruption of the blood-brain barrier in PCNSL.¹⁵ We assessed the integrity of the blood-brain barrier in our patient's initial biopsy specimen. With electron microscopy, multiple features of endothelial cell damage and discontinuities of the endothelial compartment of the blood-tumor barrier were demonstrated. On ultrastructural review of our patient's biopsy, a few capillaries demonstrated changes thought to be detrimental to blood-brain barrier competency. These changes included the focal degradation of endothelial cells (Fig 3A), reduplication of the basal lamina surrounding capillary endothelial cells (Fig 3B), and areas in which abutting endothelial cells lacked tight junctions (Fig 3C).

It is also possible that the blood-brain barrier may have an increased permeability during normal pregnancy. A recent study demonstrated an increased blood-brain barrier permeability of 6.5- and 18-fold when exposed to normal pregnant (median of 34 weeks gestation) plasma and pre-eclamptic plasma, respectively.¹⁶

With a combination of pathologic and potentially physiologic changes, it seems likely that the penetration of rituximab to the CNS lymphoma in our patient greatly exceeded that previously reported in the literature, despite a suggestion by some that dexamethasone can decrease the permeability of the blood-brain barrier. This is supported by the dramatic and immediate response experienced by our patient after experiencing progressive symptoms during treatment with high-dose corticosteroids.

With the immediate life-threatening nature of her malignancy and a fetus weeks away from viability, potential therapeutic options other than dexamethasone with the potential to balance the fetal and maternal risk were not available. Herein, we have presented a therapeutic option with predictable fetal responses (initial B-cell and immunoglobulin depletion for 12-16 weeks) and the potential for a high level of lymphoma activity. By receiving rituximab as a bridging strategy to definitive HD-MTX and/or autologous peripheral blood stem-cell transplantation, our patient was able to deliver a viable child without significant complications and without compromising the potential for curing the mother's malignancy.

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The author(s) indicated no potential conflicts of interest.

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