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INSIGHTS

Family reflections: refractory stage IV neuroblastoma

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DIAGNOSIS

In February 2021, our 8-month-old baby experienced escalating symptoms of appetite loss, recurrent fevers, milestone regression (ceased assisted-walking, crawling, and standing), paleness, and hourly night-waking. In April 2021, after two misdiagnoses, my husband and I were shocked to be told our baby had cancer. The treating team were determining if it was lymphoma, one of three types of leukaemia, or 'other'. The consultant described that the spread was almost everywhere: bone marrow, lymph nodes, liver and bones (long bones, pelvis, vertebrae, ribcage, and skull).

The next day, after more tests, they told us that our baby had neuroblastoma and to not look it up. Even though our baby had Stage IV/M spread, they were classed as 'INRG intermediate-risk' because they were 10 months old and their primary tumour had non-amplified MYCN. The consultant reassured us that there was well over 90% event-free 2-year survival, and to expect a healthy and well child in 6 months.

Due to the extensive tumour burden causing a fracture risk for the femurs and pelvis, the orthopaedic team placed our baby in a rhino hip brace for 3 months, with strict instructions for no weight-bearing. Our baby was just about to start walking, had been crawling since 6 months old, and standing since 7 months old. But we had to stop all that. Their play changed to activities while sitting.

TREATMENT

The treating team followed the SIOPEN LINES group 10 protocol for Stage M, <12 months old, non-amplified MYCN, and intermediate-risk neuroblastoma. The treatment was Carboplatin and Etoposide ×2–4 cycles, ± CADO ×2–4, ± surgery. CADO consisted of Cyclophosphamide, Vincristine, Doxorubicin, Dexrazoxane, and Filgrastim. Scans were every two cycles. Surprisingly, the Curie score increased from 23 to 24 after two cycles, hence four cycles of CADO commenced.

After three cycles, our baby had a successful stem cell harvest via their central venous catheter, procuring enough for a tandem transplant. The consultant reassured us that this was a rainy day fund. The four cycles of CADO reduced the Curie score to 13, then 6. From that point on, all of the subsequent scan results have been similar: the tumours were decreasing but too slowly.

Our baby turned one in a treatment room on a paediatric oncology ward while receiving chemotherapy. Soon after getting the all-clear from our orthopaedic surgeon to wear the hip brace only at night, our toddler started walking and running. Unfortunately, during the sixth cycle, our toddler was diagnosed with VOD. CADO ceased and Carboplatin and Etoposide were

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administered for the seventh to eighth cycles. During the induction therapy, our toddler received 31 transfusions: 10 were packed red blood cells and 21 were platelets.

In October 2021, our toddler's primary tumour above their left adrenal gland was removed during a 2.5 h laparoscopy. These radical resections usually require open surgery but the tumour was well-circumscribed and chemotherapy had reduced it from 8 to 3 cm. Only a two-night stay was required and our toddler has three keyhole scars.

Unfortunately, the Curie score remained stable at 6 and our toddler was classed as having Refractory cancer (chemotherapy-resistant). One possible reason being the primary tumour had segmental chromosomal abnormalities. Chemoimmunotherapy treatment commenced consisting of Temozolomide, Irinotecan, Dinutuximab, and Sargramostim (ANBL1821 Regimen A). This inpatient treatment causes a large amount of family separation which takes a toll emotionally and mentally. It is hard as a parent to battle through the significant constant stress of hoping the treatment is working, waiting for scan results, and concerns about potential late side effects of treatment.

It has been a year since diagnosis. We have completed 8 cycles of the Refractory treatment. The Curie score is 4, with two tumours resolved and the rest reduced. We are now a part of the PRISM Clinical Trial (NCT03336931) for extra genetic testing, especially to see if an ALK, Mek or PARP inhibitor is required.

Although the diagnosis was intermediate-risk, because the tumours are refractory the treating team are considering administering consolidation and maintenance therapies that are typical to high-risk neuroblastoma. These include high-dose chemotherapy with autologous stem cell transplant, and maintenance of more immunotherapy (Dinutuximab) and 6 months of Isotretinoin. The extended treatment duration due to Refractory cancer has been tough on our family. We were initially told that it would only take six months but it has been a year and our toddler is still not in remission.

FUTURE RESEARCH

The biggest issues facing our child are why some cancers are refractory and how to achieve remission, and the role of high-dose chemotherapy with stem cell transplant.

I would like to see researchers in this area continue to work on offering personalised medicine and improving its availability, especially at diagnosis. This includes whole genome and transcriptome sequencing, in vitro high-throughput drug sensitivity testing, and liquid biopsies. Another issue I would like help with is how our toddler's primary tumour had 1p loss, 2p gain, 3p loss, and 17q gain, and for any treatment impact to be identified. I would like for markers of Refractory neuroblastoma to be discovered and screening to occur at diagnosis. I would like for an individualised treatment protocol to be determined for Refractory neuroblastoma that has reduced toxicity and better outcomes.

I would like to see more research on reducing treatment toxicity. A big issue is whether high-dose chemotherapy with stem cell transplant has a role or whether less toxic options of immunotherapy, vaccine, and low-dose long-term maintenance chemotherapy, such as DFMO, result in similar or better outcomes.

I would like to see improved availability of immunotherapies, vaccines and low-dose long-term maintenance chemotherapies for neuroblastoma, which would reduce financial burden and international travel for many families. I hope research continues to aim to reduce the unacceptably high rates of relapse and find a cure for neuroblastoma.

TO RESEARCHERS

Thank you to all researchers in this area. My hope for you is that you witness progress and improvements in outcomes during your life's work. Our children are lucky to have you on their side.