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Case Report

Successful Multimodal Treatment of an Isolated CNS Relapse Following Stage IV Neuroblastoma

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Abstract

Isolated CNS relapse after stage IV neuroblastoma is a rare event and prognosis is very poor. We report about a girl with stage IV neuroblastoma at the age of 13 months, who developed isolated CNS relapse at age of 5 years after primary treatment according to the GPOH-NB2004 protocol. The girl was successfully treated with complete resection of the singular cerebral tumor lesion, extracorporeal photon irradiation of the craniospinal axis with local radiation boost on the tumor bed and systemic chemotherapy using irinotecan and temozolomide. Treatment was well tolerated and finished within 7 months. Until today, the now 17 years old girl is free of second neuroblastoma relapse. We conclude that isolated CNS relapse after stage IV neuroblastoma may be successfully treated using a systemic backbone chemotherapy regimen including irinotecan and temozolomide in addition to local treatment including neurosurgery and craniospinal irradiation.

Keywords: CNS relapse; Neuroblastoma, Craniospinal irradiation; Chemotherapy; Irinotecan; Temozolomide

Introduction

Neuroblastoma is the most common extracranial solid tumor in children [1]. More than 50% of patients are diagnosed with metastatic disease, mostly involving lymph nodes, liver, bone marrow and bones. Metastases of the Central Nervous System (CNS) at diagnosis are rare. Due to improving treatment strategies including autologous stem cell transplantation and antiGd-2 immunotherapy, the poor prognosis of stage IV neuroblastoma has improved during the last decades [2]. Compared with other childhood malignancies the risk of relapse of high-risk neuroblastomas remains high and systemic relapse is associated with very poor prognosis [3]. CNS involvement as part of systemic relapse was increasingly observed over the last decades despite intensified primary therapy, possibly due to protective effects of the blood-brain barrier [4]. Isolated CNS relapse, however, occurs only in very few patients and standard treatment strategies are missing.

Case Presentation

A 13 months old girl presented with fever, paleness and tumor of the right adrenal gland. A Metaiodbenzylguanidine (MIBG) and urine catecholamine positive neuroblastoma stage IV with amplification of MYCN was diagnosed due to disseminated bone marrow involvement, bone metastases of the right base of the skull and both orbits and infiltration of the right dura mater. The patient underwent treatment according to the GPOH-NB2004 protocol [5] including neo-adjuvant chemotherapy (2xN5, 2xN6 cycles), complete resection of the primary tumor, adjuvant chemotherapy (1xN5, 1xN6 cycle), Metaiodobenzylguanidine (MIBG) therapy with 4,400 MBq ^{131}I-MIBG, myeloablative chemotherapy with Melphalan, Carboplatin and Etoposide following autologous stem cell transplantation. Treatment was completed by maintenance therapy with retinoic acid. Complete remission was achieved. Thirty months after end of treatment and 48 months after diagnosis of neuroblastoma, the five-year-old girl was diagnosed with isolated CNS relapse of neuroblastoma. One month earlier, she had presented with pain in the right arm, hemiparesis and right-sided facial nerve palsy. Cranial Computed Tomography Scan (CT) had shown an intracerebral frontoparietal hemorrhage (3x4 cm) on the left side. Dexamethasone over five days improved the facial nerve palsy. Cranial Magnetic Resonance Imaging (MRI) at that time revealed a small lesion measuring 7-8mm within the hemorrhage, which was suspicious of a focal metastatic lesion (Figure 1). However, due to a completely unsuspicious comprehensive tumor staging including urine and serum catecholamines, NSE, spinal tap, sonography and MRI of the abdomen, chest CT, Technetium-99m-(^{99m}Tc) and MIBG-scintigraphy and bone marrow aspiration, a watch and wait strategy and a second cranial MRI after seven weeks were appointed.

Six weeks later the girl presented with acute headache, vomiting, paresis and neglect of the right hand. Cranial CT showed a second acute hemorrhage at the same frontoparietal region on the left side and MRI again raised the suspicion of a focal metastatic lesion (Figure 1). Neurosurgery with complete resection of the hemorrhage was performed. Histopathology confirmed the diagnosis of a relapsed neuroblastoma with amplification of MYCN. A second comprehensive tumor staging remained unsuspicious for extracranial tumor manifestation, so isolated CNS relapse of neuroblastoma was diagnosed.

Two weeks after complete resection of the intracranial tumor, chemotherapy with intravenous irinotecan and oral temozolomide was started. Due to damaged blood brain-barrier postoperatively and due to upcoming radiotherapy, the initial two cycles of irinotecan and temozolomide were applied with reduced doses from days 1-5 (Table 1). Doses were steadily increased from the 3rd chemotherapy cycle on. In addition to R0 resection of the tumor, extracorporeal

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Table 1: Postoperative chemotherapy and irradiation regimens.

Cycle	Day of start of next IT cycle	Irinotecan iv (days)	Temozolomide po (days)	Cisplatin (days)	Radiotherapy[1]
1	12	20 mg/m² (1-5)	100 mg/m² (1-5)		
2	15	20 mg/m² (1-5)	100 mg/m² (1-5)		
3	14	30 mg/m² (1-5)	150 mg/m² (1-5)		
4	49		150 mg/m² (15-19)	7 mg/m² (2,5,9,12)	days 1-26
5	15	30 mg/m² (1-5)	150 mg/m² (1-5)		
6	13	30 mg/m² (1-5)	150 mg/m² (1-5)		
7	22	30 mg/m² (1-5) 20 mg/m² (8-12)	150 mg/m² (1-5)		
8	20	30 mg/m² (1-5) 20 mg/m² (8-12)	100 mg/m² (1-5)		
9		30 mg/m² (1-5) 20 mg/m² (8-12)	100 mg/m² (1-5)		
cumulative dose		1,400 mg/m²	5,750 mg/m²	28 mg/m²	

iv=Intravenous, po=Per Os. 1Extracorporeal photon irradiation of craniospinal axis (24Gy, hyperfractionated) followed by local boost on the tumor bed (20Gy, normofractionated).

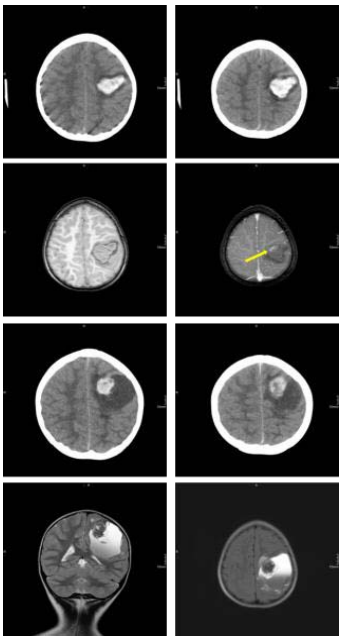

Figure 1: Cranial imaging after 1st (A-D) and 2nd (E-H) Intracerebral Bleeding (ICB) due to isolated CNS relapse of neuroblastoma.
A+B: Cranial CT after 1st ICB. Left parietal ICB with perifocal edema, transversal diameter 34x28 mm.
C+D: Cranial MRI one day after 1st ICB. T1 Fast Field Echo (FFE) sequence native (C) and after contrast (D). Circumscribed contrast enhancement suspicious of a focal metastatic lesion (yellow arrow).
E+F: Cranial CT after 2nd ICB (42 days after 1st ICB). Acute ICB at front margin of a 5 cm large oozing cave.
G+H: Cranial MRI three days after 2nd ICB (45 days after 1st ICB). T2 Turbo Spin Echo (TSE) sequence coronar (G) and Fluid Attenuated Inversion Recovery (FLAIR) sequence transversal (H). Pressurized left parietal lesion after resorption of 1st ICB with residues of 1st ICB and acute 2nd ICB with questionable arrosion of blood vessels.

photon irradiation of the craniospinal axis (hyperfractionated regime up to a total dose of 24.3 Gy, given in twice-daily fractions of 1.5 Gy and 1.2 Gy, respectively) with local boost on the tumor bed (normofractionated regime up to 20 Gy, given in daily fractions of 2 Gy) was performed during the 4th chemotherapy cycle. temozolomide was continued during radiotherapy, however, irinotecan was substituted by cisplatin to support a radio sensitizing effect (Table 1). Treatment was terminated after completion of 9 chemotherapy cycles, seven months after diagnosis of relapse.

To enable short cycle intervals, G-CSF was administered for hematologic recovery. No hospitalizations were necessary for infectious events. Transfusions of erythrocytes or thrombocytes were not required. To decrease side effects like diarrhea, loperamide and cefaclor were applicated. Nevertheless, two admissions to the hospital for severe dehydration were necessary. Moreover, loss of appetite necessitated interim parenteral feeding. Almost 12 years after completion of treatment the 17 years old girl is free of relapse and free of neurological symptoms. As late effects of initial and relapse therapy, she is affected by hypothyroidism, hypergonadotropic hypogonadism and inner ear hearing loss on both sides (Tox-Grad?), impaired growth and alopecia areata within the radiation field. Focal nodular hyperplasia of the liver is under regular control by ultrasound. In addition, insulin-dependent diabetes mellitus was diagnosed at the age of 16 years.

Discussion/Conclusion

The risk for relapse after treatment of neuroblastoma stage IV still exceeds 50%. In case of relapse, 6-20% of patients are affected by CNS disease, most often in the context of systemic disease [3,6,7]. Isolated CNS relapse is scarce, seems to occur predominantly during the first three years after end of treatment and is associated with a very poor prognosis [4]. Risk factors for CNS relapse are amplification of NMYC, age of 2-3 years [6] and high levels of serum lactic dehydrogenase (LDH >1,500 U/l) at primary disease, initially performed lumbar puncture [4] and initial bone metastasis of the skull [8]. Our patient showed three of these risk factors at primary diagnosis of neuroblastoma (amplification of NMYC, elevated LDH and metastasis of the skull). A lumbar puncture at the time of initial diagnosis was not performed. CNS relapse occurred during the third year after end of treatment.

At present, specific treatment, recommendations for isolated CNS relapse are missing. Case reports show the importance of a good local treatment with complete resection following

radiotherapy in combination with systemic chemotherapy [7]. In addition, compartmental intrathecal radioimmunotherapy targeting GD2 or B7H3 was described as part of a multimodal treatment regime including irradiation of the craniospinal axis and systemic chemotherapy [9]. Results of this small cohort of 21 treated patients seem promising with acceptable treatment related toxicity. However, the effect of intrathecal radioimmunotherapy has not yet been prospectively validated. For this reason, a multicenter phase II/III trial on ^{131}I-compartemental Omburtamab radioimmunotherapy for neuroblastoma of CNS/leptomeningeal metastases is currently recruiting patients (ClinicalTrials.gov Identifier: NCT03275402).

Irinotecan and temozolomide are known to be effective for relapsed or refractory neuroblastoma [10] and they are both capable of crossing the blood brain barrier without causing relevant neurotoxicity. This was the reason, why these two drugs were chosen as a systemic backbone for sufficient local treatment in our patient. In addition to neurosurgical resection and extended field radiotherapy supported by the radiosensitizer cisplatin [11], we were able to successfully complete treatment without a second autologous or haploid stem cell transplantation and without immunotherapy.

In contrast to our patient, complete neurosurgical, resection was not always achieved in patients included in the intrathecal radioimmunotherapy study. Reasons included localization and number of CNS lesion as well as leptomeningeal dissemination [9]. In addition, we chose a higher craniospinal radiation dose (26 Gy *vs.* 10.6-21.6 Gy) and a hyperfractionated regimen even though preoperative cerebrospinal fluid was free of tumor cells. Local tumor boost, however, was lower in our patient than described in the study by Kushner et al., (20 Gy *vs.* 25.6-30 Gy). In both regimens, irinotecan and temozolomide were used. The cumulative dose of irinotecan was higher in our regime (1,400 mg/m^2 *vs.* 500 mg/m^2), but daily doses were lower (20-30 mg/m^2 *vs.* 50 mg/m^2 per day) resulting in a lower bone marrow toxicity. The cumulative dose of temozolomide (5,750 mg/m^2 *vs.* 17,000 mg/m^2) and the overall treatment duration were much lower in our patient (7 months *vs.* 104 months).

We conclude that isolated CNS relapse after stage IV neuroblastoma may be successfully treated using a systemic backbone chemotherapy regimen including irinotecan and temozolomide in addition to craniospinal irradiation and complete neurosurgical resection, if feasible. Neurological symptoms during follow-up should prompt immediate cerebral imaging to exclude the rare event of isolated CNS relapse.

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