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Background: Peripheral primitive neuroectodermal tumour (pPNET) is typical for childhood and adolescent age. This kind of tumour belongs to the tumour family of Ewing sarcoma. The primitive neuroectodermal tumour is mainly localized in the central nervous system; less frequently it may also occur peripherally. The incidence of generalized peripheral primitive neuroectodermal tumour in adults is rare according to the available literature and treatment modalities are limited. The therapy is derived from protocols which were developed for the treatment of children.
Material and methods: Patients with peripheral primitive neuroectodermal tumours were retrospectively evaluated according to therapeutic response and overall survival.
Results: From January 2000 to December 2010 eleven patients were diagnosed with peripheral primitive neuroectodermal tumour in the Cancer Centre in Hradec Králové, where eight of them were also treated. The median of age at the time of diagnosis was 45 years. The median overall survival was 571 days. The most commonly used cytotoxic agents were ifosfamide, doxorubicin and etoposide.
Conclusions: The results of treatment in patients with peripheral primitive neuroectodermal tumour are not encouraging, despite a multimodal therapeutic approach involving chemotherapy, radiotherapy and surgical treatment. It is therefore necessary to centralize patients in cancer centres and to offer them preferably participation in clinical trials.

Key words: primitive peripheral neuroectodermal tumour, Ewing sarcoma, chemotherapy.

Our experiences in the treatment of peripheral primitive neuroectodermal tumour in the years 2000-2010 in the Cancer Centre in Hradec Králové

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Introduction

Based on cytogenetic, clinical and immunohistochemical similarities, peripheral primitive neuroectodermal tumour (pPNET) belongs to the Ewing sarcoma family of tumours [1, 2]. This group also includes Ewing's sarcoma (ES), rhabdomyosarcoma and desmoplastic small round cell tumour. All these tumours are characterized by their typical occurrence in childhood and adolescent age [3, 4].

Histopathologically, Ewing sarcoma family of tumours has similar morphology, which is found only in the neural crest during the embryonic ontogenesis [5]. The morphology is characterized by small round cells with uniform nucleoli and minimal cytoplasm [6, 7]. The tumour cells express the following molecules: CD99 [8], vimentin [9, 10], neuron-specific enolase, S-100 protein, Leu-7 [11]. Ewing's sarcoma is considered to be a tumour derived from more undifferentiated cells and pPNET rather from differentiated cells [12, 13].

The oncogenesis of pPNET has a genetic background. The most common chromosomal abnormalities in up to 85% cases are reciprocal translocations of the q-arm between chromosomes 11 and 22 [2, 14]; other aberrations can occur such as t(21,22), t(7, 22), t(16 22) [7, 15, 16].

Unlike previous reports, there is no difference in terms of prognosis between ES and pPNET [17-20]. The main prognostic sign is the presence of metastases at the time of diagnosis [18, 21-23].

Due to the less frequent occurrence of this disease in adulthood, there are used treatment protocols based on protocols used for treatment of Ewing's sarcoma/pNET in childhood.

Material and methods

pPNET diagnosis was evaluated retrospectively from January 2000 to December 2010. The diagnosis was based on tumour morphology and immunohistopathological examination – presence of CD99 antigen and a negative panel of signs which can be found in other similar tumours (e.g. cytokeratin, chromogranin, synaptophysin, actin, desmin, myogenin, CD20, CD3). In some cases the diagnosis was confirmed by genetic examination. There were diagnosed 11 patients (7 men and 4 women). All patients were consulted with the Cancer Centre in Hradec Králové, where eight patients were then also treated (see their characteristics in Table 1). The most common primary tumour site was the retroperitoneum (Table 2).

Table 1. Characteristics of treated patients

Age of patients to diagnosis time	Primary dissemination of tumour	Progression or dissemination during treatment
72	No	No
42	No	No
35	No	No
56	No	No
49	No	Yes
26	No	Yes
53	Yes	Yes
42	Yes	Yes

Table 2. Primary localization of tumour at diagnosis time

Retroperitoneum	4
Kidney	1
Adrenal gland	1
Thorax wall	1
Nose cavity	1
Muscle	1
Bone	1
Unknown origin	1

Results

From January 2000 to December 2010, there were diagnosed 11 patients with histological verification of peripheral primitive neuroectodermal tumour. The age range at the time of diagnosis was 8-72 years. At the time of diagnosis 8 patients were without evidence of dissemination. Three patients were sent after consultation with our department for further treatment to another cancer centre (the patients were 8,12 and 45 years old). During the therapy new local recurrence or metastatic involvement was verified in two patients. In three patients the therapy is ongoing since 31.12.2010. Median survival to the date 31.12.2010 was 571 days (range between 174 and 1517 days). In two patients there was administered more than one cytostatic line therapy. Five patients had as the therapeutic modality radiotherapy (Table 3). An overview of used cytostatics is shown in Table 4.

Discussion

Peripheral primitive neuroectodermal tumour is a tumour typical for childhood and adolescent age [3, 4, 24]. Peripheral primitive neuroectodermal tumour belongs to rare tumours with unsatisfactory treatment outcomes [25].

The main prognostic factor in ES/ pPNET is the presence of metastases at the time of diagnosis [18, 21-23, 26]. Five-year survival of patients with metastatic pPNET is according to available literature 9% to 33% [18, 21, 23, 27, 28]. Patients with lung metastases tend to have a better prognosis compared with patients with metastases involving the axial skeleton or bone marrow [23, 27].

Other negative prognostic signs are the primary location of the tumour, especially in the pelvic and axial bones [18, 22, 26, 29, 30], tumour size over 100 ml [18, 19, 31], chromosomal aberrations [32] and the failure of first-line chemotherapy or failure of response to induction chemotherapy [28, 30, 33, 34].

Parameters such as immunohistochemistry or extraosseous tumour localization have no great prognostic significance. Age as a negative prognostic sign is reported in some studies as significant [18, 19, 26], while other studies show no link between age and long-term survival [35, 36].

Table 3. Characteristics of treatment modalities and overall survival

Age of patients to diagnosis time	Overall survival from diagnosis time	Number of cytostatic regimes	Radiotherapy
72	275 ongoing treatment	1	Yes
42	830 ongoing treatment	1	Yes
35	174 ongoing treatment	1	No
56	1517	1	Yes
49	1058	3	No
26	1265	3	Yes
53	313	1	Yes
42	241	1	No

Table 4. Overview of used cytostatics: VIDE – vincristine, iphosphamide, doxorubicin, etoposide; IVAD – iphosphamide, vincristine, actinomycin D, doxorubicin; VAC – vincristine, actinomycin D, cyclophosphamide; MAID – mesna, doxorubicin, iphosphamide, dacarbazine

Name of cytostatics	Total number of cycles	Number of treatment line	Used
Cisplatin/etoposide	7	1 and 2	2
VIDE	12	1	3
IVAD-3	6	1	1
VAC	6	1	1
Iphosphamide/etoposide	3	2	1
Cisplatin/cyclophosphamide	3	3	1
Irinotecan monotherapy	3	3	1
Doxorubicin, etoposide, cisplatin	6	1	1
MAID	6	1	1
Radiotherapy			5

Because of uncharacteristic symptoms, pPNET is often diagnosed already in an advanced stage. The most common sites of pPNET are soft tissue, bone, chest wall, small pelvis and extremities. Primary extraosseous occurrence is not frequent; there are described cases of primary pPNET in visceral organs such as pancreas, vulva, uterus, or, as in our patients, in the kidney or adrenal gland [37-41].

According to tumour localization there are various symptoms such as bone pain, cough, chest pain, dyspnoea, back pain or neurological symptoms. Within the diagnostic process it is often necessary to use multiple investigative techniques from X-ray and ultrasound to CT and MRI examination, which provide basic information on the extent of the disease.

Within the differential diagnosis the following diseases should be considered: osteosarcoma, primary lymphoma of bone, sarcoma, metastatic tumours of other primary tumours. To determine the definitive diagnosis of ES/pPNET and thus to establish the optimal treatment options, histological verification should be carried out. Often it is not easy to make the diagnosis based only on the pathological description. A very helpful method today to provide the right diagnosis is cytogenetic examination. In our Cancer Centre this diagnostic tool has become a standard method.

There are limited data about treatment of pPNET in adults, because of its rare occurrence. Treatment of pPNET itself is based on a multidisciplinary approach and is often derived from the protocols used for the treatment of neuroectodermal tumours in childhood. Cooperation among the clinical oncologist, surgeon, radiotherapist, pathologist and radiologist is a prerequisite for the proper therapeutic strategy. The optimal therapeutic procedure, which is also preferred nowadays in our Cancer Centre, is neoadjuvant chemotherapy followed by radical surgery and adjuvant chemotherapy in combination with or without radiotherapy.

The cancer treatment of pPNET involves a combination of cytostatic agents given for long time even in seemingly nonmetastatic disease due to high risk of early haematological metastasis. Preferred cytostatics have changed over time. The basic cytotoxic agents used in our Cancer Centre include vincristine, doxorubicin, actinomycin D, cyclophosphamide, iphosphamide and etoposide. Peripheral PNET is a highly chemosensitive disease and nowadays the most frequently used therapy in our centre is based on the EuroEWING99 protocol. This protocol consists of 6 cycles of chemotherapy composed of vincristine, iphosphamide, doxorubicin and etoposide (VIDE) and one cycle of vincristine, actinomycin D and iphosphamide (VAI). For metastatic disease, high-dose chemotherapy is indicated with autologous transplantation [42].

The introduction of a multimodal approach into the treatment combining intensive chemotherapy with local treatment has improved the prognosis for patients with locally advanced disease [53]. However, this approach does not improve the prognosis in patients with metastases [44].

High-dose chemotherapy with autologous transplantation has been implemented for patients in the complete therapy response after induction chemotherapy since the 1980s. Some works have shown therapeutic benefit [45], but others have not [46]. The most commonly used cytotoxic agents in the myeloablative schemes are melphalan, etoposide, carboplatin, busulfan and cyclophosphamide [46].

In our centre we very often use radiotherapy for patients with pPNET. According to the most widely used protocol, EuroEwing 99, there are two modes: 1. Hyperfraction accelerated regime with two factions of 1.6 Gy per day with a total dose of 44.8 Gy, stopping for 7-10 days after half of the total dose, with the possible irradiation of residual disease to a total dose of 54.4 Gy; 2. Conventional regime after chemotherapy with a total radiation dose of 45 Gy with fractionation of 1.8 Gy per day [42].

Conclusions

The introduction of new therapeutic approaches in chemotherapy, radiotherapy or surgery has led to improvement of the treatment outcomes in patients with localized pPNET. However, the situation is different

in patients with generalized disease, where the response is inadequate. For this reason, it is appropriate to offer to these patients participation in clinical trials. The therapy should be centralized in cancer centres because of the rare occurrence of pPNET in adulthood.

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