THE SKIN DISCOLORATION AS AN ADVERSE EFFECT OF TREATMENT WITH SUNITINIB IN PEDIATRIC PATIENT WITH OSTEOSARCOMA

Lenka Součková1, 2, Pavel Mazánek2, 3, Peter Múdry2, 3
1Masaryk University, Faculty of Medicine, Department of Pharmacology
2University Hospital Brno, Department of Pediatric Oncology
3Masaryk University, Faculty of Medicine, Department of Pediatric Oncology

Sunitinib, a multikinase inhibitor, is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumor (GIST) in adults after failure of imatinib treatment due to resistance or intolerance. Another indication is the treatment of advanced/metastatic renal cell carcinoma (MRCC) or treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults. There are clinical experiences with the use of sunitinib also in pediatric oncology patients, e.g. with refractory solid tumors, GIST. The authors report a case of seven year old girl with progressive metastatic osteosarcoma treated with sunitinib and low dose chemotherapy. The sunitinib was administered in theranostic setting based on the results of genetic testing and proteomics. In connection with the use of sunitinib occurred the reversible adverse effect – skin discoloration. This adverse effect of sunitinib is the first mentioned in Czech literature in pediatric patient.

Key words: pediatric oncology, osteosarcoma, sunitinib, adverse effect.

Introduction
Sunitinib is an inhibitor of multiple receptor tyrosine kinases that are involved in tumor growth, pathologic angiogenesis, and metastatic progression of cancer, for orally use. Sunitinib is present in form of salt – sunitinib maleate, and belongs to the class of antineoplastic agents (ATC code L01XE04) with the trade name Sutent® (1).

Mechanism of action and pharmacodynamics
Sunitinib acts as inhibitor of both the receptor and non-receptor tyrosine kinases, in particular is able to inhibit of the platelet-derived growth factor receptors (PDGFRα and PDGFRB), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R) and the glial cell-line derived neurotrophic factor receptor (RET) (2).

Sunitinib compared to imatinib, which also has ATP receptor affinity towards PDGF and KIT, inhibits more VEGFR kinases, which are not the intervention target site of imatinib. This difference in interference target structures is determined by differences in the chemical structure of the two products (3). Sunitinib can thus be used for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumor (GIST), where there was a failure of imatinib treatment due to resistance or intolerant. Another indication is the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) or the treatment of patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET) with disease progression (2, 4).

Pharmacokinetics
Absorption
After oral administration of sunitinib, maximum concentration (C_max) are generally observed from 6 to 12 hours (T_max) after administration. Food has no effect on the bioavailability of sunitinib.

Distribution
During in vitro studies, the binding of sunitinib and its primary active metabolite to human plasma protein was 95% and 90% respectively, with no apparent concentration dependence. The apparent volume of distribution (Vd) for sunitinib was large – 2.230 l, indicating distribution into the tissues.

Metabolic interactions
The calculated in vitro Ki values for all cytochrome (CYP) isoforms tested (CYP1A2, CYP2A6,
to avoid co-administration of potent CYP3A4 inducers (dexamethasone, phenytoin, carbamazepine, St. John’s Wort) or inhibitors (azole antifungals, clarithromycin, grapefruit juice) because the plasma levels of sunitinib may be altered.

**Clinical experiences with the use of sunitinib in pediatric patients**

Within Pediatric Indication Pipeline (PiP) the sunitinib clinical trials are conducted in various cancer indications in pediatric patients (5, 6). In the year 2011 was completed clinical phase I trials in pediatric patients with refractory solid tumors, where the maximum tolerated dose set at 15 mg/m²/day for 28 days followed by a 14-day break, which ended the entire 6 week cycle (7). It is expected the approval of the use of sunitinib in pediatric GIST (gastrointestinal stromal tumor) in the same algorithm as for adults, after the failure of imatinib treatment due to resistance or intolerance (8).

There are the case reports on the effect of sunitinib in the treatment of osteosarcoma in children (9).

**Possibilities of osteosarcoma treatment in pediatric patients**

Osteosarcoma is the most common malignant tumor in children and adolescents aged between 10 to 20 years, it is often associated with growth acceleration (frequency: 5.6 to 1 million children under 15 years of age/1 year) (10). It is a highly malignant tumor based on the skeleton of mesenchymal tissue, which is located mostly in the metaphyseal area fastest growing long bones (femur, tibia, humerus) (11), the occurrence in the pelvic gland and the shaft of bones is also possible. The disease affects more boys than girls. Increased risk of OS occurs in patients with hereditary retinoblastoma and Li-Fraumeni syndrome.

The first clinical symptom of osteosarcoma is pain localized at the affected area. Sometimes it is manifested as joint pain, followed by edema and reduced mobility. Approximately in 15% of patients the osteosarcoma is diagnosed with primary metastases, most commonly in the lungs, or in other parts of the skeleton or in the lymph nodes (11). The fundamental diagnostic method is X ray of bone: which gives basic radiograph picture of tumor. The another imaging method is CT scan or magnetic resonance imaging of the affected area, to the exclusion of metastatic disease is made bone scintigraphy and the lung CT (12).

Current multimodal therapy consists of preoperative (neoadjuvant) chemotherapy, the second stage resection or amputation surgery followed by postoperative (adjuvant) part of chemotheraphy. Among the most commonly used drugs that showed antitumor effect in the long term treatment of osteosarcoma are cisplatin, doxorubicin, ifosfamide, and high dose methotrexate (13, 14).

The 5-year survival rate comes up to average 60–70% of children. The 5-year survival rate in diagnosed patients with metastatic disease reaches only 10–30% (14). One of the important prognostic markers that significantly influence the survival is the extent of necrotic changes in the tumor after completion of neoadjuvant chemotherapy. More than 90% of necrotic tumor cells is considered as a good response to neoadjuvant therapy, on the contrary, when less than 90% of necrotic tumor cells are in the resected tumor, it is considered as a weak response to treatment (15).

Osteosarcoma cells are not easily killed by radiation, so radiation therapy is used as a palliative therapy in inoperable tumors and especially for the analgesic effect e.g. when osteosarcoma in pelvis with multiple dissemination (16).

The efficacy of immunotherapy in the treatment of osteosarcoma was confirmed in the use of medical product Mepact® (mifamurtid or muramyl tripeptide phosphatidylethanolamine (MTP-PE). The addition of mifamurtid to chemotherapy results in statistically significant improvement in overall survival in newly diagnosed localized disease in the age group of children and young adults (17).

Even another immunotherapy in the treatment of osteosarcomas has very promising potential to improve survival and quality of life of patients with osteosarcoma. Tumor infiltrating lymphocytes and selected tumor antigens have been identified as key elements in the pathophysiology of osteosarcoma, and treatments that are able to influence, they can cause a significant break-through in the treatment of osteosarcoma (18).

For patients with the disease currently resistant to available treatments must be sought new therapeutic approaches for the use of immunotherapy and targeted therapy. This seems like a potentially promising therapeutic approach,
which could increase survival and improve the quality of life of these patients (19).

When using the approaches of personalized medicine is the ability to real-time to determine the molecular profile of the patient’s tumor and acquired knowledge to use in selecting targeted therapy of osteosarcoma (20). An example might be a targeted therapy of osteosarcomas via tyrosine kinase inhibitors, wherein the choice of the inhibitor is based on the molecular biological profile of activation (phosphorylation) kinases in cancer patients: e.g. when the proof of activation (phosphorylation) of VEGF and PDGF receptors in the tumor tissue, it is possible to use the multikinase inhibitor sunitinib inhibiting the activation of both signaling pathways of VEGF and PDGF and thus affects not only the osteosarcoma cell survival, but also inhibit angiogenesis which is essential for local progression and spread of cancer (21).

Case Report

Seven year old girl complained of a painful thigh of the right leg above the knee for 3 weeks in the winter of 2012. This was associated with a fall while skating. But the pain had been escalated especially at night. Gradually the edema of the distal third of the thighs appeared, the girl saved her limb during normal daily activities. The girl was examined at the catchment orthopedics. On a plain radiograph and subsequently on MRI there was seen the extensive tumor process in the distal third of the femur of the right leg that led to acute biopsy confirmation and histologic diagnosis of high-grade osteosarcoma with intra-epiphysis extension with and huge soft-tissue component. The staging was concluded as locally advanced disease, Enneking IIIB. There were detected several micronodules on chest CT scan, not fulfilling the criteria for metastases with size up to 5 mm.

The patient started the neo-adjuvant induction treatment with doxorubicin, cisplatin and high dose methotrexate according to the protocol AOST0331 (22) in May 2012, followed by an limb sparing surgery in August 2012, when the radical resection of the distal femur with bone substitute composite homograft from tibia was performed. The good response to neoadjuvant chemotherapy was confirmed by histological examination. The 95% of necrosis have been described and radial edges were wide at least 5 mm. The patient continued in the maintenance adjuvant chemotherapy according to the protocol AOST0331. In October 2012 mifamurtid has been added to treatment, and its administration was terminated in April 2013.

In April 2014, 2 years and 1 month after initial diagnosis, the metastatic relapse was observed in the proximal part of the left tibia. The patient underwent a biopsy. The metastasis of osteosarcoma were confirmed by histology, there were clearly present the signs of angi-invasion. The bilaterally inoperable multiple metastases in lung were reported on the chest CT scan.

In June 2014, the second line of chemotherapy was initiated. Ifosfamide and etoposide were administered in combination with zolendronic acid.

The effect of partial remission in the lungs was proven by the control chest CT scan. In August 2014, treatment was discontinued at the request of parents and started an alternative treatment outside the clinic with preparation Ukrain (23). In September 2014 the chest CT scan was made up, where unfortunately the massive progression of pulmonary metastases was documented. Followed by administration of two more units of conventional chemotherapy with ifosfamide, etoposide and zolendronic acid, through which it was possible to document partial regression of pulmonary metastases again.

In January 2015 the third-line treatment was initiated. Given the poor organ tolerance (nephrotoxicity) by the ifosfamide/etoposide blocks the metronomic therapy was started with celecoxib, etoposide, temozolomide, fenofibrate, ergocalciferol and pazopanib according to the modified protocol COMBAT III (24, 25). In May 2015 the CT scan, bone scintigraphy and FDG PET were carried out, for all imaging tests the ongoing partial response were described. Upon further re-examination in September 2015 there was unfortunately detected the progression of lung metastases size by the chest CT and the treatment schedule according to the metronomic COMBAT III was stopped.

In October 2015 the fourth line chemotherapy was initiated – 2 blocks a high dose of methotrexate. But it was possible to documented only minimal treatment response in both the lung and tumor tibia left leg. Given this clinically expressed resistance to conventional chemotherapy there was provided the proteomic analysis of tumor tissue from the time of relapse to determine the activation/phosphorylation of tyrosine kinase receptors. On the basis of results, the highest activity was observed with the phosphorylation of EGFR, VEGFR 1.2.3., PDGFRα, PDGFRβ and M-CSFR, the treatment was designed by multikinase inhibitor, sunitinib.

The treatment with sunitinib was started on December 21st 2015 at a dose of 12.5 mg/day. Given the good tolerance of the patient after one week using sunitib, the dose was increased of 25mg/day. During the visit on January 4th 2016, after 14 days of sunitinib using, the patient indicates that the 3rd day after an increasing the dose the pain of shin left leg was reduced in a tumor progressing area, but the parents pointed to a skin discoloration throughout the body – yellowing of the face, trunk, limbs and back (Fig. 1). The girl had orally given medication with cyclophosphamide 25 mg/day, Vigantol two drops daily, Potassium chloride 3 × 1 tablet tramadol 37.5 mg after 6 hours, and acetaminophen 500 mg 1–2 times daily or ibuprofen.

Fig. 1. Skin discoloration after treatment with sunitinib.
REFERENCES

2. SPC Sutent.

Fig. 2. Restoration the original skin color. 400 mg 1~2 times daily. The suspected icterus was disproved by a detailed clinical examination (yellowing scleral missing, absent icteric gradient), and also by biochemical tests of liver function, when levels of ALT 0.31, AST 0.83, ALP 1.58 (all U/L), bilirubin 14.8 mmol/L were within normal limits. The ultrasound examination confirmed normal liver size without enlargement or edema or changes in the echo structure of the liver. It was recommended to continue treatment with sunitinib at the same dose of 25 mg/day to next visit if the condition does not worsen (yellowing sclera, dark urine, itching, abdominal pain).

During further visits on the January 11th, 18th and 25th 2016 the yellow color of the skin persists, but the sclera are still anicteric. During the visit was done the physical examination of organs – heart, lungs without pathological changes. The patient is without lymphadenopathy, objectively and in good condition with excellent performance status (PS) Lansky 80. She only complains greater fatigue. The values of liver and renal parameters are still within normal range from the biochemical analysis: bilirubin 11.2, ALT 0.34, AST 0.86, creatinine 55, urea 2.6. During the visit on February 1st 2016, the yellow color of the skin is less noticeable, sclera are still anicteric without changes color (Fig. 2).

Conclusion

In the Sutent SPC in Part Special warnings and precautions for use is indicated that skin discoloration, probably due to the yellow color of sunitinib maleate, is a very common side effect, occurring in approximately 30% of patients. This side effect of sunitinib is first mentioned in Czech literature in child patient. Finally, we can recommend the implementation of differential diagnosis yellowing of the skin in patients treated with sunitinib for resolution yellowing due to hepatic damage that may be caused by this drug.