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Design and Methods

Study patients and controls

All imatinib treated CML patients at Sahlgrenska University Hospital were identified 17 of whom (11 males, 6 females; 60±11 years) fulfilled the study inclusion criteria: (i) imatinib treatment duration ≥24 months, and (ii) a state of complete cytogenetic remission. Seventeen healthy, sex and age matched individuals served as controls (11 males, 6 females; age 59±11 years).

The diagnosis of CML was confirmed prior to imatinib treatment by typical peripheral blood and bone marrow morphological findings, and detection of a t(9;22)(q34;q11) translocation by conventional karyotyping or fluorescence *in situ* hybridization (FISH) for the *BCR-ABL* fusion gene.

The imatinib dose was 400 mg per day in 16 out of 17 patients; one patient was treated with 600 mg imatinib per day. The treatment duration was 50±19 months (range 24-73). The treatment response was routinely monitored by conventional cytogenetics, interphase FISH and real-time reverse transcriptase polymerase chain reaction for *BCR-ABL* transcript number. At the time of study all patients were in complete cytogenetic remission (CCgR), in first chronic phase of the disease, with low and stable levels of *BCR-ABL* transcripts. The study was approved by the local research ethics committee.

Biochemical assays

All blood samples were collected in the morning, between 8 a.m. and 10 a.m., after breakfast and intake of imatinib. Serum and urine analysis was performed at the Department of Clinical Chemistry, Sahlgrenska University Hospital, accredited according to the international standard ISO/IEC 17 025. The serum levels of calcium, phosphate, magnesium, creatinine, and total urine excretion of calcium and phosphate over 24 hours were measured with photometry using the Modular Analytics instrument (Roche Diagnostics Scandinavia AB, Bromma, Sweden).

The levels of spot urine calcium, serum ionized calcium, serum sodium and serum potassium were measured using an ion-selective electrode and the Modular Analytics instrument.

Serum parathyroid hormone was determined using a chemiluminescent immunometric assay (ADVIA Centaur, Bayer Healthcare LLC, Leverkusen, Germany) with an ADVIA Centaur Immunochemistry Analyzer (Bayer Healthcare LLC). Radioimmunoassays and a gamma counter (PerkinElmer Inc., Waltham, MA, USA) were used to determine the serum levels of 25-hydroxy vitamin D (DiaSorin, Stillwater, MN, USA), 1,25-dihydroxy vitamin D (DiaSorin), osteocalcin (CIS Bio International, Gif-sur-Yvette, France), carboxyterminal cross-linked telopeptide of type I collagen (ICTP; UniQ™ICTP, Orion Diagnostica, Espoo, Finland), and bone-specific alkaline phosphatase (Tandem®-R Ostase®, Beckman Coulter, Immunotech, Marseilles, France).

The plasma level of erythropoietin was determined in an immunoenzymometric assay (Quantikine® IVD®, R&D Systems, Minneapolis, MN, USA) using an iEMS analyzer (Labsystems, Helsinki, Finland). Full blood counts were measured using the CellDyn Sapphire Analyzer (Abbott, Abbott Park, IL, USA).

Bone measurements

Dual energy X-ray absorptiometry (DXA)

The areal bone mineral density (areal BMD; g/cm^2) of the lumbar spine and hip of the left leg was determined using the Lunar Prodigy DXA (GE Lunar Corp., Madison, WI, USA). The coefficient of variation (CV) for the areal BMD measurements ranged from 0.5 to 3%, depending on application.

Peripheral quantitative computerized tomography (pQCT)

A pQCT device, using single energy X-ray (XCT-2000; Stratec Medizintechnik, GmbH, Pforzheim, Germany) was used to scan the distal leg (tibia) and the distal arm (radius) of the nondominant leg and arm respectively. The pQCT was calibrated every week using a standard phantom and once every 30 days using a cone phantom provided by the manufacturer. A 2-mm-thick single tomographic slice was scanned with a voxel size of 0.50 mm. The cortical volumetric BMD (mg/cm^3) and the cortical cross-sectional area (mm^2), and cortical thickness (mm) were measured using a scan through the diaphysis (at 25% of the bone length in the proximal direction of the distal end of the bone) of the radius and tibia. The cortical volumetric BMD is the true cortical volumetric BMD, not including the marrow compartment. Trabecular volumetric BMD (mg/cm^3) was measured using a scan through the metaphysis (at 4% of the bone length in the proximal direction of the distal end of the bone) of these bones. All the pQCT analyses were performed by one technician using one pQCT. The CVs were less than 1% for all pQCT measurements, as previously reported.[1]

Statistical analysis

The results are given as mean ± standard deviation (SD) unless otherwise indicated. Differences between patients and controls were evaluated using independent sample *t* test. The relationship between variables was tested using the non-parametric Spearman correlation. A p-value ≤0.05 was considered statistically significant.

References

1. Lorentzon M, Mellstrom D, Haug E, Ohlsson C. Smoking is associated with lower bone mineral density and reduced cortical thickness in young men. J Clin Endocrinol Metab 2007; 92:497-503.