Consensus guidelines for the management of bone disease in multiple myeloma

1. Indication for bisphosphonate use – should they be used in patients with and without bone disease, osteoporosis, newly diagnosed vs. relapsed multiple myeloma (MM); and MGUS.
    - Guidelines for the use of bisphosphonates in MGUS are not yet clear except for patients with osteoporosis– Dexa's should be considered for patients with MGUS or SMM because of the reported increase in skeletal-related events in these patients compared to age-matched controls (1,2). If the Dexa shows osteoporosis (T score<2) consider treating in a similar manner as patients with osteoporosis.
    - SMM; for low and intermediate risk SMM, if osteoporosis is identified by Dexa then consider treating with bisphosphonates as above, for osteoporosis. For high-risk SMM and if one cannot differentiate between MM-related versus age-related bone loss providers should consider using dosing and schedule of bisphosphonates as with symptomatic MM, especially in patients with abnormal MRIs.(3,4)
    - Plasmacytoma – for patients with a solitary lesion and no evidence of osteoporosis- no therapy is indicated. If osteoporosis is present then treat as osteoporosis. If multiple lesions are present, on MRI ,the patient has MM bone disease and should be treated accordingly (5,6).
    - MM patients without bone lesions – it is still unclear if bisphosphonates should be used in patients without bone lesions. MRC IX trial

demonstrated the benefit of zoledronate in patients without bone disease (7).

- MM with diffuse osteopenia and active MM - use bisphosphonates as recommended by the ASCO guidelines for MM bone disease.
- MM with bone lesions - use bisphosphonates as recommended by ASCO guidelines.
- Further discussion should center on whether bisphosphonates might be used in an adjuvant setting as anti-myeloma drugs in patients with MGUS or SMM analogous to patients with high-risk breast cancer without metastases (8). The recent Azure trial was negative in terms of benefit for patients with breast cancer except for post menopausal patients (9), further clouding the issue. Since there is no clinical trial data on the adjuvant use of bisphosphonates in MGUS or SMM, it should not be recommended except for a clinical trial in high-risk patients.

2. Use of bisphosphonates:
    a. Type of bisphosphonate - oral vs. IV.

    The MRC IX trial data demonstrate a survival benefit in patients treated with zoledronate independent of bone disease (7). A significant proportion of patients in this trial did not have bone disease when they started bisphosphonates, and the development of bone disease was decreased while in the trial. This trial clearly shows the superiority of zoledronate over an oral bisphosphonate, so the recommendation should focus on the use

of intravenous bisphosphonates. Zoledronate is the only bisphosphonate shown to increase survival in a prospective randomized trial (7).

b. Dose - The Nordic trial compared 30 mg versus 90 mg of pamidronate IV in 500 newly diagnosed MM patients and found these doses to be equivalent (10). However, all other trials have used bisphosphonate doses that are used to treat bone disease in MM. Thus, the use of standard doses would appear to be most appropriate for now. The MRC IX trial used 4 mg of zoledronate as well.
c. Frequency - until data from the Bismarck and other trials using bone resorption markers to dictate the frequency of care, administration of IV bisphosphonates every 3-4 weeks appears most appropriate (11,12).
d. Duration – 2 years or longer? There is no randomized prospective data on using bisphosphonates beyond two years. Consideration for discontinuing bisphosphonates after 2 years should be based on an assessment of risk and benefit by the treating physician, although no data is available to help guide that assessment (11,12). The incidence of ONJ was low and acceptable on the MRC IX trial in patients with adequate dental monitoring who were treated on the trial for 3.7 years (7). However, the average duration of bisphosphonate therapy was much shorter. The actual duration of bisphosphonate therapy in these patients versus the development of ONJ is currently unknown. The risk of development of atypical femoral fractures that has been reported in patients on very long-term oral bisphosphonates is extremely low and the association has not been

confirmed (13,14). Berenson and co-workers recently reported the occurrence of metatarsal stress fractures in 6 MM patients on long-term (>5yr) IV bisphosphonates, raising a note of caution (15).

e. Patients on long-term steroids – Patients on high dose steroids will probably require long-term bisphosphonate therapy (16), but it may be administered less frequently. This is being re-evaluated by investigators in the bone field.

f. Monitoring of the toxicity – Patients should avail themselves of the opportunity for dental consultation. It is clear that dental screening prior to starting bisphosphonates and maintaining good dental hygiene while on bisphosphonates decreases the incidence of ONJ (17). The current practice is to stop bisphosphonates for 90 days before and after invasive dental procedures (tooth extraction, dental implants and surgery to the jaw). Bisphosphonates do not need to be discontinued for routine dental procedures including root canal. There is no randomized prospective data demonstrating that holding bisphosphonates for three months impacts the development of ONJ. There are multiple guidelines already published, which can be followed by the treating physician. Providers should ask patients about dental procedures every month when the creatinine is checked.

g. Potential anti-MM activity of bisphosphonates and its application – There is emerging data that bisphosphonates have anti-myeloma activity

both in vitro and in patient studies (7,18,19). However, their use as a single agent for their anti-myeloma activity is not indicated.

h. Use of associated drugs – Vitamin D, calcium, etc. – 60% of MM patients are vitamin D deficient or insufficient (20,21). Vitamin D and calcium supplementation has been routinely used in trials of bisphosphonates in MM patients. New guidelines are available on what are the appropriate levels of vitamin D in patients, but these guidelines are currently being debated (22). Since vitamin D deficiency increases bone remodeling, in particular PTH levels, it is very important that patients be calcium and vitamin D sufficient. Calcium supplementation should be used with caution in patients with renal insufficiency.

i. Newer agents – their role and indication. There are a variety of new agents in development to block osteoclastic bone resorption or stimulate bone formation. Denosumab, an Activin A receptor antagonist, anti-DKK-1, etc. <u>Current data on all these agents is not adequate to recommend their routine use.</u>

3. Managing bone disease.

   a. Kyphoplasty, vertebroplasty - The CAFÉ study has shown that kyphoplasty is an effective and safe treatment that reduces pain and improves function (23). The role of vertebroplasty for myeloma patients is less clear. Two randomized trials have failed to show a benefit of vertebroplasty for patients with osteoporotic fractures compared to

conservative therapy (24-26). No similar randomized trial results are available for patients with myeloma.

b. Surgery guidelines - Surgery for patient with myeloma is usually directed toward preventing or repair of axial fractures, unstable spinal fractures and spinal cord compression. Patients with myeloma appear to tolerate palliative surgery well (27). Consideration and indications for surgery should be done in consultation between the treating oncologist/hematologist and the orthopedic and neurosurgeon to determine when MM treatment can be safely restarted.

c. Radiotherapy – The use of radiotherapy for local disease control and palliation should be used judiciously and sparingly depending on patient's presentation, need for urgent response, and prior treatment history and response. It should be limited as much as possible to spare the patient's marrow function. Current novel agents work rapidly and should decrease the need for palliative XRT.

References:

1. Minter AR, Simpson H, Weiss BM, Landgren O. Bone disease from monoclonal gammopathy of undetermined significance to multiple myeloma: pathogenesis, interventions, and future opportunities. Semin Hematol. 2011 Jan;48(1):55-65.

2. Berenson JR, Anderson KC, Audell RA, Boccia RV, Coleman M, Dimopoulos MA, Drake MT, Fonseca R, Harousseau JL, Joshua D, Lonial S, Niesvizky R, Palumbo A, Roodman GD, San-Miguel JF, Singhal S, Weber DM, Zangari M, Wirtschafter E, Yellin O, Kyle RA. Monoclonal gammopathy of undetermined significance: a consensus statement.Br J Haematol. 2010 Jul;150(1):28-38. Epub 2010 May 9.

3. Terpos E, Moulopoulos LA, Dimopoulos MA Advances in Imaging and the Management of Myeloma Bone Disease.J Clin Oncol. 2011 Apr 11. [Epub ahead of print] PMID: 21483016

4. Jakob C, Zavrski I, Heider U, Bollow M, Schulz CO, Fleissner C, Eucker J, Michael R, Hamm B, Possinger K, Sezer O. Serum levels of carboxy-terminal telopeptide of type-I collagen are elevated in patients with multiple myeloma showing skeletal manifestations in magnetic resonance imaging but lacking lytic bone lesions in conventional radiography. Clin Cancer Res. 2003 Aug 1;9(8):3047-51. PMID: 12912955

5. Fechtner K, Hillengass J, Delorme S, Heiss C, Neben K, Goldschmidt H, Kauczor HU, Weber Staging monoclonal plasma cell disease: comparison of the Durie-Salmon

and the Durie-Salmon PLUS staging systems.MA.Radiology. 2010 Oct;257(1):195-204. PMID: 20851941

6. Dimopoulos M, Terpos E, Comenzo RL, Tosi P, Beksac M, Sezer O, Siegel D, Lokhorst H, Kumar S, Rajkumar SV, Niesvizky R, Moulopoulos LA, Durie BG; IMWG.International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma.Leukemia. 2009 Sep;23(9):1545-56. Epub 2009 May 7. Review. PMID: 19421229

7. Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ, Navarro-Coy N, Drayson MT, Owen RG, Feyler S, Ashcroft AJ, Ross F, Byrne J, Roddie H, Rudin C, Cook G, Jackson GH, Child JA; National Cancer Research Institute Haematological Oncology Clinical Study Group.First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial.Lancet. 2010 Dec 11;376(9757):1989-99. Epub 2010 Dec 3. PMID: 21131037

8. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, Jakesz R, Seifert M, Hubalek M, Bjelic-Radisic V, Samonigg H, Tausch C, Eidtmann H, Steger G, Kwasny W, Dubsky P, Fridrik M, Fitzal F, Stierer M, Rücklinger E, Greil R; ABCSG-12 Trial Investigators, Marth C.Endocrine therapy plus zoledronic acid in premenopausal breast cancer.N Engl J Med. 2009 Feb 12;360(7):679-91. Erratum in: N Engl J Med. 2009 May 28;360(22):2379. PMID:19213681

9. Coleman RE, Thorpe HC, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Davies C, Bell R. Weston Park Hospital, Sheffield, United Kingdom; University of Leeds, United Kingdom; AZURE (BIG 01/01) Investigators Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer. The AZURE Trial (BIG 01/04). San Antonio Breast Cancer Symposium Abstract [S4-5]

10. Gimsing P, Carlson K, Turesson I, Fayers P, Waage A, Vangsted A, Mylin A, Gluud C, Juliusson G, Gregersen H, Hjorth-Hansen H, Nesthus I, Dahl IM, Westin J, Nielsen JL, Knudsen LM, Ahlberg L, Hjorth M, Abildgaard N, Andersen NF, Linder O, Wisløff F.Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial.Lancet Oncol. 2010 Oct;11(10):973-82. PMID: 20863761

11. Terpos E, Sezer O, Croucher PI, García-Sanz R, Boccadoro M, San Miguel J, Ashcroft J, Bladé J, Cavo M, Delforge M, Dimopoulos MA, Facon T, Macro M, Waage A, Sonneveld P; European Myeloma Network.The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network.Ann Oncol. 2009 Aug;20(8):1303-17. Epub 2009 May 22. Review. PMID: 19465418

12. Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, Orlowski RZ, Roodman DG, Twilde P, Anderson K; American Society of Clinical Oncology.

American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma.J Clin Oncol. 2007 Jun 10;25(17):2464-72. Epub 2007 May 21. PMID: 17515569

13. Gunawardena I, Baxter M, Rasekh Y Bisphosphonate-Related Subtrochanteric Femoral Fractures.Am J Geriatr Pharmacother. 2011 Apr 4. [Epub ahead of print] PMID: 21470918

14. Giusti A, Hamdy NA, Dekkers OM, Ramautar SR, Dijkstra S, Papapoulos SE Atypical fractures and bisphosphonate therapy: A cohort study of patients with femoral fracture with radiographic adjudication of fracture site and features..Bone. 2011 May 1;48(5):966-71. Epub 2010 Dec 31. PMID: 21195812

15. Gabriel N Waterman, B.A.;Ori Yellin, M.D.;Kamran Jamshidinia, D.P.M.;Regina A Swift,RN;James A Tamkin, M.D.;Robert A Audell, M.D.;James R. Berenson, M.D. Metatarsal Stress Fractures in Six Multiple Myeloma Patients Treated with Long-Term Bisphosphonates. JBJS 2011 (In press)

16. Compston J.Management of glucocorticoid-induced osteoporosis.Nat Rev Rheumatol. 2010 Feb;6(2):82-8. Review. PMID: 20125175

17. Dimopoulos MA, Kastritis E, Bamia C, Melakopoulos I, Gika D, Roussou M, Migkou M, Eleftherakis-Papaiakovou E, Christoulas D, Terpos E, Bamias A. Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. Ann Oncol. 2009 Jan;20(1):117-20. Epub 2008 Aug 9. PMID: 18689864

18. Kondo H, Mori A.Anti-tumor activity of pamidronate in human multiple myeloma. Leuk Lymphoma. 2002 Apr;43(4):919-21. PMID: 12153188

19. Baulch-Brown C, Molloy TJ, Yeh SL, Ma D, Spencer A. Inhibitors of the mevalonate pathway as potential therapeutic agents in multiple myeloma.Leuk Res. 2007 Mar;31(3):341-52. Epub 2006 Sep 22. PMID: 16996129

20. Laroche M, Lemaire O, Attal M.Vitamin D deficiency does not alter biochemical markers of bone metabolism before or after autograft in patients with multiple myeloma.Eur J Haematol. 2010 Jul;85(1):65-7. Epub 2010 Feb 26. PMID: 20214677

21. Badros A, Goloubeva O, Terpos E, Milliron T, Baer MR, Streeten E.Prevalence and significance of vitamin D deficiency in multiple myeloma patients.Br J Haematol. 2008 Jul;142(3):492-4. Epub 2008 May 8. No abstract available. PMID: 18485049

22. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know.J Clin Endocrinol Metab. 2011 Jan;96(1):53-8. Epub 2010 Nov 29. PMID: 21118827

23. Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, Bastian L, Ashraf T, Vrionis F; Cancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a

multicentre, randomised controlled trial.Lancet Oncol. 2011 Mar;12(3):225-35. Epub 2011 Feb 16. PMID: 21333599

24. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B.A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures.N Engl J Med. 2009 Aug 6;361(6):557-68 PMID: 19657121

25. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik JG.A randomized trial of vertebroplasty for osteoporotic spinal fractures.N Engl J Med. 2009 Aug 6;361(6):569-79. PMID: 19657122

26. Chew C, Craig L, Edwards R, Moss J, O'Dwyer PJ.Safety and efficacy of percutaneous vertebroplasty in malignancy: a systematic review.Clin Radiol. 2011 Jan;66(1):63-72. Epub 2010 Nov 16. Review. PMID: 21147301

27. Utzschneider S, Schmidt H, Weber P, Schmidt GP, Jansson V, Dürr HR Surgical therapy of skeletal complications in multiple myeloma.Int Orthop. 2010 Sep 23. [Epub ahead of print] PMID: 20862584