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UKRAINISCHES INSTITUT FÜR KREBSBEKÄMPFUNG

erhalten 29.5.09

Herrn
Ärztlichem Direktor
Univ.-Prof. Dr. Helmut Gadner
St. Anna Kinderspital
Kinderspitalgasse 6
1090 Wien

Wien, 29.5.2009

Sehr geehrter Herr Professor,

aus den Medien habe ich von der Erweiterung des Forschungslabors in Ihrem Spital erfahren und freue mich, dass Sie in Zukunft versuchen wollen, den krebskranken Kindern noch besser zu helfen.

In diesem Zusammenhang möchte ich Sie auf die Webseite www.ukrain.ua aufmerksam machen. Mit dem Medikament Ukrain konnte bereits vielen Kindern geholfen werden. Auch in Ihrem Hause wurden 1983 Therapieerfolge eines an Ewing Sarkom erkrankten, 9-jährigen, polnischen Mädchens röntgenologisch dokumentiert und volle Remission festgestellt. Auch die Kinder Stefan Dan und Marianna Katic wurden in Ihrem Hause diagnostiziert und behandelt. Beide Kinder wurden als austherapiert nach Hause geschickt. Nachdem sie jedoch mit Ukrain bahandelt wurden, leben sie bis heute (siehe Beilagen).

In Deutschland hat Dr. Burkhard Aschhoff ein an Ewing Sarkom erkranktes Kind behandelt, mit so gutem Erfolg, dass darüber auch im Fernsehen berichtet wurde. Die damalige 10-hährige Patientin lebt bis heute und ist 20 Jahre alt. Dr. Aschhoff erzeilte auch in anderen Fällen sehr gute Resultate - 57% volle Remission, 43% partielle Remission. Alle diese Fälle wurden in der Fachliteratur beschrieben (siehe Beilage).

Trotz der klar auf der Hand liegenden guten Ergebnisse wurde in Österreich leider kein einziges Kind mit einer derartigen Diagnose mit Ukrain behandelt. Seit diesem Zeitpunkt sind in Österreich etwa 500 Kinder an Ewing-Sarkom erkrankt. Die Patienten haben dabei eine durchschnittliche 5-Jahres-

Überlebensrate von etwa 50%. Das bedeutet, dass etwa 250 von diesen Kindern leider gestorben sind.

Es liegt doch wirklich im Sinne der Patienten, wenn Sie das Potential des Präparates Ukrain so schnell wie möglich überprüfen wollten und dabei feststellen, inwieweit Sie mit diesem Präparat den an Krebs erkrankten Kindern helfen könnten. Ukrain ist sicher und unbedenklich in Anwendung, was in mehreren – auch in Österreich vom Österreichischen Forschungszentrum Seibersdorf – durchgeführten Studien in vitro und in vivo bestätigt wurde.

Da die angesprochene Problematik nicht nur eine nationale, sondern eine internationale Angelegenheit ist, werde ich mir erlauben, diesen Brief sowie Ihre geschätzte Antwort darauf im Internet zu veröffentlichen. Ich nehme an, dass Sie nichts dagegen einzuwenden haben.

Mit freundliche Grüßen

Dr. Wassil Nowicky

INT J. IMMUNOTHERAPY **XIX**(2-4) 99-103 (2003)

TREATMENT OF GENERALIZED LYMPHANGIOMATOSIS WITH UKRAIN: A CASE REPORT

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Summary: *We report on the first case of the use of Ukrain in the treatment of generalized lymphangiomatosis complicated with decubital ulcers in a child. Lymphangiomas presented in various parts of the body. Despite a highly unfavorable prognosis, the therapy with Ukrain proved to be of significant value, benefiting the general development of the young patient and ameliorating the course of the disease.*

Introduction

Lymphangioma, or cystic hygroma, or lymphatic malformation, is a localized or generalized growth of anomalous lymphatic channels and cysts (1). These are relatively rare congenital malformations and make up approximately 6% of all benign lesions in children (2). Lymphatic anomalies occur in both sexes with equal frequency and in all races (3). Seventy to 90 percent are clinically evident at birth or become noticeable within the first two years of life (4). Lymphangiomas are usually found in the head and neck region. The axilla and mediastinum are the second most frequent location sites, and may be encountered as primary sites or as the extension of a neck lymphangioma. The retroperitoneum and the extremities are rare sites for this tumor.

There are three main groups of lymphatic malformations. The first and most common group consists of hypoplasia or aplasia of lymph vessels and nodes leading to inadequate clearance and presenting as lymphedema. The second group consists of disorders of the circulation of chyle. The third group, presenting in our patient, consists of solitary or multiple cystic lymphatic malformations. Multicystic lymphatic malformations can be micro- or macrocystic (4). Transillumination is highly characteristic of macrocystic lymphangiomas (5).

The characteristic history of a lymphatic malformation is enlargement commensurate with the child's growth, with intermittent periods of swelling due to hemorrhage into the lesion.

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Lymphangiomas may cause marked disfigurement; recurrent infections; respiratory obstructions; malocclusion; and dysphagia, dysphonia and dysarthria, as a result of the infiltration and compression of neighboring structures.

Lymphangiomas may occur in association with venous malformation. Pure venous malformations can occur in any tissue in the body and can widely infiltrate skin, muscles, joints and, sometimes, bones. Combined lymphatic-venous lesions are often associated with skeletal elongation and hypertrophy. There was no evidence in our patient of bone involvement with the malformation, which was consistent with the main element being lymphatic.

We report on the treatment of generalized lymphangiomatosis in a child with the drug Ukrain. Lymphangiomas presented in various parts of the body and the course of the disease was unfavorable.

Case report

The patient, S.D., male, was born on September 22, 1992, at 7 months of gestation, as the fourth child in a family. No congenital disorders had been observed previously in the family, and the mother subsequently gave birth to three more children without any congenital problems being observed.

A large soft tissue tumor on the left dorsal thorax wall was observed following delivery. A computed tomography (CT) scan carried out the day after delivery revealed a paravertebral lymphangioma in the left posterior mediastinum, and another in the area of the dorsal body wall. Clear communication between the tumors could not be seen on the CT. Both tumors were clearly separated from the spinal canal. A magnetic resonance imaging (MRI) scan performed on October 1, 1992, showed that the tumors were lymphangiomas, or cystic hygromas. The second paravertebral tumor had reached the arch of the aorta in the cranial direction.

During the first month of life, the swelling on the thoracic wall expanded and a skin infection occurred, following which the patient was admitted to the hospital. On admission, the patient was in good general condition, weight gain was adequate, and spontaneous motor activity was well developed. As before, there was a large, soft, fluctuating, brownish, blurred tumor.

On November 11, 1992, partial resection of the extrathoracic tumor was carried out. Under histological examination, lymphangiomatosis was verified and a residual tumor was confirmed. Wound healing proceeded very slowly and was complicated by relapsing infections treated with antibiotics.

An ultrasound examination carried out on April 20, 1993, revealed no free fluid in the abdomen and a small pleural effusion on the left side. Lymphangioma in the left inguinal area and bilateral scrotal hydrocele were diagnosed.

In June 1993, bilateral otitis media with purulent inflammation and perforation occurred and was treated with antibiotics.

A CT scan performed on November 9, 1993, revealed substantial growth of the existing tumors compared with September 1992, with partially intrathoracic and partially extrathoracic soft tissue tumors. The intrathoracic tumor surrounded the descending aorta and left clavicular artery. An MRI scan carried out on November 19, 1993, showed extended infiltration of the tumor into the spinal canal from Th1 to Th8, with maximum infiltration in Th4 to Th7; right upper dorsal lobar atelectasis was also revealed.

A CT scan performed on January 27, 1994, revealed clear extension of the extrathoracic tumor while the intrathoracic and spinal components remained unchanged. Neurological examination revealed an incomplete paraplegia, most likely L5-S1. Physical and neurosurgical examination revealed that due to the substantial tumor growth, the tumors were inoperable. Therapy with alpha-interferon (IFN)-2a (Roferon®-A3, Hoffmann-La Roche AG, Grenzach, Germany), 3

billion U/m²/day, s.c., was initiated. During IFN therapy, infections occurred frequently and were treated with antibiotics. Echocardiography revealed clear diminished left ventricular function, with the superior vena cava and vena azygos significantly dilated. Digitalis therapy with digoxin 0.125 mg p.o. (Lanicor®: Boehringer Mannheim, Mannheim, Germany) was initiated.

An ultrasound examination on March 8, 1994, revealed diffuse expansion of the tumor in the left thoracic area, and an MRI scan on April 8, 1994, showed no changes in the spinal canal.

Unfortunately, IFN therapy did not have any impact on the course of the disease and was discontinued after 4 months. No further therapy other than palliative care could be recommended by the physicians in charge of the case. The patient's general condition was extremely poor, since he could neither speak nor move. He was discharged from the hospital to home care with a very unfavorable prognosis, with the parents being told that the child would never walk or speak.

In April 1995 therapy with Ukrain (Nowicky Pharma, Vienna, Austria) was started on an outpatient basis, initially at a dose of 10 mg, i.v., on alternate days, and later at 5 mg, i.v., twice a week. Informed consent of the parents was received before the start of therapy. A letter from the Drug Council of the Austrian Ministry of Health, Sport and Consumer Protection dated June 23, 1993, approved the use of Ukrain on an outpatient basis. The patient's state improved gradually.

On July 17, August 22 and September 19, 1995, three punctures of intra-abdominal cystic lymphangiomas were performed, with 3.5, 0.5 and 1 l of hemorrhagic fluid drained, respectively (Fig. 1).

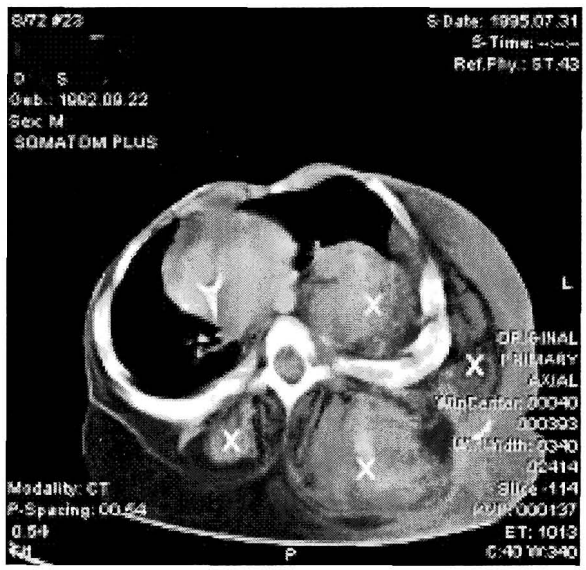

Fig. 1 Multiple lymphatic malformations (x) and a chest wall deformation are clearly seen under computed tomography scan, July 31, 1995.

In November 1995, after a total dose of 220 mg Ukrain had been administered, the patient began to move, and in December 1995, after a total administered dose of 260 mg, he began to speak his first words. By 1996, the patient could stand, and by 1997 the patient could both speak and walk.

However, on the basis of Decree GZ 21.405/1117-II/A/8/93 of February 25, 1994, of the Austrian Ministry of Health, Sport and Consumer Protection, Ukrain therapy was discontinued.

On October 9, 1998, partial resection of a left intrascrotal lymphangioma and a left thoracic lymphangioma with subsequent drainage were performed.

At the beginning of 2000, the patient's condition worsened. Tumor progression caused spinal cord compression, and paraplegia occurred. On January 15 the patient could no longer walk. On March 23, 2000, an extended resection of a thoracolumbal lymphangioma on the back and complex grafting were performed in the Department of Pediatric Surgery at the Donauspital in Vienna. The body weight before surgery was 22 kg and the weight of the ablated tumor was 10 kg. Following surgery the patient remained in a coma for 6 weeks. The patient was on assisted ventilation due to the weakness of the respiratory muscles, and morphine was administered four times a day due to severe pain.

In August 2000, two decubital ulcers developed over the right trochanter and the right shoulder blade. Paraparesis extended to Th5. The decubital ulcers were treated surgically. After discharge from the hospital, a portable ventilator had to be used and morphine administration continued at home. The patient's state seemed hopeless to the hospital physicians (Donauspital, Vienna) and they recommended resumption of treatment with Ukrain.

Therapy with Ukrain 5 mg, i.v., twice a week was resumed on an outpatient basis. Additionally, topical application of Ukrain in gauze compresses was begun. After 3 months of treatment, the patient no longer complained of pain, and morphine administration was discontinued. After 2 years of therapy, the ventilator was no longer needed. The decubital ulcers healed without skin defects.

Discussion

Treatment options for lymphangioma include surgery and sclerotherapy. Surgical treatment is challenging. Complete excision is often impossible due to the risk of damage to vital or functionally important surrounding structures. In addition, the cosmetic outcome after such radical surgery may be unacceptable, especially in children. Generally, the results of surgical treatment are currently assessed as unsatisfactory with a high incidence of recurrence and nerve damage. The case presently reported also demonstrates the high risk which accompanies surgical treatment of lymphangioma.

Several other treatment options have been used to treat lymphangioma. These include laser therapy (6); IFN-alpha (7); and various intralesional sclerosing agents, *e.g.*, boiling water, quinine, sodium morrhuate, urethane, iodine tincture, nitromin, steroids, hypertonic saline and ethanol. While little success has been reported using these options, various side effects have been observed (8). In the present case described, 60% dextrose solution was used for intralesional sclerosing therapy with little success. OK-432 (Picibanil) and bleomycin are currently the most frequently used sclerosing agents, giving quite good results (1, 9-13). However, in patients who have undergone prior surgery, the success rate is significantly lower than in primary cases due to the obliteration of communications between cysts following the earlier therapy (9).

This is the first case report of the use of the anticancer drug Ukrain in the treatment of a benign multiple tumor. Ukrain is known for its low toxicity, and its

safety was confirmed in this case. Although the course of the disease was complicated by major psychomotoric and developmental problems, the use of Ukrain was of clear benefit and improved both the general development of the young patient and the course of the disease.

The positive dynamics of the disease following the administration of Ukrain, the recurrence of disease after discontinuation of Ukrain, and the improvement in status after resumption of Ukrain therapy, all indicate that the therapeutic benefit was not a coincidence, but rather the result of the specific activity of Ukrain. The period in which administration had to be discontinued for nonclinical reasons must be regarded as a lost opportunity to heal a growing child.

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INT. J. IMMUNOTHERAPY **XIX**(2-4) 95-97 (2003)

UKRAIN TREATMENT OF ASTROCYTOMAS IN GIRL WITH TUBEROUS SCLEROSIS: A CASE REPORT

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Summary: *A 13-year-old girl with tuberous sclerosis and subependymal giant cell astrocytomas was treated with Ukrain. Although neurosurgical operations were also performed, complete tumor excision was not possible. Ukrain led to a great improvement in clinical status and also to partial regression of astrocytoma growth, which can be observed to date.*

Introduction

Ukrain, a semisynthetic drug, is a chelidonine thiophosphoric acid derivate with immunomodulatory and cancerostatic properties in cancer patients (1). Its efficacy has been shown in humans in a number of tumors with different localization: mammary gland, stomach, large intestine, lung, ovaries, urinary bladder, kidney, melanoma, cholangiocarcinoma, sarcomas, *etc.* (2). In view of these data and the description of good efficiency of Ukrain in two cases of astrocytoma (3, 4), we proposed the use of Ukrain in the case of tuberous sclerosis with subependymal giant cell astrocytomas.

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Tuberous sclerosis, or Bourneville-Pringle disease, is a complex genetic disorder characterized by the formation of multiple hamartomas of different organ systems (5). Since the first description of the classic triad of adenoma sebaceum, epilepsy and mental retardation by Vogt (6), various manifestations have been added to the clinical picture of the disease: classic shagreen patch; ungual fibroma; retinal hamartomas; renal angiomyolipomas; cardiac rhabdomyoma; and bilateral polycystic kidneys (7). Less than 2% of patients have subependymal giant cell astrocytoma (8).

Patient and method

A 13-year-old girl complained of severe headache when she was first observed in our clinic in

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October 1996. The patient was also depressed and uncommunicative. The clinical features of tuberous sclerosis, seizures and adenoma sebaceum, were present. Computed tomography (CT) scan of the brain showed a 2.2-cm tumor in the region of the septum pellucidum, extending into Monro's foramen and consequently obstructing the cerebrospinal fluid (CSF) pathway, especially at the left side. Following two previous interventions to evacuate the epidural hamartoma and to drain the left ventricle due to hydrocephalus, respectively, the patient underwent an operation for partial tumor extraction in November 1996. On histological examination, a giant cell astrocytoma was found.

After the operation severe headache remained, vomiting two to three times per week appeared, and CT scan showed cerebral hypertension. In December 1996, magnetic resonance imaging (MRI) showed the presence of five nodes with diameters ranging from 7 mm to 3.4 cm on both sides of the brain; however, the tumor seen previously by CT scan in October 1996 was not shown. On February 14, 1997, ventriculoperitoneal shunt surgery was carried out.

The patient and her parents were informed about the possible side effects of Ukrain (Nowicky Pharma, Vienna, Austria) and agreed to undergo the therapy with it. The first Ukrain injection was administered on January 1, 1997, and the course lasted until February 13, 1997. Ukrain was administered intravenously at a dose of 5 mg (5 ml) twice a week, and the total dose administered over the course of treatment was 35 mg (35 ml). In general Ukrain-monotherapy was carried out until June 1997 with the same dosage regimen.

Results

Even after the first relatively short course of Ukrain therapy, on February 15, 1997, examination by X-ray did not reveal any progressive tumor growth nor appearance of any new nodes. The patient's neurological condition improved and postoperative CT scan showed no hydrocephalus. During the treatment period both psychic and somatic status improved, the girl was lively and friendly, and managed to study at school. All follow-up CT examinations showed the regression of the non-operated nodes; only two nodes instead of five remained, with diameters of 2.5 cm and 4 mm, respectively. Furthermore, the CSF pathway obstruction was not shown. No side effects or allergic reactions were associated with Ukrain administration. The patient remains in remission to date.

Discussion

In view of the young age of the patient and the development of the clinical picture of hypertension in CSF pathways, the therapeutic approaches in this case were limited. While a number of symptomatic neurosurgical operations were performed, progressive growth of intracranial tumors made the prognosis unclear.

Ukrain administration led to a great improvement in clinical status and also to partial regression of astrocytoma growth, which can be observed to date. Accordingly, we propose the use of Ukrain as a cytostatic and immunomodulatory agent in the case of tuberous sclerosis with astrocytoma development.

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DRUGS EXPTL. CLIN. RES **XXIV** (5/6) 241-242 (1998)

UKRAIN AND HYPERTHERMIA TREATMENT IN A PATIENT WITH EWING'S SARCOMA (CASE REPORT)

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Summary: *A 10-year old girl with Ewing's sarcoma in the right femur was treated with Ukrain and hyperthermia. Six weeks after the first therapy series, computer tomography showed that progress of the disease had been halted. Following two more therapy series no negative changes could be detected.*

Introduction

Ukrain is a semisynthetic compound from *Chelidonium majus L.* and thiophosphoric acid triaziridide. Investigations show that it may trigger apoptosis in cancer cells while leaving normal cells unaffected (1). To date Ukrain has been used in more than 800 patients with various types of cancer. It can induce partial and complete remissions in different oncological diseases (2). In addition to its cytotoxicity, Ukrain has the effect of encapsulating the tumour (3).

The use of heat or fever as a therapeutic principle has its origin in ancient Egypt. The first treatment of a sarcoma by means of artificially induced high fever was carried out by Busch in Germany in 1866 and the first medical apparatus for the induction of local hyperthermia for the treatment of cancer was developed in 1898. It has been demonstrated *in vitro* and *in vivo* that exposure to temperatures between 42.5 °C and 45 °C for 10-60 min can lethally damage cells (4). Various tumours treated with local hyperthermia as monotherapy showed a response rate of 50% and even complete response in 10% of cases (5). Ewing's sarcoma represents 5% of cancer incidence in children, appearing mainly between the ages of 10 and 15, in the pelvis, thigh or lower leg bones. The 5-10-year survival rate lies between 10% and 60% (6). Ukrain had previously brought about a complete remission of Ewing's sarcoma in a 9-year old girl where chemo- and radiotherapy had had no effect (7). Chemotherapy and sometimes amputation is the conventional method for treating this disease.

Patient and methods

The patient, a 10-year old girl, was first diagnosed as having Ewing's sarcoma in the right femur in March 1996. She came under my treat-

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ment on October 13, 1997. All therapy possibilities previously administered had had no influence on tumour growth. The tumour had shown itself to be resistant to both chemo- and radiotherapy and the patient's immune system was totally suppressed. Reports from the hospital where she had been treated wrote unanimously of the progression of the disease. She had received polychemotherapy in accordance with EICESS 92, including 2 EVAIA and 12 VAIA blocks, as well as radiotherapy up to a total dose of 54 Gy. MRI examination of the pelvic region on September 1, 1997 showed a progression of the cystic-edematous process. She was then treated with combined Ukrain and local hyperthermia therapy where tumour tissue is heated to a temperature above 42.5 °C by means of a frequency of 13.56 MHz. The first therapy series consisted of 15 mg Ukrain in an infusion with 250 ml glucose and 5 g vitamin C followed by local hyperthermia treatment. Treatment was administered every second day up to a total of 10 therapy sessions.

Results

Six weeks after the first therapy series computer tomography showed no further tumour growth. Therapy series were repeated in February-March and June-July 1998 and subsequent examinations revealed complete remission of the tumour.

Discussion

Treatment was extremely well-tolerated with no side effects and the quality of life for the patient gradually improved until it was possible for her to lead a normal life for a girl of her age. Although further therapy series are necessary, the results achieved so far are extremely convincing and indicate that Ukrain should be used in cases of Ewing's sarcoma in children immediately after diagnosis.

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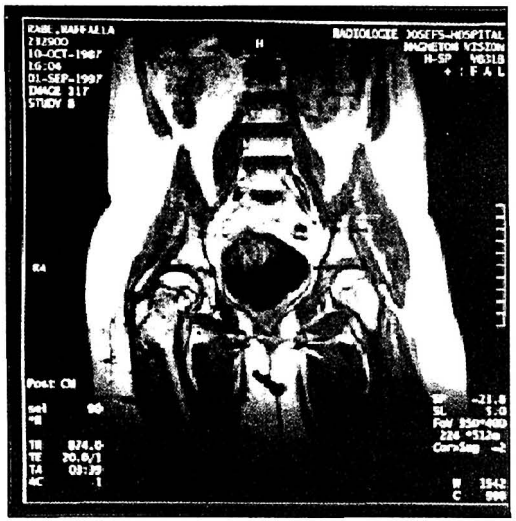
Ewing's-Sarkom, erstmalig diagnostiziert am 18. 3. 1996, histologisch bestätigt, resistent sowohl gegen Chemotherapie wie auch Strahlenbehandlung. Die Behandlung mit UKRAIN begann am 13. Oktober 1997 [115].



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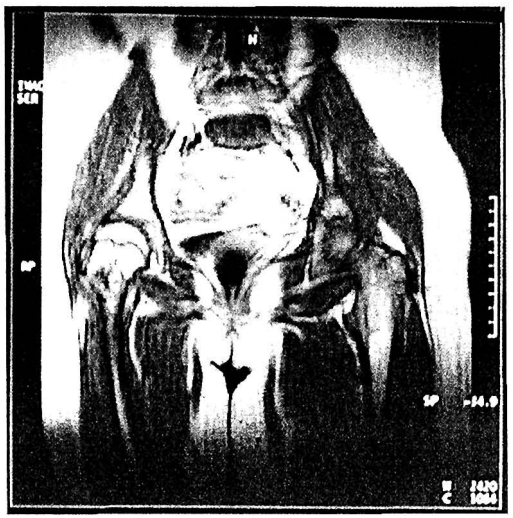
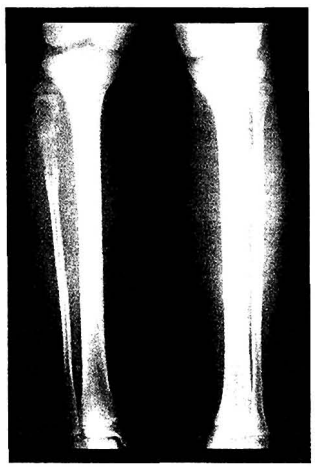


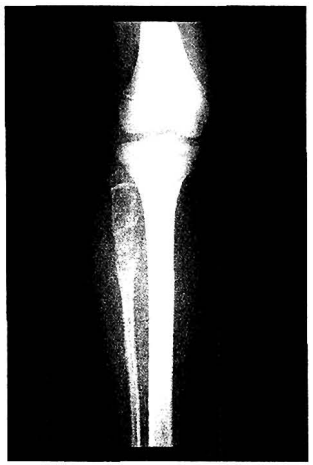
1.2.2001

Die Patientin, ein 10 Jahre altes Mädchen, wurde in der Gruppe mit hohem Risiko der EICESS 92-Studie behandelt. Die MRI-Untersuchung des Beckenbereiches am 1.9.1997 zeigte ein Fortschreiten des zystisch-ödematösen Prozesses. Danach wurde sie mit Ukrain, kombiniert mit lokaler Hyperthermie, behandelt. Die Therapie erfolgte mit 15 mg Ukrain in einer Infusion mit 250 ml Glukose und 5 g Vitamin C, gefolgt von lokaler Hyperthermie-Behandlung. Die Behandlung wurde jeden zweiten Tag verabreicht, bis zu einer Gesamtanzahl von 10 Therapiesitzungen. Die MRI-Untersuchung am 8.1.1998 zeigte keine Weiterentwicklung des Tumors. Nachfolgende Therapiezyklen bewirkten eine Regression des Tumors (siehe MRI am 15.6.1999 und 1.2.2000). MRI am 1.2.2001: Restlicher zystischer Defekt im rechten Femur (Oberschenkelknochen), der bereits in vorangegangenen Untersuchungen beobachtet worden war. Keine Anzeichen eines Rückfalles oder von Metastasen.

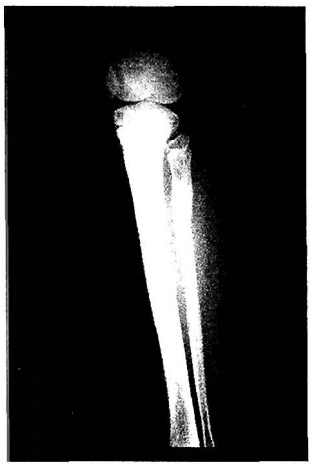
Ewing's Sarkom, erstmalig diagnostiziert am 22. 11. 1983, histologisch bestätigt, resistent sowohl gegen Chemotherapie wie auch gegen Strahlenbehandlung. Die UKRAIN-Therapie begann am 21. Jänner 1984 [28].



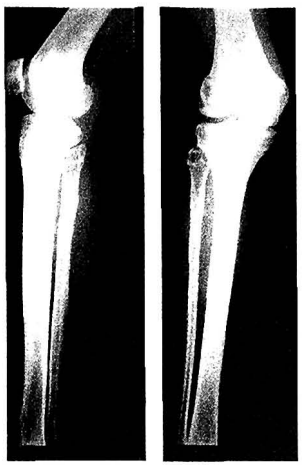
22.11.1983



18.1.1984



14.12.1984



31.10.1990

Ein 9 Jahre altes Mädchen hatte im November 1983 nach einer leichten Verletzung starke Schmerzen im rechten Kniegelenk. Im Röntgenbild erkannte man ein Ewing-Sarkom in der Nähe des rechten Wadenbeins. Im Krankenhaus wurde mit Chemo- und Kobalttherapie behandelt. Röntgenbilder bestätigten, daß der Tumor weder auf die Bestrahlung noch auf die Chemotherapie angesprochen hatte, und die Tumormasse stieg rasch an. Einen Monat nach dem Ende der Chemotherapie wurde mit einer UKRAIN-Behandlung begonnen, in der Dosis von 5 mg i.m., insgesamt waren es 10 Injektionen, kombiniert mit örtlicher tiefer Hyperthermie. Die erste Serie der UKRAIN-Therapie bestand aus drei gleichen Behandlungsabläufen mit einer Pause von zwei Wochen dazwischen. Sechs Serien dieser UKRAIN-Behandlung wurden im Verlauf eines Jahres verabreicht. Wiederholte Röntgenaufnahmen zeigten eine Reduktion der Tumormasse.