Bisphosphonates (Bis) combined with sunitinib (Su) may improve the response rate (RR), progression free survival (PFS) and overall survival (OS) of patients (pts) with bone metastases (mets) from renal cell carcinoma (RCC)

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Abstract

Background: Bis are used to prevent skeletal events of bone mets, and may exhibit anti tumor effects. We aimed to evaluate whether Bis can bring a RR, PFS, and OS benefit to pts with bone mets from RCC that are treated with Su

Methods: We performed an international multicenter retrospective study of pts with bone mets from RCC who were treated with Su. Pts were divided into Bis users (group 1) and nonusers (group 2). The effect of Bis on RR, PFS and OS, was tested with adjustment for known prognostic factors using a chisquare test from contingency table and partial likelihood test from Cox regression model

Results: Between 2004-2011, 244 pts with metastatic RCC were treated with Su. 92 pts had bone mets, 41 group 1 and 51 group 2. The groups were balanced regarding the following known prognostic factors: past nephrectomy, clear cell/non clear cell histology, initial diagnosis to sunitinib treatment (tx) time, the presence of ≥ 2 mets sites, presence of lung/liver mets, ECOG performance status, anemia, calcium level > 10 mg/dL, elevated alkaline phosphatase (AP), pre-tx neutrophil to lymphocyte ratio (NLR) >3, sunitinib induced HTN, and the use of angiotensin system inhibitors. They were also balanced with regard to past cytokines/targeted tx, and mean sunitinib dose/cycle. Objective response was partial response/stable disease 85% (n=35) vs 71% (n=36), and progressive disease 15% (n=6) vs 29% (n=15) (OR 3.287, p=0.07) in group 1 vs 2, respectively. Median PFS was 15 vs 5 months (HR 0.433, p =0.035), and median OS not reached with a median followup time of 43 vs 12 months (HR=0.398, p=0.003), in favor of group 1. In multivariate analysis of the entire pt cohort(n=92), factors associated with PFS were Bis use (HR 0.433, p=0.035), pre-tx NLR ≤ 3 (HR 0.405, p=0.016), and elevated AP (HR 3.63, p=0.012). Factors associated with OS were Bis use (HR 0.32, p=0.003), elevated AP (HR 3.18, p=0.002), and Su induced HTN (HR 0.193, p < 0.001)

Conclusions: Bis may improve the outcome of Su tx in RCC with bone mets. This should be investigated prospectively, and if validated applied in clinical practice and clinical trials

Background

1) An understanding of the pathogenesis of RCC and randomized clinical trials, have established the standard role of the orally administered VEGFR and PDGFR inhibitor sunitinib for the treatment of RCC (1)
2) 33% of pts with metastatic RCC suffer from bone mets (2)
3) Bis are used to prevent skeletal events of bone mets, and may exhibit anti tumor effects (3)
4) The role and efficacy of bisphosphonates in conjunction with modern targeted agents is currently unknown (4)

Aims

To evaluate whether Bis can bring a RR, PFS, and OS benefit to pts with bone mets from RCC that are treated with sunitinib

Methods

1) 244 pts with metastatic RCC were treated with su between 2004-2011, in 6 centers across 2 different countries. Of these, 92 pts with bone mets comprised the study group
2) Data were retrospectively collected
3) Statistical analysis
   a. Pts were divided into Bis users and nonusers.
   b. Baseline clinical characteristics and known prognostic factors were compared between Bis users vs non users, by either chi-square test (for categorical measures) or two-sample t-test (for continuous measures) after proper transformation
   c. for the entire patient cohort, a univariate analysis (unadjusted) of association between each clinicopathologic factor and clinical outcome was performed. Factors with significant association in the univariate analysis were included in multivariate Cox proportional hazards regression model to determine their independent effects
   d. Survival probabilities and median survival times were estimated from Kaplan–Meier curves

Results

1) Patient characteristics: Among the 92 pts (median age 63, male 72%) with mRCC and bone mets that were treated with sunitinib, 41 were Bis users and 51 nonusers

2) The groups were balanced regarding the following known prognostic factors: past nephrectomy, clear cell/non clear cell histology, initial diagnosis to sunitinib tx time, the presence of ≥ 2 mets sites, presence of lung/liver mets, ECOG performance status, anemia, calcium level > 10 mg/dL, elevated AP, pre-tx NLR >3, sunitinib induced HTN, the use of angiotensin system inhibitors, past cytokines/targeted tx, and mean sunitinib dose/cycle

3) Outcome:
   a. Objective response: partial response/stable disease 85% (n=35) vs 71% (n=36), and progressive disease 15% (n=6) vs 29% (n=15) (OR 3.287, p=0.07) in group 1 vs 2, respectively
   b. Median PFS was 15 vs 5 months (HR 0.433, p =0.035), and median OS not reached with a median followup time of 43 vs 12 months (HR=0.398, p=0.003), in favor of group 1(figures 1-2)
   c. In multivariate analysis of the entire pt cohort(n=92), factors associated with PFS were Bis use (HR 0.433, p=0.035), pre-tx NLR ≤ 3 (HR 0.405, p=0.016), and elevated AP (HR 3.63, p=0.012). Factors associated with OS were Bis use (HR 0.32, p=0.003), elevated AP (HR 3.18, p=0.002), and Su induced HTN (HR 0.193, p < 0.001)

Conclusions

Bis may improve the outcome of Su tx in RCC with bone mets. Whether this is generalizable to other TKIs is not known. This should be investigated prospectively, and if validated applied in clinical practice and clinical trials

References

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4. Sahi C, et al. Ther Adv Med Oncol. 2010; 2:75-83

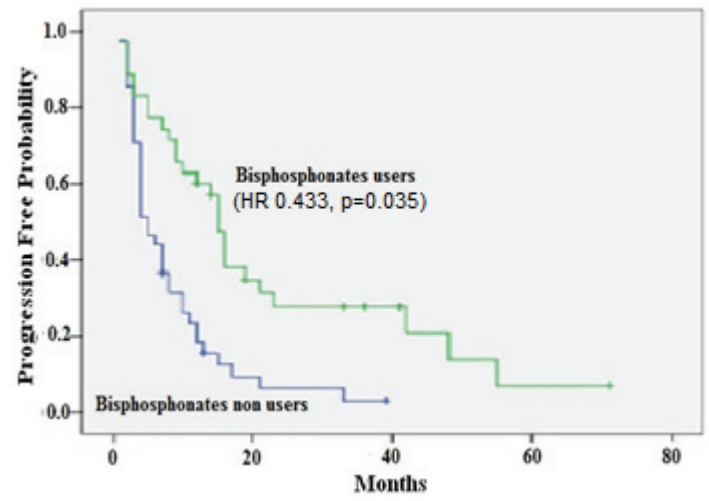**Figure 1**: Kaplan–Meier Estimates of PFS

Figure 2: Kaplan-Meier estimates of OS