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Advanced renal cell carcinoma: pathology and systemic therapy with a new role of zoledronic acid in management of skeletal metastases

Zaawansowany rak nerki: patologia, leczenie systemowe z nową rolą kwasu zoledronowego w postępowaniu z przerzutami do kości

Gabriel Wcisło

Department of Oncology, Military Institute of Medicine, Warsaw

Renal cell carcinoma (RCC) continues to represent a major therapeutic challenge.
There is still observed the increased rate of incidence of RCC at the level of 2% per annum. Unfortunately, approximately 30% of patients develop distant metastases at first presentation. Progression of RCC accounts for additional 20% of cases with distant metastases to make up totally 50% of all RCC patients. The median survival of these patients is approximately 1 year, and the probability of survival at 2 years is 10% or even less. Metastatic RCC is extremly resistant to conventional chemotherapy. On the other hand, spontaneous regressions have been reported in some patients which suggests a role of immunity in fighting the malignancy. Thus, immunotherapy with infusions of interleukin-2 and interferon alfa have shown reproducible effects in patients with metastatic RCC. Some clinical trials have demonstrated the synergistic activity of the cytokines and anticancer agents (5-fluorouracil, vinblastine). The combination chemo-immunotherapy has revealed encouraging results of 15% to 45% response rate. Other studies have not confirmed the primary results. It has been estimated that bone metastases will develop in approximately 30% of patients with RCC. Bone metastases cause considerable skeletal morbidity, including bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy. Bisphosphonates are the promising group of drugs with activity against activated osteoclasts which in turn lyse bone. Zoledronic acid provides clinical benefits for patients with bone metastases originating of RCC and other solid tumors. The drug delays the onset of skeletal-related events.

Key words: renal cell carcinoma, bone metastasis, bisphosphonates, zoledronic acid.

Introduction to pathology, biology, and therapy of renal cell carcinoma

Renal cell carcinoma (RCC) appears to be an increasing health problem in Western countries. Anatomic location of kidneys enables tumor formation without early-warning signs. On the other hand, this malignant disease has resistant phenotype to radiotherapy and chemotherapy by which it is hard to control. Nevertheless, there is a potential role for immunomodulation the inhibition of the tumor growth.

RCC accounts for 3% of adult cancers and most commonly occurs between the ages of 50 and 70 years. In Polish population the 2000 incidence of RCC was noted at the level of 10.9/100 K in male and 16.5/100 K in women, respectively. The percent rate of patients accounts for 3.6% among men and 4.5% among women, respectively. The mortality due to RCC was noted at the level of 6.1/100 K in men and 2.4/100 K in women, respectively. Epidemiological data from the 60s to 90s have shown the steady increase of incidence and mortality in patients suffering from RCC. The US cancer statistics showed 35,710 (male – 22,080, female – 13,630) new RCC patients in 2004. There was noted 12,480 deaths because of this cancer (men – 7,870, women – 4,610) in the same year. A rate of incidence approximately 2% yearly has been increasing for last two decades [1, 2].

Little is known about the etiology of RCC but a number of environmental, hormonal and cellular factors has been studied. Smoking, obesity, long-term use of phenacetin and acetaminophen, presence of kidney stones, and exposure to cadmium, thorotrast, petroleum products, and other industrial chemicals are important risk factors for developing renal cancer. Clear-cell type makes up 80-85% of renal cancer. Kidney cancer is extremely rare in the first two decades of life. Patients below 40 years of age are diagnosed seldom, either. However, the most prevalent patients are individuals over age 60. Other histologic types include chromophil (eosinophil, basophil) cancer – 15%, chromophobe (typical, eosinophil) – 5%. Additionaly, two types comprise collecting duct carcinoma presented in 2% patients, and renal oncocytoma – 5% of cases. All types of renal cancer are in agreement with the Mainz classification [3].

The Mainz classification is now widely accepted and some cytogenetic studies have confirmed genetic changes in each tumor type. In 1960, Olberling et al. [4] showed evidence on the origin of renal cancer from proximal renal tube, and their study was based on the ultrastructural features. Since the

Rak nerki stale jest poważnym wyzwaniem dla onkologów z powodu braku znacznego postępu w leczeniu zaawansowanej choroby. Badania epidemiologiczne wskazują stały wzrost zachorowań o ok. 2 proc. rocznie. Znacząca grupa chorych na raka nerki ma 30 proc. szans pojawienia się ognisk przerzutowych w chwili rozpoznania. W wyniku progresji raka nerki kolejne 20 proc. rozwija przerzuty, co razem daje 50 proc. Średni czas przeżycia chorych na raka nerki z ogniskami odległymi wynosi ok. roku, a prawdopodobieństwo przeżycia 2 lat wynosi 10 proc., a nawet mniej. Przerzutowy rak nerki jest wybitnie oporny wobec cytostatyków. Z drugiej strony, spontaniczne regresje były odnotowane, co wskazuje na duży udział układu odpornościowego. Obecnie wlewy z interleukiny-2 i interferonu pozwalają uzyskać powtarzalne wyniki. Niektóre badania kliniczne wskazują na synergistyczne działanie cytokin razem z cytostatykami (5-fluorouracyl, winblastyna). Chemioimmunoterapia pozwoliła uzyskać odsetek obiektywnych odpowiedzi od 15 do 45 proc. Wyniki te nie zostały potwierdzone i ta metoda leczenia nie jest powszechnie akceptowana. Przerzuty do kości w przebiegu raka nerki pojawiają się u ok. 30 proc. chorych, co powoduje bóle kości, złamania patologiczne, kompresyjne złamania kręgosłupa oraz hiperkalcemię. Bisfosfoniany stanowią grupę leków hamującą lizę kości poprzez hamowanie aktywności osteoklastów. Kwas zoledronowy oferuje kliniczne korzyści u chorych na raka nerki i inne nowotwory lite z przerzutami do kośćca. Lek ten znacząco wydłuża czas potrzebny do powstania poważnych powikłań szkieletowych.

Słowa kluczowe: rak nerki, przerzuty do kości, kwas zoledronowy.

achievement, the tumor of kidney was renamed renal cell adenocarcinoma or renal cell carcinoma.

Clear-cell RCC is characterized histologically by compact alveolar, tubular, and cystic architecture, clear cytoplasm, low nuclear:cytoplasm ratio. As far as for cytogenetics, there are noted: losses of 3p, 3:8 reciprocal translocation and 5q gains.

Chromophil RCC has histologically papillary architecture with aggregates of foamy histiocytes, basophilic cytoplasm and low nuclear:cytoplasm ratio or eosinophilic cytoplasm and high nuclear:cytoplasm ratio. Cytogenetically, there are trisomy and tetrasomy 7 and 17, and loss of Y chromosome.

Chromophobe RCC while looking through a microscope comprises compact solid structure, clear or eosinophilic cytoplasm, well-seen cell membranes, great variability in cell size, and positive colloidal iron stain. Cytogenetics reveals losses of chromosomes 1,2,6,10,13,17,21.

Collecting duct carcinoma is characterized by medullary location, tubular and glandular architecture, and desmoplastc stroma. And again cytogenetically some chromosomes are lost mostly 1,6,14,15,22.

True oncocytomas are always benign and conservative surgery should be considered. But they may resemble RCC and in turn this may lead to radical nephrectomy [3].

RCC occurs in hereditary as well as nonhereditary (sporadic). Up to 4% of all RCC cases may be hereditary on the basis of family history. There are three forms of hereditary RCC: 1. hereditary clear-cell RCC, 2. Von Hippel-Lindau, 3. hereditary papillary RCC. The first one is charcterized by development of RCC in 50% of offspring. The second form is associated with Von Hippel-Lindau. The latter is a hereditary cancer syndrome in which angiomas appeared in retina, hemangioblastomas located in central nervous system, cystes in kidney, pancreas, and pheochromocytomas. The third type of hereditary RCC is diagnosed in individual persons at early onset in comparison with sporadic RCC when most patients are between 50 and70 years [5].

It is well accepted that neoplasms are of clonal origin. Accumulation of molecular events leads to existence of a tumor which in turn progresses. The feature of cancer progression renders fatal outcome. In RCC, almost 30% of patients are with developed metastatic lesions. Molecular hide-out needs to be elucided to determine key pathways responsible for progression. A help hand comes from molecular technology of microarrays. This method now is utilized in clinical studies to develop a method of classifying cancers to specific diagnostic categories based on gene expression signatures [6]. The technology gets insight into large number of defined gene fragments approximately 20 K to 60 K [7, 8]. Despite novel technology, basic systems to classify RCC comprises the Mainz classification of RCC and TNM staging [9]. Staging of RCC is expressed in two common in use systems 1. TNM and 2. modified Robson staging. The actuarial 10-year survival rate of all patients with RCC is 50%, and prognosis and survival are clearly dependent on the stage of the disease at the onset.

A therapy of RCC is complex and is associated with cooperation among urologist, oncologist, radiation oncologist. Surgical excision remains the cornerstone of treatment for RCC. The radical nephrectomy (resection of kidney, perirenal fat, and ipsilateral adrenal gland) was established in the early 60s. Benefit of lymphadenectomy is still under scrutiny. Although, in from 10 to 20% of patients nodal involvment is observed at surgery without clinical manifestations [10]. Partial nephrectomy (nephron sparing surgery) is used in patients with bilateral tumors or in case of existence only one kidney. This operative technique provides higher rate of local recurrences that is from 4% to 10% [11].

As shown previously, 30% patients are diagnosed with RCC have already metastatic lesions presented in the body at first presentation. In this clinical situation, the only therapeutic procedure relies on systemic therapy. In spite of the number of studies conducted so far non of anticancer agents

(chemotherapeutics) is accepted as a standard therapy. Potential benefits in patients with distant metastases, are tightly linked to immunotherapeutic agents: IL-2 (interleukin-2) and IFN-a (interferon-alfa). There have been conducted many studies in which alone IL-2 or alone interferon-alpha or their combination have been tested in RCC patients. The acumulating evidence has shown conflicting results of various therapy settings of utility of the cytokines. Some studies showed benefits in metastatic RCC patients who underwent front-line nephrectomy followed by combination cytokine treatment [12-16]. Mechanisms of action of cytokines is complex and unknown. Although, the cytokines bind to their receptors and initiate intracellular signaling cascades in immunocompetent cells. One of the latest trials in which high dose of IL-2 was compared with subcutaneous IL-2 and interferon-alfa showed better results in patients, i.e. 23.2% response rate after high dose IL-2 versus 9.9 % after combination IL-2 and interferon [17].

Chemoimmunotherapy is a combination regimen consisting of cytokines (IL-2 and intreferon), antineoplastic agents (5FU, vinblastine), and modulator as 13-cis-retinoic acid. Since many years Atzpodien et al. [18] have shown results in favor for combination therapy with IL-2+5FU+13-cis-retinoic acid. Others couldn't obtain comparable results. Perhaps, the differences come from varius performance status of enrolled patients. If so, there has been needed better prognostication with the usage of vehement parameters. The prognostic and predictive factors have been indicated to use them in clinical practice [19].

As shown, chemotherapy, immunotherapy, and their combination are able to offer limited benefits in patients with advanced RCC. Table 1 summarizes the results of some clinical trials focused on chemoimmunotherapy for advanced RCC. Therefore, it is a great hope to introduce novel therapeutics based on various mechanisms of activity which will be the results of translatory research. Now a number of such new drugs are tested in many clinical trials. Prolific results of laboratory work make up new drugs as CCI-779 (mammalian terget of rapamycin kinase inhibitor)[20], monoclonal antibody G250 [21], bevacizumab [22], autologous renal tumor cell vaccine tested in adjuvant setting [23].

A bone metastasis: pathophysiology and clinical relevance in patients with RCC

Bone is an engineering construction involved in vertical posture of a human being. It can be divided, microscopically, into an outer part known as cortical or compact bone and an inner part called cancellous, trabecular, or spongy bone. The first structure of bone accounts for 80% of the total skeleton. The basic unit of bone is bone structural unit. In cortical bones, there are osteons or Haversian systems that represent its basic structural bulding elements. Osteon is made of hollow cylinders (lenght approximately 2 mm), concentric lamellae between them the osteocytes are located. Osteons are separeted from one another by cement lines. The spongy bone also is made of structural units called packets. The chemical structure of bone is comprised of mineral, a fibrillar organic matrix, a cellular part, and water. Minaerals constitue 65% and are mede of hydroxyapatite. Matrix (35%) has in its structure collagen (90%), other proteins , and lipids. The cellular part of bone consists of osteoblasts, osteoclasts, osteocytes, lining cells [24].

Osteoblasts are cells which derived from mesenchymal progenitors and are involved in synthesis of the bone matrix. They are very active metabolically. Osteoblasts form an epithelial-like structure in bone at surface with connection by gap junctions containing connexins. An essential role in the control of osteoblast formation and function has a family of cell adhesion molecules. Osteoblasts secrete undirectionally the osseous organic matrix which further calcifies extracellularly. There are many biologically active substances that stimulate bone formation: fluoride, parathyroid hormone (PTH), prostaglandins cytokines. The latter are bone morphogenic proteins (BMPs), tumor growth factor beta (TGF-beta), insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF). On the other hand, corticosteroids are the strongest suppressive factors againt bone formation.

Lining cells aslo known as resting osteoblast are those osteoblasts that are not in the process of bone forming. They are flat and constitute a blood-bone barrier. Osteocytes are a kind of osteoblasts which stopped synthesizing matrix and become embedded within bone. They are the most numerous cells in bone and their function is poorly understood. However, there are some data on their role in the homeostasis of bone fluid and plasma calcium.

Osteoclasts are large multinucleated or mononucleated cells located on the surface of both cortical and spongy bones. They reside in depressions called Howship's lacunae. The main role of the cells is to resorb bone. The process relies on dissolving the bone mineral by H^+ ions originating from H_2CO_3 which in turn comes from activated osteoclast. The H_2CO_3 degradation to form free H^+ ions is a result of activity of carbonic anhydrase, and the H^+ inons are pumped out by a means of proton ATPase. Osteoclasts are firmly attached to bone matrix by the clear zone that has high expression of integrins which recognize specific peptide sequences in the matrix. There are many substances that increase bone resorption: parathyroid hormone (PTH), parathyroid-hormone-related peptide (PTHrP), calcitriol, thyroxin, interleukins – 1,6,11,17, fibroblast growth factors (FGFs), receptor activator of NF-kappaB ligand (RANKL), tumor necrosis factor-alfa (TNF-alfa), TNF-beta, tumor growth factor-alfa (TGF-alfa), stem cell-derived factor (SCF), macrophage-growth factor (M-CSF), granulocyte-macrophage growth factor (GM-CSF). Also, there are known factors playing a role in inhibiting activity of osteoclasts: calticonin, estrogens, testosteron, tumor growth factor-beta (TGF-beta), interferon-gamma (IFN-gamma), interleukins – 4,10,13,18, and osteoprotegerin.

Bone mass is maintained by a constant balance between the activity of osteoblasts, which form bone, and osteoclasts, which brake it down. In physiologic conditions, bone formation and bone resorption are closely coupled processes involved in the normal remodelling of bone. Osteoblasts make bone by producing a matrix that then becomes

mineralized. Also, osteoblasts regulate osteoclasts activity through expression of many cytokines (see the previous passage) [25].

The balance between the activities of osteoblasts and osteoclasts determines a phenotype of metastatic bone lesions. The two kind of bone cells are involved in formation of metastases confined to the skeleton. Bone metastases with a bone-forming (osteoblastic) phenotype are the results of stimulation of osteoblasts or inhibition of osteoclasts (or both) by the cancer cells. However, metastases with a bone-lysing (osteolytic) phenotype reflect inhibition of osteoblasts or stimulation of osteoclasts function (or both) by the cancer cells. Metastases from prostate cancer nearly always form osteoblastic lesions in bone. By contrast, bone metastases from kidney, lung, breast cancers more often are osteolytic [26].

Metastases of RCC are very often (19-30%) located in bone. In the study of Zekri et al. [27] there was the rate of 30% patients with RCC who developed symptomatic radiologically confirmed skeletal metastases. The metastases were typically lytic, predominantly affecting the axial skeleton and associated with considerable skeletal morbidity. Solitary bone lesions occured in 45% patients affected by skelatal changes. The median survival of patients with bone metastases was 12 months. Hypercalcemia was rather common in patients both with – 29% and without – 44% bone metastases.

While looking at the patients in the course the RCC, the additional rate of distant metastases occurred somewhere makes up from 30% to 50% of initially localized tumors. Thus, more then 60% of patients with RCC have metastaic disease in its course. There is the clinical study in which molecular technology of microarrays was used to attempt establish a genetic profile of bone metastases in RCC. Junker et al. [28] tried to define specific genetic alterations which should be common in bone metastases in RCC. Tumor DNA from 31 metastases and 13 related primary tumors was extracted. Degenerate oligonucleotide-primed polymerase chain reaction (PCR) was done to amplify the whole DNA. After labelling by PCR, comparative genomic hybridization was performed. The mean number of aberrations in one metastatic lesion was 6.1 (1-13). Losses of chromosomes 3p (76%), 6 (20%), 8p (20%), 9 (32%), 14q (27%), 18 (20%). Moreover, there were some gains of chromosomes 5 (45%), 8q (34%), 17 (27%). In 7 cases, at least one identical alteration was found in both primary and metastases. But in general, the frequency of alterations was higher in metastases.

Initial steps to form bone metastases are similar to those of metastases to any other organs and sites. Primary tumor cells invade the surrounding normal tissues by producing protelytic enzymes to spread out within the vicinity and then invade blood and/or lymphatic vessels. After entering circulation, the cancer cells that survived are able to settle down in the bone marrow cavity and are positioned to become bone meatstases [29, 30].

The mechanisms by which cancer cells cause osteolytic metastases are complex. Osteoclasts play a key role in the bone osteloysis in RCC and other cancers with propensity to form bone lesions [31]. Parathyroid-hormone-related peptide (PTHrP) is a main activator of osteoclasts which affects bone. Most studies focused on bone metastases in breast cancer have shown that high expression of PTHrP predicts the bone metastatic potential. The biologically active molecule is associated with tumor osteolytic bone destruction in many cancer, as well. Since Thiede et al. [32] showed expression of parathyroid hormone-like peptide in RCC, PTHrP has been associated with bone invasion, and hypercalcemia syndrome that occures in RCC patients [33, 34]. Hypercalcemia in one of the most common life-threatening complications in cancer patients which occurs in approximately 10-20% such patients. Parathyroid hormone-like peptide or parathyroid hormone-related protein is a mediator of hypercalcemia [35]. All biologic activity of the substance depends upon its quantity. If the production of PTHrP is regulated by cytokines its concentration is small. On the other hand, occured burden of PTHrP indicates the huge production by tumor and it works like a classic hormone. There are known other factors which stimulate hypercalcemic state as following: transforming growth factors (TGFs), active metabolites of vitamin D, prostaglandins, interleukin-6 (IL-6), RANKL [36].

Taken together, acumulating data provide molecular insight into a basis of occured metastases to bone, allow determine novel mechanisms with potential advantage in the treatment metastatic maliganat diseases by using target drugs. To reach that aim, it is a need for more studies focused on molecular biology both in experimental systems and, more important, in human samples. So far, there have been conducted a number of such studies. Weber et al. [37] showed that blockade of epidermal growth factor receptor (EGFR) signaling had rendered the inhibition of RCC growth in the bone of nude mice. The EGFR and ligands epidermal growth factor (EGF) and tumor growth factor-alfa (TGF-alfa) are overexpressed in human RCC as compared with normal renal tissue. Those cytokines are produced by RCC cells and play a main role of autocrine and paracrine factors in stimulating proliferation malignant cells after their binding to EGFR. Among new mechanisms involved in formation of bone metastases the activation of CXCR4/CXCL12 (SDF-1, stromal derived-cell factor-1) pathway plays a key role in a progression of some cancers – breast, prostate, kidney [38, 39].

Zoledronic acid offers benefits in patients with advanced RCC and skeletal metastatic lesions

The skeleton is considered as one of the most common organ affected by metastatic breast, prostate, lung, kidney, and thyroid cancers. Skeletal morbidity includes pain requering radiotherapy, hypercalcemia, pathological fracture, and spinal cord or nerve root compression. Metastatic disease may remain confined to the skleteon with the decline in quality of life and eventual death due to skeletal complications. All signs are noted in approximately half of patients with solid tumors that metastasize to bone. In 80% of patients with bone metastases from RCC will develop a skeletal complications without bisphosphonate therapy. Bone pain is frequently the first sign of metastatic disease and approximately 80% of breast cancer patients will develop bone paint that requires treatment. A prolonged

disability is pathologic fracture (rib fracure, vertebral collapse) which is the second most common complication of bone metastases occuring in 10 to 20% patients. Additionally, from 10 to 15% of patients will develop hypercalcemia due to malignancy where elevated serum calcium levels of bone destruction may lead to gastrointestinal, renal, and central nervous system dysfunction. Spinal cord compression occurs in up to 5% of patients with metastatic bone disease [40].

Treatment of bone metastases has merged various procedures as radiotherapy, orthopedic surgery, systemic anticancer treatment, and bisphosphonates. External beam radiotherapy provides excellent palliation for localized metastatic bone pain. This good result can be achieved with a short treatment swchedule of one to five fractions. Moreover, several randomized clinical trials have indicated that a single fraction of 8 Gy is adequate for pain relief.

Radiopharmaceuticals are available for the palliation of metastatic bone pain either. Strontium-89 has been used extensively in fighting prostate cancer localized to skaleton. The isotope preferentially is taken up at sites of new bone formation. Samarium-153 is linked to bisphosphonate ethylene diamine tetramethylene phosphonic acid and the isotope emits both alfa and gamma particles. It is taken up at sites of new bone formation, therefore, has been tested in breast and prostate cancer.

Metastatic destruction leads to microfractures, and subsequently total loss of bone integrity appears. Rib fractures and vertebral collapses are most common. The probability of developing a pathological fracture increases with the duration of the metastatic involvment. Orthopedic management should be intervened before a fracture occurs. Radiographic assessment gives information on the size of a lesion and the extent how seriously bone is destroyed. When less than one – third of the diameter of a long-bone is affected, pathological fracture is unusual, but when more than 50% of the cortex is destroyed the fracture possibility increases markedly to approximately 80%. In clinically broken bones, surgical therapy is needed because untreated pathological fractures rarely heal. Potential clinical benefits in patients with bone metastases after chemotherapy are highly dependent upon the cancer chemosensitivity. There is little established role for systemic therapy in RCC and malignant melanoma, while in lymhoma and germ cell tumors involving bone combination chemotherapy may be curative [41].

Bisphosphonates are characterized by a phosphorus-carbon-phosphorus central structure which promotes their binding to the mineralized bone matrix. Additionally, there is a variable chain that determines the relative potency, side effects, and seems to have influence on the strength of action. Following administration, bisphosphonates bind to exposed bone mineral around resorbing resorbing osteoclasts leading to very high local concentrations of the drug in the resorption lacunae. Bisphosphonates are internalized by the osteoclast where they cause disruption of the biochemical processes involved in bone resorption. Moreover, bisphosphonates also cause osteoclast apoptosis. But the molecular processes responsible for the programmed cell death are not known. Clinical utility of the drugs includes the treatment of hypercalcemia of malignancy, a means for pain relief, and as adjunctive therapy in metastatic bone disease. Intravenous bisphosphonates, in conjunction with rehydration, are established as the treatment of choice for hypercalcemia.

Seventy to ninety percent of patients achieve normocalcemia and relief of symptoms, and improved quality of life within 4-6 days from the beginning of such therapy. The effect of bisphosphonates on pain is probably independent of the nature of the tumor or radiographic occurance of the metastases. Sclerotic lesions respond similarly to lytic metastases for the bisphosphonates infusions. An increasing number of clinical studies has shown clinical benefits from combination therapy of bisphosphonates and anticancer agents. Most studies have been carried out in breast and prostate cancers. Bisphosphonates by inhibiting osteoclast-mediated resorption of bone matrix are veru useful drugs in decreasing the incidence of skeletal-related events in many tumor types and may complement antineoplastic therapies. An assessment of of treatment of bone metastases is rather by a lack of effective methods to measure disease response. There are some radiological methods (plain radiography, computerized tomography, magnetic resonance imaging, bone scintigraphy) and under investigation currently are biochemical methods with a leading one, namely, assessment of I collagen telopeptides as a marker of bone resorption [42-44].

Zoledronic acid is a nitrogen-containing bisphoshonate that is at least 100-fold more potent than pamidronate in preclinical models of osteoclast-mediated bone resorption. It has a substantial biological activity against tumor cells of breast, pancreas, and other cancers. The main action of the zoledronic acid is to induce antiproliferative and pro-apoptotic effects [45, 46]. Moreover, the antiangiogenic property of zoledronic acid through a significant and long-lasting reduction in serum VEGF (vascular endothelial growth factor) levels has been seen [47]. Zoledronic acid gained worldwide regulatory approval for the treatment of hypercalcemia of malignancy with serum calcium levels above 12 mg/dl. Two large randomized trials have shown better results of therapy in patients with hypercalcemia of malignancy. Now, based on more than 3,000 patients with bone metastases, it is recommended dose of 4 mg of zoledronic acid infused in 100 ml solution over 15 minutes with mild toxicity [48, 49].

Berenson et al. [50] showed results of randomized multicenter phase II study of comparison of zoledronic acid with pamidronate in patients with bone metastases. Two hundered eighty patients with breast cancer or multiple myeloma were enrolled onto the study. The study group was treated in 4 arms: 1. zoledronic acid 0.4 mg iv, 2. zoledronic acid 2 mg iv, 3. zoledronic acid 4 mg iv, 4. pamidronate 90 mg iv. The delay of progression of bone metastatic lesions was compared in zoledronic acid 2mg and 4 mg arms with pamidronate arm.

It has been reported that zoledronic acid offers greater convenience and is as effective and well tolerated as

Table 1. Results of chemoimmunotherapy for advanced RCC
Tabela 1. *Wyniki chemioimmunoterapii u chorych na zaawansowaną postać raka nerki*

Authors	Patients	Treatment	Phase study	Clinical benefit
Negrier [14]	Total - 131 Immunotherapy - 70 Chemoimmunotherapy - 61	Arm A immunotherapy IL-2 9 MIU/d s.c. for 6 days per week at weeks 1,3,5,7 + IFN-alfa 6 MIU/dsc thrice a week at weeks 1,3,5,7 Arm B immunotherapy + 5-Fu continuous infusion i.v. for 5 days at 600 mg/m^2 at weeks 1 and 5	Phase II randomized two arms	Arm A: PR - 1 pt (1.4%) Arm B: PR - 5 pt (8.1%) no difference between arms 1 year curnival in arm A 12% and B 15%
Elias [15]	35	5 treatment dozys weekly for 4 weeks every 6 weeks; weekly 5-Fu 1750 mg/m^2 continuous i.v. infusion over 24 hr followed by IL-2 6 MIU/m^2/d as continuous i.v. infusion for 4 days IFN-alfa 6 MIU/m^2 s.c. d 1,2,5	Phase II one arm	CR - 1 pt (2.1%) PR - 3 pts (6.3%) OR - 11% (95% CI: 3-27%)
Atzpodien [16]	Total - 78 Chemoimmunotherapy - 41 Tamoxifen - 37	Chemoimmunotherapy arm IFN-alfa s.c. 5 MIU/m^2 d1 week 1 and 4 days 1,3,5 weeks 2+3; and 10 MIU/m^2/d days 1,3,5 weeks 5-8 + IL-2 s.c. 10 MIU/m^2/d twice daily days 3-5 weeks 1+4; and 5 MIU/m^2/d days 1,3,5 weeks 2+3 + 5-Fu 1000 mg/m^2/d1 weeks 5-8 Tamoxifen arm: Tamoxifen p.o. 80 mg twice daily	Phase II randomized two arms	Chemoimunotherapy arm CR - 7 pts (17.1%) PR - 9 pts (21.9%) OR - 39.1% (95% CI:24.2-55.5%) overall survival 24 months Tamoxifen arm: no objective remissions reported
McDermott [17]	Total - 192 Combine immunotherapy - 96 High dose IL-2 - 96	Combine immuotherapy arm: Il-2 5 MIU/m^2 s.c. every 8 hr for 3 doses on day 1 then daily 5 days/week for 4 weeks + IFN- alfa 5 MIU/m^2 s.c. 3x per week for 4 weeks every 6 weeks High dose IL-2 arm: IL-2 600 K U/kg/dose i.v. every 8 hr on days 1 through 5 and 15 to 19 every 12 weeks	Phase III randomized two arms	Combine immunotherapy OR - 9.9% Median survival - 13 months Median response duration - 7 months High dose IL-2: OR - 23.2% Median survival - 17.5 months Median response duration – 14 months Significance between arms OR p= 0.018 Median survival p= 0.24 Median response duration p= 0,14 DFP at 3 years in favor for hight dose IL-2 p= 0.082
Atzpodien [18]	Total - 341 arm A - 132 arm B - 146 arm C - 63	arm A: (s.c. IL-2 + IFN- alfa + 5-Fu) INF- alfa s.c. 5 MIU/m^2/d1 weeks 1+4 days 1,3,5, weeks 2+3; 10 MIU/m^2 days 1,3,5 weeks 5 to 8 + IL-2 s.c. 10 MIU/m^2 twice daily days 3 to 5 weeks 1+4 and 5 MIU/m^2 days 1,3,5 weeks 2+3 + 5Fu IU 1000 mg/m^2 day 1 weeks 5 to 8 arm B: treatment as in arm A + 13-cis- retinoid acid p.o. 3x daily over 8 weeks arm C: IFN-alfa s.c. 5 MIU/m^2 days 1,3,5 week 1; 10 MIU/m^2 days 1,3,5 weeks 2 to 8; vinblastine i.v. 6 mg/m^2 weeks 2,5,8	III randomized three arms	Arm A: OR - 31% Median survival - 25 months Arm B: OR - 26% Median survival - 27 months Arm C: OR - 20% Median survival - 16 months DFP in arm B but not arm A showed significance compared with arm C (p= 0.0248)

Abberations: IL-2 - interleukin-2; IFN-alfa - interferon-alfa; s.c. - subcutaneous injection; p.o. - orally; i.v. - intravenous; MIU - million international units; K - kilo= 10^3 ; hr - hour; CR - complete response; PR - partial response; OR - overall response; CI - confidence interval; DFP - disease free progression; pt - patient; pts - patients

Table 2. Zoledronic acid therapy for bone metastases in RCC and other solid tumors
Tabela 2. *Skuteczność kwasu zoledronowego w leczeniu przerzutów do kości w przebiegu raka nerki i innych guzów litych*

Authors	Patients	Treatment	Phase study	Clinical benefit
Major et al. [48]	Total - 275 HCM pts Zol 4 - 86 Zol 8 - 90 Pam - 99	zol 4: zoledronic acid 4 mg i.v. zol 8: zoledronic acid 8 mg i.v. pam: pamidronate 90 mg i.v.	Pooled analysis of two randomized, controlled clinical trials	zol 4: CR HCM by day 10 - 88.4% (p= 0.02) zol 8: CR HCM by day 10 - 86.7% (p= 0.015) pam: CR HCM by day 10 - 69.7% * normalization of serum calcium by day 4 in 50% after treatment with zoledronic acid and 33% after pamidronate treatment
Berenson et al. [50]	Total - 280	zol 0.4 zoledronic acid 0.4 mg i.v. zol 2 zoledronic acid 2 mg i.v. zol 4 zoledronic acid 4 mg i.v. pam pamidronate 90 mg i.v.	III randomized double - blind	End points proportion of pts receiving radiation to bone skeletal-related event bone mineral density (BMD) bone markers (bone resorption markerN- telopeptide) ECOG status Pain and analgesic score Conclusion: A 5-minute infusion of 2 mg or 4 mg zoledronic acid was at leart as effective as a 2-hour 90 mg pamidronate infusions 0.4 mg dose of zoledronic acid was significantly lers effective
Rosen et al. [51]	Total - 773 NSCLC - 124 SCLC - 17 RCC - 27 CUP - 18 Head and neck - 6 Thyroid - 2 Other - 60	zol 4: zoledronic acid 4 mg i.v. (254 pts) zol 8/4 zoledronic acid 8 mg i.v. or zoledronic acid 4 mg i.v. if renal toxicity occured (265 pts) placebo: 247 pts	III randomized double - blind multicenter placebo controlled	zol 4: skeletal-related event - 38% time to first event - 230 days zol 8/4 skeletal-related event - 35% time to first event - NG placebo skeletal-related event - 44% time to first event - 163 days Significance zoledronic acid groups reduced skeletal-related events compared with placebo p= 0.023 zol 4 increased time to first event compared with placebo p= 0.023
Lipton et al. [52]	74 anly RCC	zol 4 zoledronic acid 4 mg i.v. (27 pts) zol 8/4 zoledronic acid 8 mg i.v. or zoledronic acid 4 mg i.v. of renal toxicity (28 pts) placebo 19 pts	A retrospective subset analysis pts enrolled in to Rosen et al. [51] study	zol 4 skeletal-related event - 37% annual incidence of skeletal-related events - 2.68 zol 8/4 skeletal-related event - 50% annual incidence of skeletal - related events - 1.67 palcebo skeletal-related event - 74% annual incidence of skeletal - related events - 3.38 significance reduced proportion of pts with skeletal- related events after zol 4 compared with placebo p= 0.015 zol 4 reduced annual incidence of skeletal - related events p= 0.014 multiple event analysis showed reduced by 61% the risk of developing skeletal - related events compared with placebo (hazard ratio: 0.394; p= 0.008)

Abberations: pts - patients; i.v. -intravenous; NSCLC - non-small cell lung cancer; SCLC - small cell lung cancer; RCC - renal cell carcinoma; CUP - cancer unknown primary; ECOG status - Easter Cooperative Oncology Group performance status; CR - complete response; HCM - hypercalcemia of malignancy; NG - not given

pamidronate in the treatment of bone metastases from breast cancer and multiple myeloma. Zoledronic acid has substantial activity in the treatment of bone metastases in patients with advanced prostate cancer. With the encouraging results, it has been conducted a phase III study to determine the activity of zoledronic acid vs. placebo in the treatment of bone metastases in the course of lung cancer and other solid tumors.

Rosen et al. [51] on behalf of The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group showed the results of the study in which 733 patients were enrolled. Among the investigated individuals, 74 RCC patients with bone metastases were performed. The whole population of patients was randomly divided into three arms. The first arm received therapy of zoledronic acid 4 mg (254 patients – 27 RCC patients), the second arm – zoledronic acid 8 mg (265 patients and 28 RCC patients), but in case of renal toxicity the dose reduction to 4 mg was done instead, and the third arm constituted the control group (247 patients, 19 RCC patients) who were given placebo. The primary efficacy analysis was proportion of patients with at least one skleletal-related event defined as pathologic fracture, spinal cord compression, radiation therapy to bone, and surgery to bone. Secondary analyses assessed the rate of hypercalcemia.

In this study, the proportion with a skeltal-related event was reduced in both zoledronic acid groups compared with the palcebo group (38% for 4 mg zoledronic acid, 35% for 8/4 mg zoledronic acid, and 44% for the placebo group, p=0.127). Moreover, 4 mg zoledronic acid increased time to first event (median 230 vs. 163 days for placebo, p=0.023). The most common adverse event in all treatment groups included bone pain, nausea, anemia, and vomiting. The results of the study have shown for the first time the reduction skeletal complications in patients with bone metastases other than breast and prostate cancers.

It has been reported that approximately 81% of patients with RCC and bone metastases require radiotherapy, 42% are affected by pathological fracture, and 29% of patients need orthopedic surgery. Additionally, bone metastases respond incidentally to systemic immunotherapy (interleukin-2, interferon – alfa) for RCC. Lipton et al. [52] analyzed a subset of patients with RCC and bone metastases from the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group [51]. Seventy four patients were enrolled onto the study. All patients were randomized to one of the three arms characterized in the third prior passage. For the selected patients skeletal-related events were reduced after therapy with zoledronic acid (37% in zoledronic acid group vs. 74% for placebo; p=0.015). Moreover, zoledronic acid significantly reduced the mean skeletal morbidity rate (2.68 vs. 3.38 for placebo; p=0.014) and extended the time to the first skeletal event. A multiple event analysis demonstrated that the risk of developing a skeletal-related event was reduced by 61% compared with placebo. And median time to progression of bone lesions was significantly longer in the zoledronic acid group. Toxicity of zoledrinic acid in the patients was mild and reversible. Renal failure occured in 5.6% of patients after 4 mg zoledronic acid infusion, and not reported in 8/4 mg zoledronic acid group. Mechanisms which could be responsible for activity of zoledronic acid are complex and poorly understood [53]. Clinical benefit in a patient with advanced RCC and occured bone metastases was shown by Michaelson et al. [54]. Table 2 summarizes some clinical trials of therapy bone metastases in patients with solid tumors and RCC.

Conclusions

Immunotherapy of RCC is growing in many directions. The low frequencies response which are recorded after such a therapy are rather disappointing. The steady increase of incidence of RCC renders a need for pursuing novel strategies of therapy. Biology in – depth for RCC is a right direction to establish significant pathways which could be blocked by target therapy agents. Zoledronic acid is the first bisphosphonate that demonstrates significant and durable clinical benefit in reducing skeletal complications in patients with bone metastases from various malignant diseases as breast, prostate cancers, multiple myeloma, lung cancer, and RCC. Long term treatment with zoledronic acid has been shown to be safe and well tolerated during its use in clinical practice. Renal function monitoring will rule out any kidney complications.

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Corresponding author

Gabriel Wcislo, MD
Department of Oncology,
Military Institute of Medicine
128 Szaserow Str., 00-909 Warsaw
phone/fax +48 22 610 30 98
email: Gabriel.9318030@pharmanet.com.pl