Prevention of bone disease and early detection of impending fractures in multiple myeloma patients can reduce morbidity and mortality: the necessity of interdisciplinary state-of-the-art treatment

Georg W. Herget,[1,2] Ralph Wäsch,[2,3] Lukas Klein,[1,2] Hagen Schmal,[1,2] Evangelos Terpos[4] and Monika Engelhardt[2,3]

[1]Department of Orthopaedics and Trauma Surgery, Medical Center, University of Freiburg, Faculty of Medicine, Freiburg, Germany; [2]Comprehensive Cancer Center Freiburg (CCCF), Medical Center University of Freiburg, Freiburg, Germany; [3]Department of Medicine I Hematology and Oncology, Medical Center, University of Freiburg, Faculty of Medicine, Freiburg, Germany and [4]Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra General Hospital, Athens, Greece

E-mail: GEORG W. HERGET - georg.herget@uniklinik-freiburg.de

doi:10.3324/haematol.2019.245423

Multiple myeloma (MM), the second most common hematologic cancer, is an indolent B-cell malignancy characterized by clonal expansion of terminally differentiated, immunoglobulin-producing, transformed plasma cells in the bone marrow.[1] In spite of the substantial improvement in overall survival (OS) seen in in MM over the last decades, it accounts for approximately 20% of hematologic malignancy-related deaths and for 2% of all cancer deaths.[2-4] Although causes of cancer-related deaths often include the underlying disease, infections and organ dysfunction, one essential complication in MM throughout the disease course are skeletal-related events (SRE). SRE, including pathological bone fractures, spinal cord compression, the need for radiation, and the need for surgical intervention on bones, are the leading symptom and feared complication in MM.[5,6]

At the time of MM diagnosis, the majority of patients present various skeletal abnormalities: osteolytic lesions, osteopenia and (secondary) osteoporosis, or a combination of these. Moreover, during the course of the disease, up to 90% of MM patients develop osteolytic lesions.[7] The cause of bone disease lies in the interaction between malignant plasma cells and the bone microenvironment, which leads to osteoclastic bone destruction, reduced osteoblast function, and blocking of bone repair.[8]

Bisphosphonates are the current mainstay of treatment of bone disease in MM, as they reduce SRE and bone pain.[9-12] Newer drugs, such as the anti-RANKL monoclonal antibody denosumab, have already been approved in MM.[13] Bone anabolic agents such as romosozumab, licensed for the treatment of post-menopausal osteoporosis, are currently under investigation and may represent further promising tools in the treatment.[14] However, even after appropriate treatment with anti-myeloma agents and osteoclast-targeting therapy with bisphosphonates, denosumab or others given at initial diagnosis, pathological bone fractures frequently occur during the course of the disease. Indeed, in a recent study, the authors found SRE in newly diagnosed MM patients who very frequently had osteolytic disease: two-thirds of patients had an SRE before study enrolment, an additional 44% had at least one on-study SRE, with 60% of all first SRE occurring within the first three months, and 81% occurring within the first six months.[13]

While pathological fractures can occur in almost every bone (but most commonly vertebras), the long bones (femur and humerus) and the ribs are often affected. However, their impact on patients' mobility depends on their location, with fractures of the long bones along with vertebral fractures, especially in combination with spinal cord compression, being the most harmful. Figure 1 illustrates different manifestations and locations of osteolyses in MM patients, including operative treatment options.

As a consequence, the detection of bone lesions is crucial for the investigation and subsequent treatment of MM. SRE-prevention and treatment in MM is aimed at avoiding or minimizing such events. However, these are often present at initial diagnosis and upon relapse, and, therefore, often drive treatment decisions, i.e. of systemic and/or operative and radiation treatment, as well as of additional supportive measures.[10,11,15]

In this issue of the journal, Thorsteinsdottir *et al.* report results of their large retrospective population-based study "Fractures and Survival in Multiple Myeloma".[16] They used data from 14,013 MM patients diagnosed in Sweden in the years 1990-2013, who had been identified by the Cancer Registry. Information on date of birth, MM diagnosis, fractures, and death were collected from central registries. Their aim was to compare survival in patients with and without fractures at MM diagnosis, including certain subtypes of fractures. Furthermore, the authors compared the effect of fractures on survival in MM before and after the introduction of novel agents that have generally improved OS in MM patients.

In their impressive study, the authors show that MM patients with a fracture at the time of diagnosis had an inferior survival rate compared to those without a fracture at diagnosis. Moreover, patients who developed a fracture during the course of the disease had a 2-fold risk of death compared to those that did not develop a fracture. This risk of death was significantly increased in nearly all subtypes of fractures except for ankle fractures: e.g. for vertebral fractures [hazard ratio (HR)=1.74; 95% confidence interval (CI): 1.61-1.87], hip fractures (1.99; 95%CI: 1.82-2.18), humerus fractures (2.57; 95%CI: 2.31-2.85) and femoral fractures (2.62; 95%CI: 2.32-2.98). Furthermore, the risk of death for elderly MM patients ≥70 years of age at the time of MM diagnosis with a fracture was significantly increased compared to those without.[16] Results from other studies are in line with these and these authors observed that pathological fractures increase the risk of death by 20-40%.[17]

Underlying causes for the observations of Thorsteinsdottir *et al.* are plentiful, the most likely being that SRE may hamper intensified systemic anti-MM treatment and impair patient constitution/fitness levels.[2] Moreover, cancer patients may indeed have a better outcome when impending pathological fractures are prevent-

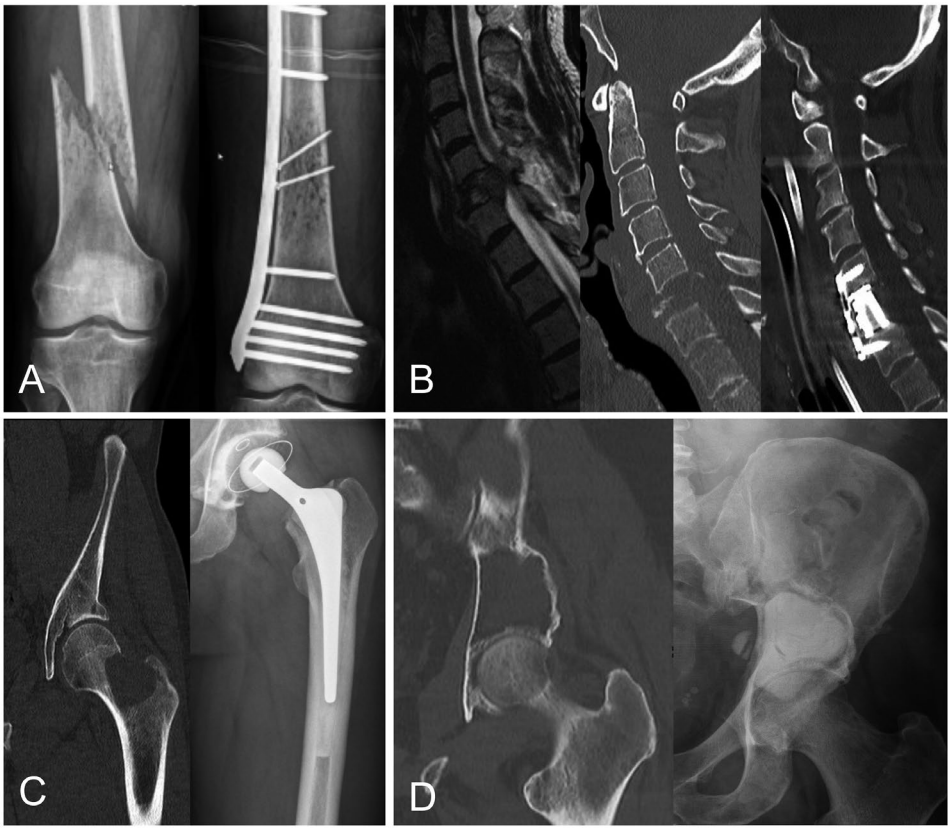

Figure 1. Different manifestations and locations of osteolyses in multiple myeloma patients. (A) Pathological fracture of the femur, stabilized by an LISS (less invasive stabilization system) plate. (B) Almost complete destruction of the sixth cervical vertebral with spinal cord compression followed by vertebral body replacement. (C) Osteolysis of the left femoral neck which threatens stability. Prophylactic stabilization by total hip replacement. (D) Extended osteolysis of the left ilium stabilized by pelvic bone cementoplasty.

ed (i.e. by surgical intervention) than patients with actual pathological fractures. Substantial differences were observed with less average blood loss, shorter hospital stays, greater likelihood of discharge, and greater likelihood of resuming support-free ambulation.[6,18,19]

If pathological fractures do occur, they are mainly treated surgically to stabilize the fractured bones and to improve patients' quality of life *via* pain relief and restoration of function and mobility.[20] Palliation, not cure, is usually the surgical objective of treatment of MM-related bone disease.

The findings of Thorsteinsdottir *et al.* deserve the interest of interdisciplinary teams of MM experts. However, further investigations are needed to corroborate and better understand these findings, i.e. that the risk of death after suffering a fracture has not significantly decreased compared to patients who do not develop a fracture after the introduction of more effective treatment agents in MM. Moreover, subsequent analyses should study the risk of death after fracture in MM patients compared to patients without cancer. This is of particular importance since elderly patients in general have a higher morbidity and mortality after fractures.

As a consequence of Thorsteinsdottir *et al.'s* and previous findings, the early recognition of an impending fracture remains highly relevant in MM and other cancer patients. This includes taking a detailed general medical history, especially if aggravating or novel pain occurs or reoccurs. The following questions should be asked: "Is there any new onset of pain?" "Is there pain at night?" "Is pain independent of movement?" etc. In addition, radiographic imaging, such as low-dose whole-body computed tomography (WB-CT) is mandatory as part of the diagnostic process to detect possible osteolyses that may threaten stability. Moreover, during the course of the disease follow up, when symptoms occur or reoccur, imaging may be required to guide changes in therapy and disease management that may prevent or delay the onset of clinically significant morbidity and mortality as a result of SRE.[15]

Most importantly, optimal treatment strategies for fractures or impending fractures as part of SRE are achieved by discussion of patients' history of disease and image scans in interdisciplinary tumor boards, taking into consideration the actual status of the disease, prognosis, and background of the individual patient.[21] This interdisciplinary approach should involve a team of MM specialists in hematology-oncology, radiology, radiotherapy, orthopedics, pathology/molecular scientists, and other specialized disciplines if required (i.e. nephrologists, cardiologists, neurologists).[22] We are happy and fortunate that a highly-skilled interdisciplinary team of this kind is well established at our institution.

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Animal models of thrombotic thrombocytopenic purpura: the tales from zebrafish

Paul Coppo[1] and Bernhard Lämmle[2,3,4]

[1]Service d'Hématologie, Centre de Référence des Microangiopathies Thrombotiques, AP-HP.6, Paris, France; [2]Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Bern Switzerland; [3]Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany and [4]Haemostasis Research Unit, University College London, London, United Kingdom

E-mail: PAUL COPPO - paul.coppo@aphp.fr or BERNHARD LÄMMLE - Bernhard.laemmle@uni-mainz.de

doi:10.3324/haematol.2019.245043

Thrombotic thrombocytopenic purpura (TTP) results from systemic microvascular von Willebrand factor (VWF)-induced clumping of platelets causing thrombocytopenia, microangiopathic hemolysis, and ischemia in the brain, kidneys, heart, and other organs.[1] The identification of a severe deficiency of the specific VWF-cleaving protease, now denoted as ADAMTS13,[1] by Furlan *et al.*[2] and Tsai and Lian,[3] provided an explanation for the accumulation of extremely adhesive, unusually large VWF multimers in the plasma of patients with chronic relapsing TTP first reported by Moake *et al.* in the 1980s.[4,5] Severe deficiency of ADAMTS13 activity, caused by biallelic mutations of the encoding *ADAMTS13* gene[6-8] or, more commonly, by autoantibodies directed against various epitopes of the metalloprotease resulting in functional inhibition of the enzyme and/or the formation of immune complexes and enhanced clearance of ADAMTS13[2,3,9] underlies congenital (cTTP) and acquired, autoimmune TTP (iTTP), respectively.[10]

The novel insights into disease mechanisms identified in the laboratory during the past two decades were rapidly and successfully integrated into the clinical management, to the benefit of patients.[11] Targeted therapies were thereby progressively associated with the historical treatment empirically introduced in the 1970s-1980s, based on repeated plasma exchange, replacement of the deficient protease through fresh-frozen plasma, and corticosteroids, which had already dramatically improved the prognosis of patients with this previously mostly fatal disease.[12] The successful story of these newly introduced therapeutic approaches include B-cell-depleting monoclonal antibodies that inhibit autoantibody production,[13] and nanobodies that bind to the VWF A1 domain and inhibit the VWF-platelet glycoprotein Ib interaction.[14,15] Recently, a recombinant form of human ADAMTS13 was successfully tested in a pharmacokinetics and safety study in 15 patients with cTTP[16] and is expected to facilitate the management of cTTP and possibly iTTP in the near future. This ongoing development illustrates the strength of translational medicine when basic science and clinical research combine efficiently. This approach allowed TTP to fully enter the exciting era of targeted therapies and personalized medicine.

A crucial advance in TTP pathophysiology was the demonstration of the direct role of ADAMTS13 deficiency