ASCO 2007 Clinical Practice Guideline Update on the Role of Bisphosphonates in Multiple Myeloma: Revised Recommendations

Previous Recommendation (2002)	Current Recommendation (2007)
Lytic Disease on Plain Radiographs	
For multiple myeloma patients who have on plain radiograph(s), lytic destruction of bone, intravenous pamidronate 90 mg delivered over at least 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended.	For multiple myeloma patients who have on plain radiograph(s) or imaging, lytic destruction of bone or compression fracture of the spine from osteopenia, intravenous pamidronate 90 mg delivered over at least 2 hours or zoledronic acid 4 mg over at least 15 minutes every 3 to 4 weeks are recommended. In light of data from Zervas et al showing a 9.5-fold greater risk for the development of osteonecrosis of the jaw with zoledronic acid compared to pamidronate, patients may prefer pamidronate to zoledronic acid until more data become available on this adverse effect of bisphosphonate therapy. Clodronate is an alternative bisphosphonate approved worldwide except for the United States for either oral or intravenous administration.
Monitoring	
In patients with pre-existing renal disease and a serum creatinine less than 265 µmol/L or less than 3.0 mg/dL, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates in patients with worse function has been minimally assessed. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Panel recommends intermittent evaluation (every 3 to 6 months) of all patients receiving chronic pamidronate or zoledronic acid therapy for the presence of albuminuria and azotemia. In patients experiencing unexplained albuminuria (defined as more than 500 mg/24 hours of urinary albumin) or azotemia (defined as an increase of ≥ 0.5 mg/dL in serum creatinine or an absolute value of more than 1.4 mg/dL among patients with normal baseline serum creatinine levels), discontinuation of the drug is warranted until the renal problems are resolved. These patients should be reassessed every 3 to 4 weeks (with a 24-hour urine collection for total protein and urine protein electropheresis) and pamidronate reinstituted over a longer infusion time (≥ 2 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline.	Due to increased concerns over renal adverse events, new dosing guidelines for patients with pre-existing renal impairment were added to the Zoledronic acid package insert. The new guidelines recommend that patients with pre-existing mild-to-moderate renal impairment (estimated creatinine clearance 30-60 mL/min) should receive a reduced dosage of zoledronic acid. No changes in infusion time or interval are required. Zoledronic acid has not been studied in patients with severe renal impairment and is not recommended for use in these patients. Pamidronate, 90 mg given over 4-6 hours, is recommended for patients with extensive bone disease and existing severe renal impairment (serum creatinine level > 3.0 mg/dL [265 µmol/L] or an estimated creatinine clearance < 30 mL/min). Although no dosing guidelines are available for patients with pre--existing renal impairment, the Update Committee recommends that clinicians consider reducing the initial pamidronate dose in that setting. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Update Committee recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. In patients who develop renal deterioration with no other apparent cause during bisphosphonate therapy, zoledronic acid or pamidronate should be withheld. Bisphosphonate therapy can be resumed, at the same dosage as that prior to treatment interruption, when the serum creatinine returns to within 10% of the baseline level. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly, although there is no evidence on which to

	base a recommendation for time intervals. The Update Committee also recommends intermittent evaluation (every 3-6 months) of all patients receiving pamidronate or zoledronic acid therapy for the presence of albuminuria. In patients experiencing unexplained albuminuria (defined as > 500 mg/24 hours of urinary albumin), discontinuation of the drug is advised until the renal problems are resolved. These patients should be reassessed every 3-4 weeks (with a 24-hour urine collection for total protein and urine protein electrophoresis) and pamidronate re-instituted over a longer infusion time (≥ 4 hours) and at doses not to exceed 90 mg every 4 weeks when the renal function returns to baseline. The Update Committee supports the use of screening urinalysis for protenuria, but underscores that a 24-hour urine collection for determination of total protein and electrophoresis is required if the screening test is positive. Although no similar guidelines are available for zoledronic acid, some Update Committee members recommend that zoledronic acid be re-instituted over a longer infusion time (≥ 30 minutes).
Duration of Therapy	
The Panel suggests that, once initiated, intravenous pamidronate or zoledronic acid be continued until there is evidence of a substantial decline in a patient's general performance status. The Panel stresses that clinical judgment must guide at what point the potential palliative benefits of pamidronate or zoledronic acid are less than the inconvenience of receiving this intravenously administered drug. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.	A single randomized clinical trial has shown no benefit of monthly bisphosphonates after a tandem transplant:[20] There was no difference in the proportion of skeletal events in the pamidronate-containing regimens (21% and 18%) compared to no maintenance (24%) after 29 months of follow up. Based on these data and on the best clinical opinion of the Update Committee, we suggest that therapy with bisphosphonates be given monthly for a period of two years. (The Attal trial suggests one year if the patient is in a CR or NCR following a tandem transplant.) At two years, the physician should seriously consider stopping bisphosphonates in patients with responsive or stable disease, but their further use is at the discretion of the treating physician. There are no data to support a more precise recommendation for duration of bisphosphonate therapy in this group of patients. For those patients in whom bisphosphonates were withdrawn after two years, the drug should be resumed upon relapse with new onset skeletal related events.
Osteonecrosis of the Jaw (ONJ)	
Not included in previous update.	Osteonecrosis of the jaw (ONJ) is an uncommon but potentially serious complication of intravenous bisphosphonates. The Update Committee agrees with the recommendations described in the revised FDA label for zoledronic acid and pamidronate, Dear Doctor letters, a white paper, and various position papers or statements. All cancer patients should receive a comprehensive dental examination and appropriate preventive dentistry prior to bisphosphonate therapy. Active oral infections should be treated and sites at high risk for infection should be eliminated. While on therapy, patients should maintain excellent oral hygiene and avoid invasive dental procedures, if possible.

This table is derived from recommendations in the ASCO 2007 Clinical Practice Guideline Update on the Role of Bisphosphonates in Multiple Myeloma. This table is a practice tool based on ASCO® practice guidelines and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This table does not purport to suggest any particular course of medical treatment. Use of the practice guidelines and this table are voluntary. The practice guideline and additional information is available at http://www.asco.org/guidelines/myeloma.