BRIEF REPORT
Treatment of Two Cases With Refractory, Metastatic Intermediate-Risk Neuroblastoma With Isotretinoin Alone or Observation

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INTRODUCTION

Outcomes for infants diagnosed with stage 4, favorable biology (MYCN non-amplified, hyperdiploid tumors, favorable histopathology) neuroblastoma are excellent [1]. These patients are classified as having intermediate-risk disease, and the vast majority of these patients are cured with a combination of chemotherapy and surgery. The minimum chemotherapy dose intensity needed to achieve cure has yet to be determined. The overall goal of the previous COG Phase III intermediate-risk clinical trials (A3961 and ANBL0531) has been to determine if high survival rates could be maintained with reduced exposure to cytotoxic chemotherapy. The treatment endpoint for both studies was complete remission (CR) of metastatic sites and at least a 90% reduction in the size of the primary tumor, defined as a very good partial response (VGPR). Further risk-stratification was added to ANBL0531 to allow high-risk patients without evidence of loss of heterozygosity of chromosomes 1p and 11q to complete therapy once they had achieved a CR of all non-liver/non-skin metastatic sites in addition to achieving at least a 50% reduction of the primary tumor. Of the 174 patients with stage 4 disease enrolled on A3961, 53 (30.5%) failed to achieve a VGPR or CR after eight cycles of chemotherapy [2]. Guidelines for the management of patients who fail to achieve these response benchmarks are lacking. Here we report two cases that illustrate that refractory metastatic disease may not portend a poor outcome for patients with favorable biology intermediate-risk neuroblastoma.

CASE 1

A 9-month-old male was diagnosed with intermediate-risk, stage 4 neuroblastoma after a 2-month history of irritability and periorbital ecchymoses. Imaging revealed a 4 cm × 4 cm calcified left adrenal mass, multiple liver lesions and extensive retroperitoneal and left supraclavicular lymphadenopathy. Bone and bone marrow disease were also detected by staging evaluation. An excisional biopsy of the left supraclavicular node revealed favorable histology and tumor biology studies showed nonamplified MYCN and hyperdiploidy (DNA index 2.07). Analyses for loss of heterozygosity of chromosomes 1p and 11q were of unsatisfactory quality.

The patient was treated per COG A3961. Given his clinical and biological features, the patient was assigned to receive eight cycles of chemotherapy. Disease evaluation at the end of eight cycles of chemotherapy revealed an approximately 60% reduction in the primary site, reduction in the number and size of metastatic sites, a persistent small focus of bone marrow disease, and 80% reductions in both the urine homovanillic acid (HVA) and vanillymandelic acid (VMA). The patient underwent a gross total resection of his adrenal primary. Because the patient did not have resolution of metastatic disease, he received additional chemotherapy with cyclophosphamide and topotecan per protocol. Re-evaluation after two cycles (cycles 9 and 10) revealed a clearance of the bone marrow disease, but persistent lesions near the liver, chest wall and the retroperitoneum. These lesions persisted after cycles 12 and 14 of chemotherapy. Additional surgery to remove refractory disease in the retroperitoneal mass was performed after cycle 13, and histology revealed persistent neuroblastoma. Six cycles of isotretinoin were given, but evaluation revealed minimal change in the chest wall and perihepatic masses (Fig. 1). No further therapy was given. The urine catecholamine normalized 14 months after completion of cytotoxic chemotherapy. The patient has remained clinically well for 28 months after completion of cytotoxic chemotherapy with stable metastatic disease in the retroperitoneum, near the thoracic spine and a peri-hepatic mass on imaging.

CASE 2

A 10-month-old female presented with a 6-week history of irritability, weight loss, fevers, cervical adenopathy, and anemia.

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Fig. 1. Representative posterior MIBG images and CT slices from Case 1. At the completion of cytotoxic chemotherapy, the patient continued to have MIBG-avid lesions in the skull and retroperitoneum (A). CT scan revealed (B) a residual mass near the thoracic spine, (C) perihepatic and retroperitoneal masses as well as (D) a residual left adrenal mass. Eighteen months after completing isotretinoin, the patient continues to have (E) an MIBG-avid lesion in the retroperitoneum (F) a thoracic mass (G) a peri-hepatic mass and (H) a retroperitoneal mass, corresponding to the area of MIBG avidity.

Fig. 2. Representative posterior MIBG images and CT slices from Case 2. At the completion of cytotoxic chemotherapy, the patient continued to have MIBG-avid lesions in the thoracic inlet and retroperitoneum (A). CT scan revealed (B) a residual mass near the thoracic inlet (C) and retroperitoneal masses. Nine months after completing cytotoxic chemotherapy, the patient continues to have (D) MIBG-avid lesions in the thoracic inlet and in the retroperitoneum with corresponding soft tissue masses seen on CT scan (E and F) to the area of MIBG avidity.
Imaging revealed a left-sided retroperitoneal primary, a right-sided thoracic paraspinal mass, a left sided thoracic inlet node, and extensive bony disease with soft tissue extension into both orbits and into the extradural space between L1 and L2. The primary mass was biopsied and found to be favorable histology neuroblastoma. Bone marrow biopsies revealed neuroblastoma infiltration. The patient was enrolled on ANBL00B1 and received one cycle of high-risk chemotherapy per ANBL02P1 [3] (topotecan/cyclophosphamide) emergently while biology studies were pending given the extent of the orbital masses. Biology studies revealed nonamplified MYCN, hyperdiploidy, favorable INPC histology, normal 1p status, and LOH of chromosome 1q. Given these findings, the patient was determined to have intermediate-risk disease and she was subsequently treated with cycles two through eight of chemotherapy as per A3961.

End of therapy evaluations revealed an 85% reduction in the size of the primary tumor, significant decreases in the size at all other disease sites but very mildly persistent MIBG avidity. Surgical resection of the primary retroperitoneal tumor was considered however was not performed due to concerns for significant surgical morbidity related to renal and mesenteric vessel encasement. Due to the persistent MIBG activity and <90% decrease in tumor mass, she was deemed to have an INRC partial response (PR) and given additional treatment with topotecan/cyclophosphamide. The patient failed to achieve more than a PR after cycles 10 and 12 of chemotherapy as MIBG avidity in the primary site as well as the thoracic inlet node, while still improving, remained positive (Fig. 2). The parents elected to forego cycle 14 of chemotherapy given the overall lack of achieving a negative MIBG. The patient has remained clinically well with stable disease 13 months after cytotoxic treatment.

DISCUSSION

Clinical factors, tumor histology and genetic features including tumor cell ploidy, MYCN copy number, and the status of chromosomes 1p and 11q are used for risk classification and treatment stratification for children with neuroblastoma. In contrast to most patients with metastatic cancer, infants with stage 4 neuroblastoma with favorable histology and genetics have excellent outcomes [4–8]. The number of cycles of chemotherapy in the sequential legacy cooperative group intermediate-risk neuroblastoma trials CCG-3881 (1989–1995) [9], POG9243 (1992–1996) [10], and COG A3961 (1997–2005) [2] has decreased from 12 to 4 for patients with favorable biology. All three trials achieved overall survival rates of 93% despite successive reductions in chemotherapy intensity [2,9,10]. The goal of the recently closed COG intermediate-risk neuroblastoma trial, ANBL0531, was a further refinement of risk-adapted treatment aimed at reducing therapy for patients with favorable biologic factors by modifying the response criteria required to stop chemotherapy from a VGPR in A3961 to a PR at the primary site and a CR at metastatic sites in ANBL0531 for all intermediate risk patients <12 months of age without loss of heterozygosity (LOH) of chromosomes 1p and/or 11q. Patients 12–18 months of age and/or those with unknown or confirmed LOH of 1p and/or 11q were required to achieve a VGPR at the primary site and a CR of metastatic sites before discontinuing therapy.

Guidelines for additional therapy in the setting of persistent disease after completion of intermediate-risk treatment are lacking, but treatment options include surgical debulking, retrieval therapy with topotecan and cyclophosphamide [11], differentiation therapy with cis-retinoic acid [12], therapy intensification with high-risk treatment protocols, and/or observation. Because the number of infants with favorable-biology disease who fail to achieve a partial response is so small, prospective trials of any of these approaches are unlikely. A sub-analysis of the outcome and off protocol therapy of intermediate-risk patients enrolled on A3961 and ANBL0531 who failed to achieve a CR of metastatic disease is warranted. While follow up time for both cases is relatively short, these cases suggest that further therapy intensification may not be required for intermediate-risk patients with favorable biology, refractory metastatic disease.

REFERENCES