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CASE REPORT

Supportive mistletoe therapy in a patient with metastasised neuroblastoma

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SUMMARY

Therapies of complementary and alternative medicine (CAM) are used increasingly in paediatric oncology. We present and discuss the influence of supportive mistletoe therapy on factors, such as quality of life, physical ability and performance, and course of disease based on the case of a female patient diagnosed at age 18 with metastasised neuroblastoma, which responded insufficiently to chemotherapy.

BACKGROUND

Neuroblastoma (NB) is a malignant disease that develops in certain types of nerve tissue, such as the sympathetic nerve trunk, adrenal medulla or other tissue in the sympathetic nervous system. With about 1.1 cases per 100 000 children, it is the most frequent extracranial solid tumour of childhood. Because NB is an embryonal tumour, the median age of patients at diagnosis is approximately 2 years. Less than 5 per cent of newly diagnosed children are over the age of 10.[1]

The initial symptoms of NB depend on the tumour location and are often vague. They can include visible or palpable swelling on the neck or abdomen, bone pain, weight loss and changes in the skin or around the eyes. Many diagnoses occur unexpectedly during routine paediatric check-ups or exams involving other concerns.

The course of disease can vary widely among individuals and depends largely on risk factors as well as the level of tumour infiltration, patient age, and molecular genetic alterations (N-Myc amplification) and chromosome 1 mutations (1p deletion, 1p imbalance or loss of heterozygosity of the 1p chromosomal arm) in tumour cells. At the time of diagnosis, about one-half of all the patients present with some form of metastasis, typically occurring in the bone or bone marrow, lymph nodes, liver, skin and, less frequently, in the CNS or lung.[2]

Standard treatment includes surgical removal of the tumour elements, chemotherapy, and radiation and administration of metaiodobenzylguanidine (MIBG) with a radioactive tracer for internal targeted radiation therapy of the NB tumour. MIBG is an organic compound that is structurally related to norepinephrine. When attached to radioactive iodine, it can be used to treat neuroendocrine tumours as well as for nuclear medicine and molecular imaging.

High-risk patients may additionally require myeloablative high-dose chemotherapy followed by autologous stem cell transplantation. This form of therapy should always be administered in a paediatric oncology setting in controlled therapy-optimisation trials.

Alongside such vital standard therapies, complementary oncological procedures are also administered in the treatment of childhood cancer. Among parents surveyed in a large population-based study, which was conducted in cooperation with the German Childhood Cancer Registry and included 1595 children with malignant tumours, 35% of respondents stated that their child's course of treatment included complementary and alternative therapies (CAM). Anthroposophic medicine, including mistletoe therapy, was an option used by 26.7% of CAM users. In terms of effect on the disease, 63% of the parents had a positive opinion of CAM.[3]

Medicinal products made from white-berry mistletoe (*Viscum album L.*) have been clinically administered in cancer patients since 1917. The products are registered in several European countries and number among the most frequently administered forms of CAM in oncological treatment.[4] Both their biologically active substances (mistletoe lectin, viscotoxins, oligosaccharides and polysaccharides, and polyphenols and flavonoids) and their pharmacological effects, such as apoptosis induction via the mitochondrial pathway, and immunomodulation and DNA protection in lymphocytes, are well documented (see[5] for an overview).

In a review of numerous clinical studies, 21 prospective randomised trials that involved the administration of oncological mistletoe therapy satisfied the strict criteria established by Cochrane.[4] In 14 out of 16 studies that examined quality of life, mistletoe therapy was linked to a positive influence on quality of life and a better tolerance of chemotherapy. Moreover, a recent study also demonstrated a significant impact of mistletoe therapy on survival of cancer patients.[6] This result is supported by previous series of studies, though their methodological quality is notably weaker.[7]

All of the above trials involved the treatment of adult cancer patients. In paediatric settings, we can draw on decades of experience in administering *V. album L.* to children in specialised anthroposophic hospitals during or after standard therapy.[8] There are also some individual case reports detailing impressive developments in the course of disease.[9–11] Yet, there is still a lack of formal clinical trials on mistletoe therapy in paediatric cancer.

Given the above situation, a prospective, multicentre randomised phase IV trial was conducted

with 340 children diagnosed with 14 different tumour entities (including NB). The trial was designed to test an anthroposophic supportive care concept consisting of the mistletoe product Helixor A, seven additional basic medicines and a defined 'when required' medication, administered during the intensive phase of a polychemotherapy regimen. Alongside the Charité Berlin as the main trial site, the university hospital in Jena (Universitätsklinikum Jena) and 10 additional university hospitals participated in the trial. No negative interactions with the standard oncological treatment could be observed. While the researchers did not find any significant differences in terms of a reduced toxicity of standard therapy, the supportive therapy did appear to have a positive influence on quality of life and performance.[12 13]

The following case report on supportive mistletoe therapy in an NB patient is intended to supplement current knowledge on mistletoe therapy in the treatment of aggressive tumours in children and adolescent patients. It was prepared following the CARE guidelines.[14]

CASE PRESENTATION

Family history

No known family history of malignant disease.

Medical history

The symptoms of the female patient began in November 2009, at age 18. She was experiencing increasing pain in the thoracolumbar region and sacrum with intermittent pain radiating into the left leg. MRI revealed an intraspinal tumour at Th10 as well as multiple bone metastases along the spinal column with a pathological fracture of the fifth lumbar vertebra.

In the neurosurgery hospital where the patient was first admitted, an open biopsy was performed at the fifth lumbar vertebra. Because the patient presented with an ataxic gait after surgery, a second operation was performed in early January 2010 with a resection of the intraspinal tumour portion at Th10. Due to pronounced spinal instability, corset application and use of a wheelchair were necessary after surgery. The patient was transferred to a hospital specialised in paediatric and adolescent medicine for further diagnosis and therapy.

Findings on admission

On admission, the patient presented with a poor general condition (Karnofsky index 40%), pre-existing arterial hypertonia and increasing bone pain. Lab results showed elevated levels of tumour markers LDH and NSE. A urine sample revealed an increase in the catecholamine decomposition products homovanillic acid (HVA) and vanillylmandelic acid (VMA), as well as moderate thrombocytopenia (85 000/µL). In addition to pronounced skeletal metastases, MRI for staging displayed a fibrous para-aortic mass near the aorta descendens. Skeletal scintigraphy showed generalised bone metastases with osteoplastic changes (spine, shoulder joints, both scapulae, sacroiliac joint, hip joints, ischium on both sides as well as the right mid-femur) and osteolytic lesions at the 11th thoracic and the 4th lumbar vertebra. A biopsy of the iliac crest confirmed a bone marrow infiltration by blast cells.

INVESTIGATIONS

Due to the histology of the vertebral tumour biopsies and the immunohistochemical marker configuration without molecular-genetic verification of a specific translocation, the patient was given a preliminary diagnosis of a primitive neuroectodermal tumour (PNET). A guideline-compliant chemotherapy (I3VA protocol containing ifosfamide, vincristine and actinomycin D, and CEV protocol containing carboplatine, etoposide and vincristine) in accordance with the CWS guidance for patients with stage IV metastatic disease was initiated.

TREATMENT

During the first two courses of chemotherapy, there was further deterioration in the patient's general condition with the need for complete immobilisation and increased pain medication. The patient also suffered from pronounced intestinal symptoms including abdominal pain, constipation, nausea and recurrent bilious vomiting over several weeks. Since the initial diagnosis, the patient had lost almost 20 kilograms of body weight.

In the same month, the histology lab revised the diagnosis in favour of an extended, regressively transformed, poorly differentiated, stroma-poor stage IV NB. An assessment of the 1 p and N-Myc status was not possible. The diagnosis was supported by the sustained increase in NB-typical tumour markers HVA and VMA in the patient's urine, an elevated NSE blood serum level, and a bone scan revealing an uptake of MIBG by all tumour clusters, indicating catecholamine-producing tumours. On the basis of the revised diagnosis, the patient's chemotherapy regimen was adjusted in March 2010 in accordance with the NB2004 trial protocol for the treatment of NB. Due to the presence of haematogenic metastases, the patient was assigned to the high risk (HR) group.

The new chemotherapy regimen resulted in an impressive and continuous improvement in the patient's general condition and in her pain levels and mobility. After two courses, she was able to walk short distances on crutches.

Nevertheless, imaging performed during therapy showed the continued presence of extended tumour foci. Following consultation with the principal investigator of the NB trial, two further chemotherapy courses (N8), as well as MIBG therapy, were administered as additive therapy. Subsequently, in October 2010, myeloablative high-dose chemotherapy was administered, along with an autologous stem cell transplantation, in accordance with the NB2004 HR trial protocol.

Still, after 3 months of treatment, imaging did not indicate any tumour regression. Both MRI and MIBG scintiscan showed no significant changes. Due to these findings, the decision was made in January 2011 to initiate an innovative form of chemotherapy (sirolimus, irinotecan, dasatinib and temozolomide) in line with the RIST HGG trial protocol. The patient was also started on bisphosphonate therapy with zoledronate every 4 weeks.

The patient had a poor tolerance to the new chemotherapy regimen. She often complained of nausea and vomiting. She also contracted multiple infections during the neutropenic phases, which required inpatient treatment with systemic antibiotics. Because subsequent diagnostic imaging in April 2011 showed only a minor tumour regression on the bone scan and no relevant changes in the MRI, chemotherapy was discontinued at the patient's request.

Course of disease after beginning anthroposophic supportive therapy

In April 2011, the patient began a regimen of anthroposophic supportive therapy, which has shown its value in the previously mentioned randomised multicentre phase IV trial.[13] The therapy concept, in this case, revolved around the subcutaneous injection of the mistletoe product Helixor A, with an initial dose of 1.25 mg (0.25 mL Helixor A 5 mg). The patient was given biweekly injections of gradually increasing doses, as per standard

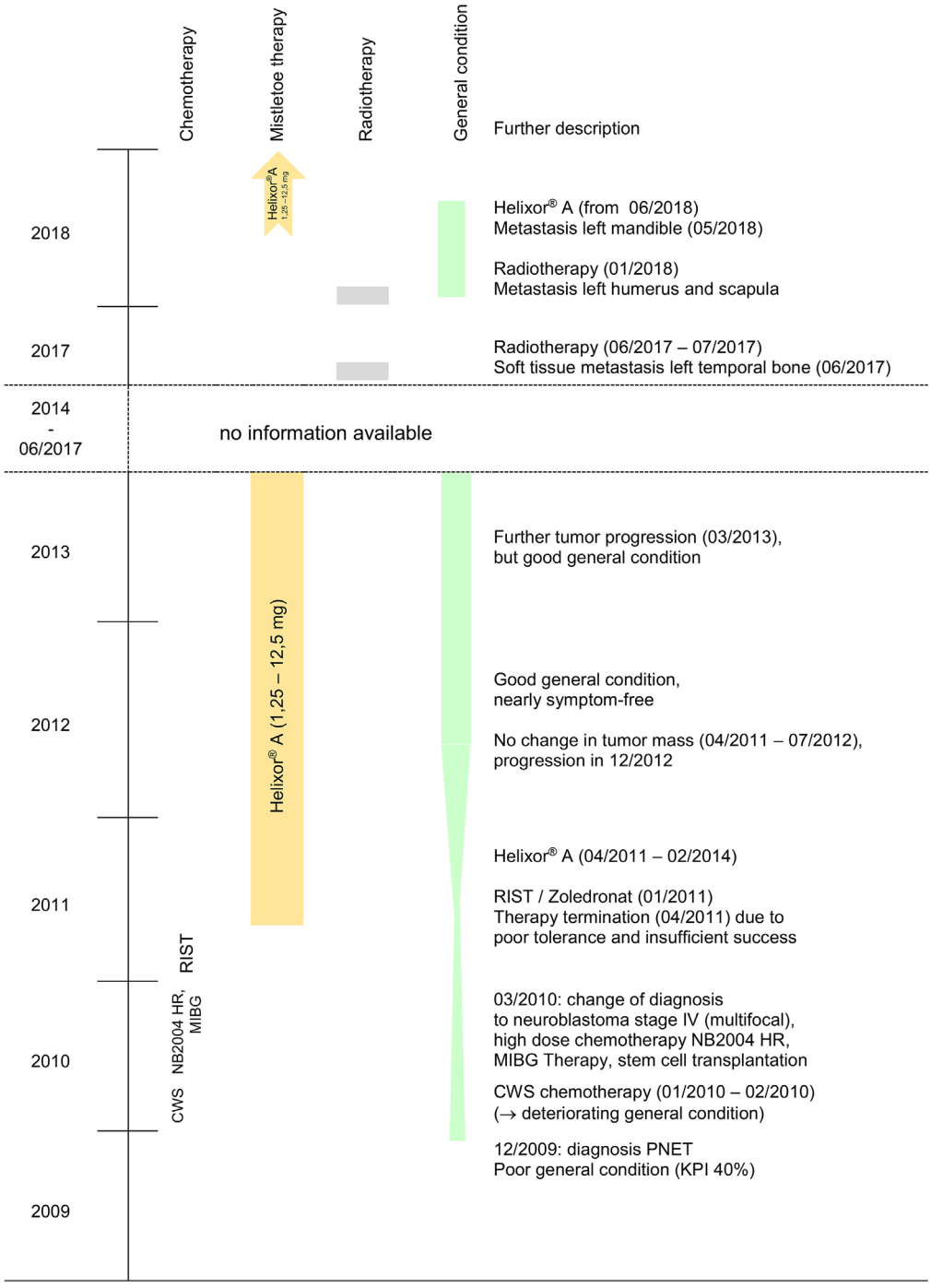

Figure 1 Treatment and course of the disease. HR, high risk; MIBG, metaiodobenzylguanidine; NB, neuroblastoma; PNET, primitive neuroectodermal tumour.

practice, up to 12.5 mg (0.25 mL Helixor A 50 mg). During this time, the patient experienced a significant increase in physical and subjective well-being. She regained her stamina to accomplish everyday activities, and even sports, such as cycling, were once again possible. The patient felt well and her symptoms had disappeared. She was able to complete her schooling in summer 2012 and start a university degree programme in psychology in October 2012.

In regular examinations (MRI and MIBG scintiscan) from April 2011 to July 2012, the patient's tumour foci initially remained constant in size. In December 2012, however, both the scintiscan and the MRI showed new tumour growth in the left proximal humerus, the second right rib, on the angulus inferior scapulae, and in the right iliac wing. Yet, the patient did not report any pain or restrictions. Diagnostic imaging in March and May 2013 showed an enlargement of the lesion in the left proximal humerus while the other tumour foci remained unchanged. Urine samples also showed elevated levels of the tumour markers HVA and VMA. On the basis of the patient's good general condition and the only remaining innovative therapy options, the treating physicians decided, together with the patient, to continue zoledronate therapy every 4 weeks, which had been

initiated in January 2011. Radiation therapy for the bone metastases, with the goal of improving bone stability, was discussed as an option, but not initiated at this point in time.

The patient regained her normal weight. She continued to receive regular biweekly subcutaneous injections of 12.5 mg Helixor A. The patient showed regularly local reactions to the injections, with redness at the injection site measuring 2–5 cm, which can be interpreted as an immunological response. About every 4–6 weeks, it was necessary to reduce the dose to 5 mg Helixor A, since the preceding local reaction to 12.5 mg was too strong. Mistletoe therapy continued to be administered in this form until February 2014.

OUTCOME AND FOLLOW-UP

The clinical course described above represents the time between the initial diagnosis in 2009 and 2013, for which exact data is available. Meanwhile, additional metastases have appeared, which were treated with conventional oncological therapies and supportive approaches. From June to July 2017, the patient received radiation therapy for soft tissue metastasis in the left temporal bone. A progressive bone metastasis in the left humerus/scapula area was treated with radiation therapy in January 2018. Radiation therapy for bone metastasis in the left lower jaw occurred in May 2018. Due to her positive experiences in the past, the patient resumed mistletoe therapy with Helixor A, previously discontinued in February 2014, in June 2018.

The clinical course is shown in figure 1. The patient still attends the university and will soon graduate with a master's degree.

DISCUSSION

Since the onset of NB, the patient was treated using several different chemotherapy trial protocols with varying degrees of success.

1. Two courses of chemotherapy according to CWS guidance and the initial PNET diagnosis, with a dramatic deterioration in general condition.
2. After the revised diagnosis, a switch to the NB2004 trial protocol with an impressive improvement.
3. Due to extended and persisting tumour foci, two additional courses of chemotherapy with additive MIBG therapy.
4. Subsequently myeloablative high-dose chemotherapy with autologous stem cell transplantation.
5. Due to the lack of tumour response, an innovative new chemotherapy according to the RIST HGG regimen was initiated but discontinued after 3 months due to insufficient response and poor tolerance. Bisphosphonate therapy, which had been initiated simultaneously, was continued.

The focus of the subsequently initiated anthroposophic supportive therapy was treated with the mistletoe product Helixor A, derived from the host tree fir.

During this treatment, the patient experienced a significant improvement in her health condition and physical ability and even the complete disappearance of symptoms, so that she could successfully resume her schooling, which had been interrupted by the disease. One year later, although the bone metastases had progressed, this development occurred, surprisingly, without any complaints or symptoms and without any impairment to the patient's general condition.

Observations of a discrepancy between good subjective well-being and the objective status of the tumour are not seldom in conjunction with mistletoe therapy. An improvement in quality of life is the most well-documented effect of mistletoe therapy in various studies and medical reports. Especially the following aspects of quality of life have been positively influenced by mistletoe therapy: cancer-related fatigue, sleep, exhaustion, energy, ability to work, nausea, vomiting and body weight, as well as pain, emotional well-being, depression, anxiety and concentration difficulties.[15] The first symptoms in this list (from energy to pain) were the most prominent in our patient and they quickly improved during treatment with mistletoe. Most impressive was the stabilisation of the patient's weight, after an initial weight loss of 20 kg.

Adolescent and adult patients with NB have a less favourable prognosis than younger patients, regardless of their N-Myc status.[2 16] In addition, the presence of haematogenous metastasis already at first diagnosis is a further prognostic disadvantage.

Patient's perspective

In late 2009, I discovered that I was ill, and was diagnosed with neuroblastoma. The diagnosis was followed by about 17 months of treatment, which included chemotherapy, high-dosage chemotherapy and a stem cell transplantation. I had extreme bone pain because of the tumours and was not able to leave my hospital bed for about 4 months. Afterwards, I still could only get around in a wheelchair or walk very short distances on crutches. Slowly, the pain subsided and I became slightly more mobile, but the side effects from chemotherapy were getting worse and worse. Nausea, loss of appetite and irritated mucous membranes were just a few.

In May 2011, the therapy was discontinued without full recovery. This was also when I started mistletoe therapy. I also began a very long and somewhat painful physiotherapy process. And I noticed improvements, almost weekly, in my condition. Gradually, I could walk longer distances and I even started driving again. Then I decided to go back to school, finish the 12th grade and attend the university. Even though I stopped chemotherapy, the tumour had not grown, and the pain in my bones was completely gone. In September 2011, I went to physical therapy in the Black Forest, where I started to do sports—very carefully, so that I would not damage my spine. But that did not stop me from climbing, testing my balance on the high-rope course or going on day trips with other patients to the surrounding countryside. I had regained the energy to enjoy everyday life without needing to take regular breaks. That would have been unimaginable just 6 months ago. As soon as I got back home, I was taking dance and vocal lessons in order to keep up with the other pupils in a musical performance in fall 2012. At school, I also had my first positive experiences and successes and my whole life felt like it was almost back to normal. I fit in with the 'normal' kids again. I returned to my regular study habits and graduated on time with my classmates in summer of 2012. And I took full advantage of the time I had before the university started in the fall. That meant spending four more weeks in physical therapy, where an extensive sports programme was waiting for me. Immediately after my return, I was off for a 2-week vacation. An entire day of sightseeing and walking through the city was no problem; I could also tolerate large crowds and tight spaces without becoming exhausted. Plus, I did not contract any colds or infections. After vacation, I moved to Leipzig to start studying psychology here in October 2012. I bike to university every day and do not have any limitations that make me different from the other students.

Given this poor prognosis and the patient's insufficient response to chemotherapy regimens, the course of disease outlined above can be considered surprisingly positive. Although the preceding courses of chemotherapy, which were at least temporarily effective after switching to the NB trial protocol, were certainly mainly responsible for the long-term stable course of disease, the significant improvement in quality of life and even freedom from symptoms, and full recovery of performance can be attributed primarily to mistletoe therapy due to the coincidence with this treatment. This is especially the case since this improvement did not co-occur with a regression of the tumour, but remained present even after new tumour growth was established.

This observation reinforces the significance of mistletoe therapy as a supportive treatment in oncology, which is primarily intended to restore well-being and performance during and following conventional therapy. With regard to children and adolescents, the effectiveness of this therapy as an element of oncological treatment, rehabilitation and aftercare should be tested in a clinical study with an appropriate number of patients focusing on mistletoe therapy, as the multicentre study,[13] cited at multiple junctures above, only allowed statements about the overall supportive concept proven involving mistletoe therapy but not about mistletoe therapy itself.

The need to account for the quality of life of young patients and potential long-term consequences of conventional therapies is increasingly finding its way into current discussions. Mistletoe therapy is capable of making an important contribution in these areas.

Learning points

- Initial chemotherapy induced regression of neuroblastoma (NB) but also reduction of quality of life.
- Significant increase in physical and subjective well-being could be achieved after beginning of mistletoe therapy in a patient with NB.
- Quality of life could be preserved for a long time even after recurrence of progression of the disease.
- To the best of our knowledge, this is the first documented case of a significant improvement in quality of life induced by supportive mistletoe therapy of a patient suffering from NB.

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