Positive effects of zoledronate on skeletal-related events in patients with renal cell cancer and bone metastases

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Introduction: *Approximately 30% of patients with renal cell cancer (RCC) develop bone metastasis causing skeletal-related events (SRE): pathologic fracture, spinal cord compression, surgery to bone and radiotherapy. Zoledronic acid demonstrated significant clinical benefit in RCC patients in a retrospective analysis.*
Primary objective of this prospective study was the proportion of patients experiencing ≥ 1 SRE during 12 months of zoledronic acid treatment and to verify the retrospective data.
Materials and methods: *Fifty patients with histologically confirmed RCC and evidence of ≥ 1 cancer-related bone lesion and ≤ 3 prior bisphosphonate applications were enrolled in 19 German centers between 2004 and 2007. The patients received 4 mg zoledronic acid every 3 weeks for 12 months followed by a follow up period for overall survival of 12 months. Bone lesions were diagnosed by bone scan or MRI-quickscan. Greater and equal to 1 lesion had to be confirmed by x-ray, CT or MRI scan. Additional bone scans were performed after completion of study treatment and if clinically indicated. In case of suspicion or evidence of a SRE it had to be confirmed radiologically.*
Results: *In total, 49 of the 50 enrolled patients were treated. Only 11 of them (22.4%) experienced any SRE until month 12. Patients with > 6 lesions and higher baseline MSKCC (Memorial Sloan-Kettering Cancer Center) score had a higher risk for SREs. Zoledronic acid was generally well tolerated and its known safety profile was affirmed.*
Conclusions: *This prospective study confirms the results of prior data about the efficacy of zoledronic acid in patients with metastatic (m)RCC, supporting its beneficial use in these patients.*

Key Words: skeletal-related events, zoledronic acid, bisphosphonates, renal cell carcinoma, bone metastasis

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Introduction

In Germany, approximately 14.000 patients are newly diagnosed with renal cell carcinoma (RCC) each year.[1] At diagnosis, approximately 20% of patients with RCC have metastatic disease (mRCC),[2] most

frequently to the lung or lymph nodes.[3] As disease progresses approximately 30% of patients with mRCC will develop bone metastases.[2] Bone metastases from solid tumors can dramatically increase bone resorption, resulting in painful and potentially life-threatening skeletal-related events (SREs) such as pathologic fractures, spinal cord compression, the need for surgery or palliative radiotherapy to the bone.[4,5] Development of SREs is associated with decreased quality-of-life and impaired functional independence as shown for patients with breast cancer and prostate cancer.[6,7] In the absence of bone-targeted therapies, most patients with metastatic bone disease will experience at least one SRE within their course of disease.[8] Pathologic fractures are often associated with an increased risk of death in most tumor types.[9] About one third of the patients with advanced RCC develop bone metastases. Once developed the patients have a short median survival of approximately 12 months and their 2 year survival rate has been only 10%-20% in the cytokine era.[10,11] Bone lesions associated with RCC are predominantly osteolytic (65%) and patients are at high risk of skeletal complications.[2] In a retrospective analysis of a randomized, phase III, placebo-controlled trial in patients with bone metastases from lung cancer or other solid tumors, 74% of patients with RCC who received placebo developed an SRE within 9 months.[12] In contrast, 49% of prostate cancer patients with basically osteoblastic bone lesions[13] and 63% of breast cancer patients with mixed bone lesions (osteoblastic and osteolytic) after 24 months treated with placebo developed SREs.[14]

Bisphosphonates which inhibit the osteoclast-mediated bone resorption are standard of care for prevention of SREs resulting from bone metastasis secondary to solid tumors and multiple myeloma. Zoledronic acid is a third-generation, nitrogen-containing bisphosphonate which has been demonstrated to exert the highest osteoclastic inhibiting activity amongst the bisphosphonates as tested in animal models.[15] Especially in advanced urologic cancer, zoledronic acid yielded clear benefits by preventing SREs. In a placebo-controlled randomized trial zoledronic acid (4 mg every 3 weeks for 15 months) reduced the risk of SREs in patients with metastatic hormone-refractory prostate cancer by 25% compared to placebo during the 24 month study.[13] Furthermore in patients with advanced bladder cancer (n = 40) zoledronic acid (4mg every 28 days for 6 months) significantly improved overall survival rates (36% versus 0%;p = 0.004) and bone health.[16]

Another randomized, placebo-controlled trial with patients with advanced breast cancer showed that zoledronic acid (given at 4 mg infusion every 3 weeks for 1 year) reduced the rate of SREs by 39% compared to placebo.[17] Long term follow up data (25 months) revealed that 4 mg zoledronic acid as a 15 minute infusion reduced the overall risk of developing skeletal complications by an additional 16% compared to 90 mg pamidronate as a 2 hour infusion in patients with multiple myeloma and breast cancer; in breast cancer patients zoledronic acid was significantly more effective than pamidronate, reducing the risk of SREs by 20% (p = 0.025) compared to pamidronate and by an additional 30% in patients receiving hormonal therapy (p = 0.009).[18]

There are limited data about the efficacy of bone-targeted therapy in patients with bone metastases from RCC, however the data of a retrospective analysis of the use of zoledronic acid are encouraging.[12] In this analysis of 74 patients with mRCC zoledronic acid significantly reduced the proportion of patients with an SRE compared to placebo (37% versus 74%; p = 0.015; 9 months follow up), reduced the mean skeletal morbidity (2.68 versus 3.38; p = 0.014), delayed the onset of the first SRE (median not reached versus 72 days; p = 0.006), and prolonged the time to progression of bone lesions (256 days versus 89 days;p = 0.014).

The study reported here is the first study with zoledronic acid that prospectively evaluates SREs in patients with mRCC and bone metastases. The aim of the trial was to confirm the clinical benefit of zoledronic acid in this patient population that was shown in the retrospective analysis.

Materials and methods

In this prospective, single arm, phase IV clinical trial 50 patients were enrolled at 19 German centers between 2004 and 2007. Each patient provided written informed consent prior to study participation. Patients were diagnosed with RCC and had evidence of ≥ 1 cancer-related bone lesion. They had received ≤ 3 prior applications of a bisphosphonate, and had an ECOG (Eastern Cooperative Oncology Group) performance status of 0-2. Patients were characterized according to the Memorial Sloan-Kettering Cancer Center (MSKCC) score.[19] Patients received 4 mg zoledronic acid every 3 weeks for a 12 month treatment period together with 500 mg of calcium supplements and a multi-vitamin tablet (containing 400-500 IU of vitamin D). The dose of zoledronic acid was adapted to baseline GFR calculated according to the Cockcroft-Gault formula. Dosing was postponed if the creatinine value was outside a predefined range.

The primary endpoint was the proportion of patients experiencing any SRE within 12 months after having entered the study. SREs were defined as pathologic bone fractures, spinal cord compression, surgery to bone and radiation therapy to bone (including the use of radioisotopes). Surgery to bone or radiation therapy to bone on the same location following a previous pathologic fracture or spinal cord compression were accounted for as separate events during the analysis. SRE occurring more than 35 days after the last application of study drug were not considered as "treatment-emergent" and were excluded from the analysis. To assess the appearance of an SRE bone scans were performed at baseline, at end of treatment and if clinically indicated (increase of alkaline phosphatase or lactate dehydrogenase > 2 times the upper limit of normal or occurrence of symptoms). The results of the bone scans were reported as Extension of Disease (EOD) score according to Soloway.[20] Suspected SREs had to be confirmed by x-ray, CT, or MRI scan. In the case a patient had experienced an SRE they could continue study treatment. Extension of disease with regard to thoracic or abdominal metastases was measured by a baseline CT or MRI scan followed by assessments if disease progression was suspected. After treatment completion, patients entered a survival follow up for up to 12 months.

The assessment of safety was based on the frequency and type of adverse events, laboratory values and notable changes in vital signs.

Data were summarized with respect to demographic and baseline characteristics, efficacy and safety observations and assessments. Summary statistics included number of observations, mean value, standard deviation, median, minimum and maximum values for continuous variables, and frequencies and percentages for categorical variables. Time to event variables were analyzed using the Kaplan-Meyer method. All statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 5%, and p values were used in a non-confirmatory, exploratory manner.

Results

In total 50 patients were enrolled into the trial, of which 49 patients were treated with zoledronic acid. One patient withdrew consent prior to administration of the first study treatment. The median age was 63 years, 59% of the patients received the diagnosis of mRCC less than 1 year ago, 80% had less than six bone metastases (EOD1) and 82% had no prior SRE, Table 1. Prior antitumor therapies are summarized in Table 2.

TABLE 1. **Patient and tumor characteristics**

	Patients n (%) (n = 49)
Age, years, median, min-max	63, 38-80
Sex (n, %)	
Female	15 (30.6)
Male	34 (69.4)
Time since diagnosis	
≤ 1 year	29 (59.2)
1-5 years	13 (26.5)
≥ 5 years	7 (14.3)
Soloway EOD score	
EOD1: < 6 bone metastases	39 (79.6)
EOD2: 6-20 bone metastases	9 (18.4)
EOD3: > 20 bone metastases but > super scan	1 (2.0)
MSKCC risk status score	
Favorable (0)	5 (10.2)
Intermediate (1 or 2)	32 (65.3)
Poor (≥ 3)	7 (14.3)
Prior SRE	
No	40 (81.6)
Yes	9 (18.4)
Patients with concomittant tyrosine kinase treatment	
Sunitinib	8 (16.3)
Sutent	6 (12.2)
Sunitinib and Sutent	5 (10.2)
Mean duration of Expore together with zoledronic acid (days)	168 (1-392)

EOD = extension of disease; MSKCC = Memorial Sloan-Kettering Cancer Center; SRE = skeletal-related event

Twenty-five (51%) of the treated patients completed the 12 months of study treatment. Fifty-seven percent of the patients received zoledronic acid for at least 271 days, whereas 24.5% of them received zoledronic acid between 1 to 90 days and 18.4% between 91 and 271 days. Agents without European licenses were not permitted during trial participation. Clinically relevant adverse events (14.3%), death (12.2%) and withdrawal of consent (8.2%) were the most frequently reported reasons for premature discontinuation.

Eleven (22.4%) of the 49 treated patients experienced any SRE until month 12, Figure 1. Seven (33.3%) patients experienced a pathologic fracture, six (28.6%) were treated with radiation or surgical therapy each, and two

TABLE 2. **Prior antitumor therapy**

Prior therapy	**Patients n (%) (n = 49)**
Surgery	48 (98.0)
Nephrectomy	46 (93.9)
Lymphatic	7 (14.3)
Osseous/musculoskeletal	7 (14.3)
Thoraric	3 (6.1)
Others	15 (30.6)
Radiation therapy	40 (81.6)
Chemotherapy	13 (26.5)
Interferons	10 (20.4)
Interleukins	8 (16.3)
Pyrimidine analogues	8 (16.3)
Investigational drug	3 (6.1)
Bisphosphonate (zoledronic acid)	1 (2.0)

(9.5%) suffered from a spinal cord compression, Figure 2. Of the 11 patients with SRE, four (36.4%) patients suffered from one SRE, another four (36.4%) patients developed two SREs and 3 (27.2%) patients experienced three SREs. The median time to the first SRE was not reached, Figure 3. No statistically remarkable differences could be seen in the rate of SREs with regard to sex and age of the patients. SREs were most frequent in patients (ITT-population) with 6-20 bone lesions and

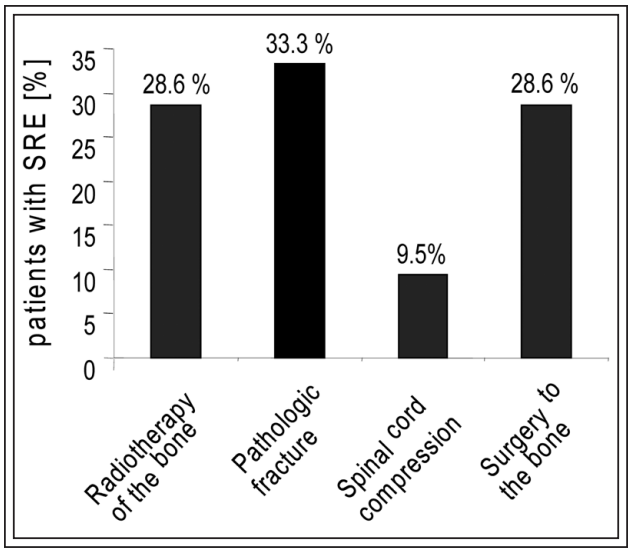

Figure 2. Nature of skeletal-related events (SREs): proportion of patients suffering from the following SREs: radiation therapy to the bone, pathologic fracture, spinal cord compression and surgery to the bone.

in the group with MKSCC score poor risk (more than 2 factors), Table 3. There was no difference with regard to on study SREs between patients having had an SRE before study entry (22.2%) and those without (22.5%).

Thirty-eight patients entered the follow up period of the study. The median duration of the follow up was 390 days. Ten patients died during the follow up

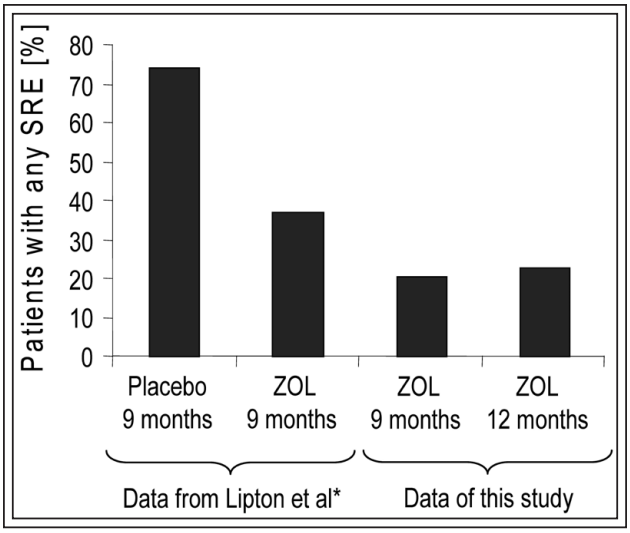

Figure 1. Patients with at least one skeletal-related event (SRE). Proportion of patients (%) treated with zoledronic acid (ZOL) or placebo: results of the treated patients of this study in comparison with the retrospective data.

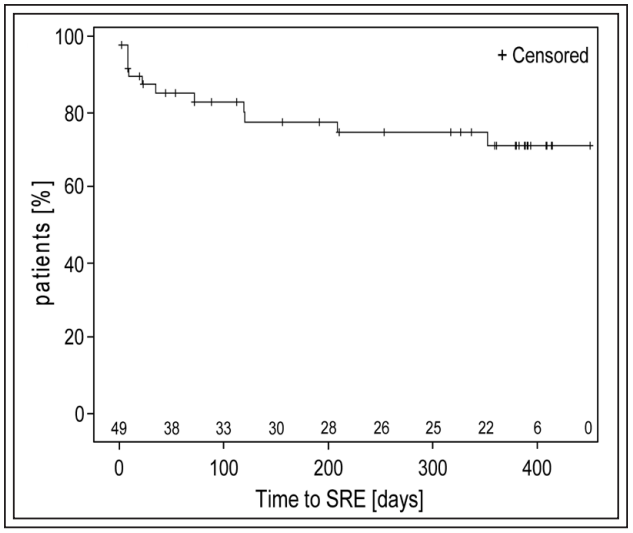

Figure 3. Kaplan-Meier plot of time to first skeletal-related event (SRE) (ITT population) including the number of patients at risk. The median time to first SRE was not achieved.

TABLE 3. **Medical history: influence on SRE occurrence**

	Patients, n	no SRE Patients, n (%)	SRE Patients, n (%)
SRE before study entry			
No	40	31 (77.5)	9 (22.5)
Yes	9	7 (77.8)	2 (22.2)
MSKCC score			
Favorable risk (0)	5	5 (100.0)	0 (0.0)
Intermediate risk (1)	15	13 (86.7)	2 (13.3)
Poor risk (2 or more)	24	18 (75.0)	6 (25.0)
Missing	5	2 (4.0)	3 (60.0)
Bone metastasis			
< 6 bone lesions	39	32 (82.1)	7 (17.9)
> 6 bone lesions	10	6 (60.0)	4 (40.0)

SRE = skeletal-related event; MSKCC = Memorial Sloan-Kettering Cancer Center

period. None of these deaths was drug-related.

In total, 48 (98.0%) patients experienced at least one adverse event. Twenty-one (42.9%) patients experienced an adverse event with a suspected drug relation, Table 4. Dose adjustments (reduced dose, prolonged interval) due to adverse events were required in eight patients (16.3%), three of the events were suspected to be drug-related (leucopenia, ONJ, toxic cutaneous reaction). The most frequently reported drug-related adverse events were flu-like symptoms (18.4%), musculskeletal and connective tissue disorders (16.3%), and gastrointestinal disorders (6.1%), Table 5. Sixty-nine (15.6%) serious adverse events were reported for 28 (57.1%) patients, Table 4. Seven serious adverse events (1.6% of total adverse events) led to permanent discontinuation, three serious adverse events were suspected to be drug-related (wound healing disorder (n = 1), osteonecrosis of the jaw (ONJ, n = 2) and four serious adverse events were not suspected to be related to study drug (cachexia, renal failure, tumor thrombosis, ileum perforation), Table 5. Three patients (EOD1, 2 patients with prior SRE) experienced ONJ (1 mild, 2 severe). All of them had a dental history (tooth extraction, dental prothesis). Six (12.2%) patients died during the duration of the study, which was either due to disease progression (n = 3), pulmonary embolism (n = 1), sepsis (n = 1) and cardiac arrest (n = 1). None of these fatal outcomes was drug-related.

TABLE 4. **Overview of adverse events**

AEs/SAEs	**Patients n (%) n = 49**
All AEs	48 (98.0)
With suspected drug relation	21 (42.9)
Leading to dose adjustment or temperature interruption	8 (16.3)
Leading to permanent discontinuation	9 (18.4)
Requiring concomitant medication/non-drug therapy	44 (89.8)
SAEs	28 (57.1)
Deaths	6 (12.2)
SAEs with suspected drug relation	4 (8.2)
SAEs leading to permanent discontinuation	7 (14.3)

AEs = adverse events; SAEs = serious adverse events

Discussion

This study is the first prospective study of zoledronic acid in patients with mRCC and bone lesions, which clearly demonstrates the efficacy of zoledronic acid in these patients. During this single-arm phase IV study SREs were experienced by 22% of the patients during 12 month treatment. These findings confirm the results of a previous retrospective study which demonstrated a strongly reduced proportion of SREs among patients with RCC who received zoledronic acid compared to placebo (37% versus 74%; p = 0.015; 9 month follow up).[12] The 9 month SRE rate of the recent study was only 20%, Figure 1. There was no different incidence of

TABLE 5. **Most frequent drug-related adverse events**

AEs/SAEs with suspected relation to study drug	**Patients n (%) n = 49**
AEs with suspected relation to study drug	**21 (42.8)**
Flue-like symptoms	9 (18.4)
Musculoskeletal and connective tissue disorders	8 (16.3)
Gastrointestinal disorders	5 (10.2)
Skin and subcutaneous tissue disorders	3 (6.1)
Ear and labyrinth disorders	2 (4.1)
Blood creatinine increased	2 (4.1)
Nervous system disorders	2 (4.1)
Respiratory, thoracic and mediastinal disorders	2 (4.1)
Vascular disorders	2 (4.1)
Infections and infestations	1 (2.0)
Metabolism and nutrition disorders	1 (2.0)
Blood and lymphatic system disorders	1 (2.0)
Psychiatric disorders	1 (2.0)
Eye disorders	1 (2.0)
SAEs with suspected relation to study drug	**7 (14.3)**
ONJ	3 (6.1)
Impaired healing	2 (4.1)
Bone lesion	1 (2.0)
Toothache	1 (2.0)

AEs = adverse events; SAEs = serious adverse events
ONJ = osteonecrosis of the jaw

treatment-emergent SRE depending on the experience of any prior SRE or no prior SRE (22% each), indicating that an SRE before start of treatment with zoledronic acid did not alter the risk for an SRE in our study population.

In the current study, the risk for SREs was higher for patients with the MSKCC category of "poor risk" (> 2 risk factors) and for patients with 6-20 bone metastases at baseline, suggesting that these patients could benefit most from an early start of treatment with zoledronic acid in a less advanced disease state. Furthermore, patients belonging to a higher risk group should be examined more frequently so that an early treatment for bone metastasis can be initiated.

The overall survival rate of 80% of the patients after 540 days follow up is remarkable as of all patients only 19 patients with a median time of 168 days received targeted agents (e.g. sunitinib or sorafenib). These latter drugs for treatment of advanced RCC were not commercially available during the main recruitment period of this study. The reported median survival for advanced RCC treated with cytokines is approximately 13 months with a 1 year survival rate of 54%.[21] The observed beneficial overall survival in the study population could be the result of a high proportion of good and intermediate risk patients (75%), the prior nephrectomy in nearly all patients or a treatment effect of zoledronic acid. The impact of all these variables on overall survival has been described previously.[21-23] In a retrospective subgroup analysis Lipton et al described a significantly increased progression free survival of almost 6 month for zoledronic acid treated RCC patients. Furthermore a combined analysis of 94 patients with RCC and bone metastases revealed that zoledronic acid treatment was associated with 46% decrease in the risk of death versus placebo (overall survival of 11.4 months for zoledronic acid versus 7.1 months for placebo; p = 0.014).[24] The positive effect of zoledronic acid on tumor progression and overall survival could be explained by the prevention of SREs and the documented antitumor properties of this bisphosphonate as described by Saad for other solid tumors or multiple myeloma.[23]

Zoledronic acid was generally well tolerated in this group of patients. Twenty-eight of 49 (57%) patients received zoledronic acid for at least 271 days. Eight of 49 patients (16%) needed a dose adjustment or temporary interruption of treatment. Only nine patients (18%) permanently discontinued the study treatment because of adverse events. Taken together, these findings confirm zoledronic acid as a safe treatment with a well known safety profile.

Emerging data from different studies using zoledronic acid in combination with radiotherapy, sunitinib and radiotherapy or interferon alpha, thalidomide and interferon-gamma fluvastatin or atorvastatin reported a reduction in metastatic bone lesions, decreased tumor size, and prevention of metastatic progression with RCC.[25-29]

Conclusion

Zoledronic acid provides clinical benefit in patients with advanced RCC and bone lesions by preventing SREs. The results of this clinical trial confirm the findings of a retrospective subgroup analysis and demonstrate the beneficial use of zoledronic acid in patients with bone metastases from RCC. In mRCC, the use of zoledronic acid as a bone targeted therapy

should be the standard for an effective treatment of bone metastases and for the prevention of skeletal related events. In addition, zoledronic acid could concomitantly influence the survival of the patients. However, as the advent of targeted therapies has changed treatment algorithms in mRCC substantially, the combination of both modalities targeting the tumor and the bone remains undefined and should be addressed prospectively.

Disclosure

Dr. K. Birkholz, Dr. A. Rübel and Dr. C. May are employees of Novartis Pharma GmbH, Germany. Dr. A. Strauss has received honorariums from Bayer, Novartis, Pfizer, Roche and Sanofi-Aventis and financial support for research from Bayer, Novartis and Pfizer. Prof. Dr. Tunn is a member of the advisory board and is a lecturer of Novartis Pharma GmbH, Lilly Deutschland GmbH and Abbott International. □

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