

SYNOPSIS

Title

NMSG 22/14

Magnolia Study. Prolonged Protection from Bone Disease in Multiple Myeloma. An open label phase 4 multicenter international randomised trial.

Design

Phase IV prospective randomised multicentre open-label study.

Rational

Treatment with zoledronic acid is associated with increased survival, reduced skeletal related event, and diminished pain. Long term treatment however is also associated with increased risk of osteonecrosis of the jaw. Trials randomising patients to active treatment have only followed patients for 2 years. Thus we do not know when the negative risk of osteonecrosis outweighs the positive benefits of contentious bone protection with zoledronic acid, and no definite recommendations can be given on what to do after two years of zoledronic acid treatment.

We wish to investigate if the risk of continued treatment of zoledronic acid from year 2 to 4 outweighs the potential benefits for the patient

Bone disease is investigated using different imaging modalities. All imaging modalities however only discover bone damage after it has happened. Biochemical markers of bone turnover, measured in the blood, reflect the velocity of bone loss. These markers may be able to detect increased bone loss before it results in osteolysis or pathological fractures.

We wish to investigate if blood samples can be used to predict bone damage before it occurs and thereby, in the future, individualise zoledronic acid treatment both patient- and time specific.

*Low dose CT is increasingly replacing conventional radiography as the investigation of choice when investigating bone disease in multiple myeloma due to higher sensitivity.

*We wish investigate if minute changes detected only on CT develop into larger osteolytic lesions or if they remain minute over time

*optional

Design

Patients with newly diagnosed treatment demanding myeloma can be included in the trial. During the first 2 years all patients will receive monthly infusions with zoledronic acid. Data concerning QoL, serum markers, and osteonecrosis will be collected every 6th month. Bone imaging (conventional radiography, low dose CT, or both *optional*) will be done yearly. After two years patients will be randomised to A) stop treatment or B) continue treatment for 2 more years. During that time period serum markers will be measured monthly. QoL and osteonecrosis will be evaluated 4 times a year. Bone imaging will be measured 2 times a year.

Patients who, outside the protocol, have received 23-25 infusions with zoledronic acid can be included in the protocol and move directly to randomisation. These patients will be followed as described above.

Objectives

- **Primary objective:**

To compare the time to progressive bone disease from year 2 to year 4 in patients treated with monthly zoledronic acid in two consecutive years compared to patients treated with monthly zoledronic acid in four consecutive years.

- **Secondary objectives (selected):**

To compare the overall survival from year 2 to year 4 in patients treated with monthly zoledronic acid in two consecutive years compared to patients treated with monthly zoledronic acid in four consecutive years.

To compare the incidence of BON from year 2 to year 4 in patients treated with monthly zoledronic acid in two consecutive years compared to patients treated with monthly zoledronic acid in four consecutive years.

To compare the development in QoL from year 2 to year 4 in patients treated with monthly zoledronic acid in two consecutive years compared to patients treated with monthly zoledronic acid in four consecutive years.

To investigate if monthly measurements of the bone markers CTX-I, PINP, bALP, TRAP5b, or the ratios of these can be used to predict the development of progressive bone disease from year 2 to year 4.

To investigate if the patients with inconsistency in bone disease status using the different imaging modalities at diagnosis are more likely to progress in bone disease compared to patients diagnosed with “no bone disease” using both modalities*.

* Sites may participate in the study without conduction both conventional radiography and low-dose CT.

Patient population

- A) Patients with newly diagnosed treatment demanding multiple myeloma
- B) Patients with multiple myeloma who already have received 23-25 infusions of zoledronic acid

Number of patients

358

Participating centers

Centers within the Nordic Myeloma Study Group