

CASE STUDY

Targeted molecular therapy (modified RIST regimen) in relapsed high risk stage IV neuroblastoma: two cases report

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Abstract: The prognosis for children with recurrent or refractory neuroblastoma remains a significant clinical challenge, and currently there are no known curative salvage regimens. In this paper we investigated the effect of imatinib with rapamycin and the chemotherapeutic agents temozolomide and irinotecan. We treated two children with recurrent neuroblastoma with this so called RIST protocol. Both patients, off therapy for 15 and 31 months, respectively are well, and developing normally, without any complications. These findings suggest that a combination regimen of RIST may provide a therapeutic benefit with a favorable toxicity profile to a unfortunate subset of patients with neuroblastoma.

Keywords: RIST therapy, Neuroblastoma, Pediatric cancer

1 Introduction

The prognosis for children with recurrent or refractory neuroblastoma remains a significant clinical challenge, and currently there are no known curative salvage regimens. Recently, a combination of temozolomide with the topoisomerase-I inhibitor irinotecan has been suggested.^[1,2] Therefore, in recent years the use of small molecule inhibitors, targeting aberrantly activated signaling cascades, has become a promising approach. Likewise the mTOR inhibitor rapamycin, a downstream target of P13K signaling, showed in several models growth inhibiting activity.^[3,4] In this paper we investigated the effect of imatinib with rapamycin and the chemotherapeutic agents temozolomide and irinotecan. We treated two children with recurrent neuro-

blastoma with this so called RIST protocol, as published by Corbacioglu.^[4] The RIST protocol has a multimodal metronomic trial design consisting of consecutive courses of rapamycin (R) and dasatinib (S) followed by irinotecan (I) and temozolomide (T) which is currently investigated in a prospective randomized international Phase II trial (Eudract Number: 2011-004062-15; ClinicalTrials.gov Identifier: NCT01467986) and which in our two cases was modified using imatinib instead of dasatinib.

2 Case Report

2.1 Case 1

A previously healthy 5-year-old male was admitted to our clinic for persistent pain to inferior legs and chest wall. A chest X-ray and CT-scan showed a posterior mediastinum swelling. MRI thoraco-lumbar confirmed this finding demonstrating a large paraspinal mass to D4-D9 vertebra. Bilateral bone marrow aspirates and trephine biopsies contains unequivocal tumor cells. Immunohistochemical studies were positive for CD56, Tirosinasi and chromogranin. ¹³¹I-MIBG (the radiolabeled norepinephrine analogue iodine-131-metabolite) scintigraphy demonstrated mediastinal, bone marrow, and bone positivity, as confirmed by ^{99m}Tc-diphosphonate scintigraphy. Urinary catecholamine metabolism (HVA and VMA) showed increased values. No amplification of the MYCN oncogene. Abdominal ultrasound and CT scan were negative.

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The global evaluation established the diagnosis of stage IV neuroblastoma MYCN not amplified. The patient began standard front-line therapy according to NB-AR-01 AIEOP-E-SIOP protocol. The reevaluation of the disease, before the maintenance treatment, showed complete remission of disease (October 2010). Five months later the child complained of increasing pain in the left hip. The diagnostic approach confirmed the local relapse of neuroblastoma. Adjuvant chemotherapy, included four courses of TVD (topotecan vincristine, and doxorubicin) and five courses of ICE (ifosfamide, carboplatin, and etoposide) were performed. Restaging evaluation of disease after the 9 cycles by bone marrow aspirate, trephine biopsy, MRI, 131I-MIBG scintigraphy, urinary HVA and VMA, and DOPA-PET revealed a complete second remission. Related to the dismal long-term outcome we started a modified RIST protocol (February 2012). A complete restaging after the end of RIST (September 2013) revealed a persistent complete response of disease. The patient has been off therapy for 31 months (April 2016), is well, and is developing normally and without any complications.

2.2 Case 2

A 7-year-old female presented to our clinic with fever and abdominal pain. Abdominal ultrasound and a CT scan showed a large mass with calcifications measuring 11 x 7.7 x 6.7 cm in the right paraspinal region. A biopsy of the mass was consistent with a ganglioneuroblastoma intermixed stroma poor. Immunohistochemical studies (CD56, chromogranin, NSE, synaptophysin) were consistent with diagnosis. Bilateral bone marrow aspirates and trephine biopsies contained unequivocal tumor cells. 131I-MIBG scintigraphy demonstrated right paravertebral region, bone marrow and bone positivity, as confirmed by TC-99-diphosphonate scintigraphy. Urinary HVA and VMA showed increased values. The diagnosis was of stage IV neuroblastoma. The patient began standard front-line therapy according to NB-AR-01 AIEOP-E-SIOP protocol. In March 2008, the patient started therapy with imatinib for the local and bone marrow residual disease and a restaging evaluation after 1 year of therapy demonstrated a complete remission of disease. Nevertheless, at 3 months off-therapy, she developed a bone metastasis (right femur) with cytological bone marrow infiltration. A salvage regimen with TVD (3 cycles) and ICE (3 cycles) was administered for 6 months manifesting a very good partial remission: This mixed response prompted a change to temozolomide and topotecan (TT). The patient completed 12 TT cycles before that a new isolate bone relapse (right tibia) (May 2012) was identified. For this reason she began salvage therapy with the

modified RIST protocol, in combination with local radiotherapy (30 Gy in 10 fractions of 300 cGy). A complete restaging after the end of RIST (January 2015) revealed a persistent complete response of disease. The patient has been off therapy for 15 months (April 2016), is well, and is developing normally and without any complications.

3 Treatment plain

The RIST design for our patients was essentially as described by Corbacioglu et al, modified using imatinib instead of dasatinib. The treatment is organized in phases, cycles and courses and is divided in three phases. Each phase consists of recurrent cycles containing the study drugs rapamycin (R), dasatinib (S; Sprycel[®]), irinotecan (I) and temozolomide (T). The treatment duration of R/S course is 4 days with a rest phase of three days: rapamycin (3 mg/m² day 1 and 1mg/m² on days 2-4) and in our case imatinib (300 mg/m²) were administered orally on days 1 to 4. Irinotecan (50 mg/m² intravenously) and temozolomide (150 mg/m² orally) were administered on the consecutive days 1 to 5.

4 Discussion

High risk stage IV neuroblastoma, >1 year of age at diagnosis, is an aggressive pediatric neoplasm marked by frequent relapses and poor overall survival. Several agents have been evaluated, but none have substantially altered long-term outcomes. Among those agents with demonstrated efficacy toward neuroblastoma the COG has demonstrated that the combination irinotecan with temozolomide has been feasible in the phase 1 setting.^[5] Therefore, temozolomide is active against relapsed solid tumors as a single agent^[6-8] and synergistic with irinotecan in a mouse xenograft model system and relapsed alveolar rhabdomyosarcoma^[9-11] Imatinib mesylate is also being studied in neuroblastoma because some tumours express c-kit and/or PDGFR.^[12,13] Both patients by our treated abided the treatment regimen relatively well with common side effects. Notably, over a long period of time (15 and 31 months) after withdrawing of therapy no evidence of disease was noted. Taken together, our data show that in a clinical setting RIST modified protocol can be considered a promising treatment strategy in relapsed/refractory high risk neuroblastoma. The metronomic application of drugs, as suggested by Corbacioglu,^[14] was designed to reduce toxic burden, emerge drug resistance and to synchronize the cell cycle phases of the individual cancer cells. Further, the altered drug administration may increase the chemosensitizing effect of the molecular targeted drugs followed by chemotherapy and may modulate the microen-

environment in a more anti-tumorigenic manner^[3,15,16] According to the results of our single-institution experience, these findings suggest that a combination regimen of RIST may provide a therapeutic benefit with a favorable toxicity profile to a unfortunate subset of patients with relapsed or refractory high risk neuroblastoma. In the absence of a more efficacious alternative, and given the need to balance disease control with quality of life for patients and families, the RIST regimen, also in our modified version using imatinib, is an attractive treatment option for patients with recurrent neuroblastoma, even in the context of extensive prior chemo-radiotherapy. In conclusion, we confirm the need of a prospective randomized multicenter trial for the treatment of patients with relapsed and refractory neuroblastoma, as is currently in progress (Eudract Number: 2011-004062-15; ClinicalTrials.gov Identifier: NCT01467986).

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