SUPPORTIVE CARE AGENTS

AMIFOSTINE
(ETHYOL®)

I. MECHANISM OF ACTION

A) Amifostine is a prodrug that is dephosphorylated to a free thiol active metabolite, WR-1065, by the plasma membrane-bound enzyme, alkaline phosphatase. Compared with tumor cells, normal cells possess better vascularity, higher pH, and higher capillary alkaline phosphatase activity, which make amifostine capable of differentially protecting normal cells.

B) The active metabolite, WR-1065 acts as a hydrogen donor to repair damaged DNA and is a free radical scavenger of reactive oxygen species created following exposure to antineoplastic agents and radiation. This activity supplements the protection provided by other intrinsic free-radical scavengers such as glutathione. The renal protective effects of amifostine are due to the presence of sulfhydryl groups. As cisplatin binds extensively to renal tubule proteins, the additional sulfhydryl groups provided by amifostine provide protection to the renal tubules.

C) Amifostine is FDA approved for reduction of cumulative renal toxicity associated with repeated administration of cisplatin in patients with ovarian cancer. It is also FDA indicated for reducing the incidence and severity of radiation-induced xerostomia.

II. PHARMACOKINETICS

A) Amifostine exhibits nonlinear kinetic behavior.

B) Oral absorption is poor; may be given subcutaneously and intravenously.

C) Distribution -distributed biphasically with a distribution half-life of 0.9 minute; volume of distribution 6 liter.

D) Metabolism- dephosphorylated hepatically to WR-33278 and WR-1065.

E) Elimination- is rapidly cleared from plasma, levels decreasing by 90% within 6 minutes after completion of a 10-second intravenous bolus or 15-minute infusion; elimination half-life of 8.8 minutes.

III. DOSAGE AND ADMINISTRATION

A) For prevention of nephrotoxicity associated with cisplatin: *Dose: 740 - 910 mg/m^2 IV over 15 minutes starting 30 minutes before chemotherapy.

B) For reducing incidence and severity of radiation-induced xerostomia: Dose: 200 mg/m^2 IV over 3-5 minutes given 30 minutes before each radiotherapy treatment or **500 mg SQ given in two, slow 1.25 mL injections at two different sites 20 to 60 minutes before each radiotherapy fraction. *Note: Lower doses of amifostine (i.e., 740 mg/m^2) result in similar efficacy and better tolerance with a decreased incidence of hypotension (1-17% vs 4-27%) and nausea/vomiting (19-58% vs 72-89%), when compared to the high dose 910 mg/m^2. **Recent studies showed that amifostine given subcutaneously achieved the similar efficacy as that given intravenously with a minimal side effect of hypotension. [Reference: *J Clin Oncol* 2000;18: 2226 - 33].

IV. TOXICITY

A) Nausea and vomiting (19-89%).
B) Hypotension (1-27%): a dose-limiting side effect of amifostine that has been reported in up to 62% of patients and is more likely to occur with infusions longer than 15 minutes and usually occurs at the end of infusion. It can be reversed with discontinuation of the amifostine, administration of saline, and placing the patient in the Trendelenburg position.
C) Hypocalcemia.

V. CLINICAL MONITORING

A) Premedicate with antiemetics including dexamethasone and a $5HT_3$ receptor antagonist.
B) Patients receiving full dose amifostine should have antihypertensive therapy interrupted 24 hours before receiving amifostine.
C) Patients should be adequately hydrated prior to administration and kept in a supine position during administration.
D) During amifostine infusion, patients should be kept in the supine position with monitoring of blood pressure every 3 to 5 minutes. If significant decreases in blood pressure or clinical symptoms occur, place patient in the Trendelenburg position, discontinue amifostine, and initiate normal saline fluid infusion. Discontinue amifostine if the systolic blood pressure (SBP) drops according to the table below:

Baseline SBP (mmHg)	Drop in SBP (mmHg)
Less than 100	20
100-119	25
120-139	30
140-179	40
≥180	50

VI. DRUG INTERACTIONS

None.

DEXRAZOXANE
(ZINECARD®)

I. MECHANISM OF ACTION

Dexrazoxane acts as an intracellular heavy metal chelator and protects against anthracycline-induced free radical damage to the myocardium. Dexrazoxane rapidly enters cardiac cells and is immediately hydrolyzed to a compound, with metal chelating properties similar to EDTA, which complexes with iron, other heavy metals, and doxorubicin to inhibit the generation of free radicals.

II. PHARMACOKINETICS

A) Dexrazoxane pharmacokinetics fit a 2-compartment model with first-order elimination kinetics. After infusion, the drug is distributed rapidly and is not bound to plasma proteins. The distribution half-life is about 15 minutes. Elimination half-life: 2 to 4 hours.
B) Dexrazoxane is hydrolyzed by dihydropyrimidine amidohydrolase (DHPase) to 1-ring and 2-ring open EDTA-like products.
C) The unchanged drug, a diacid-diamide cleavage product, and two monoacid-monoamide ring products are excreted primarily in the urine.
D) The pharmacokinetics of dexrazoxane in patients with hepatic or renal dysfunction have not been performed. However, since dexrazoxane is primarily renally excreted, it should be used with caution in patients with renal dysfunction. Since a doxorubicin dosage reduction is recommended in the presence of hyperbilirubinemia, the dexrazoxane dosage should also be proportionally reduced (maintaining the 10:1 ratio) in patients with hepatic impairment.

III. ADMINISTRATION

Administer appropriate dose by slow IV push or by rapid (i.e., 15 min) IV infusion.

IV. TOXICITY

The most common adverse reaction to dexrazoxane at cardioprotective doses is myelosuppression (neutropenia ~ 12%, thrombocytopenia ~ 4%).
Other adverse events reported include: nausea/vomiting, diarrhea, stomatitis, elevated hepatic enzymes, hyperbilirubinemia, alopecia, injection site pain, confusion, depression, phlebitis, malaise, and fever.

PALIFERMIN
(KEPIVANCE®)

I. MECHANISM OF ACTION

Palifermin is a human keratinocyte growth factor (KGF) produced by recombinant DNA technology. KGF is an endogenous protein in the fibroblast growth factor family that binds to the KGF receptor. Binding of KGF to its receptor has been reported to result in proliferation, differentiation, and migration of epithelial cells. The KGF receptor has been reported to be present on epithelial cells in many tissues examined including the tongue, buccal mucosa, esophagus, stomach, intestine, and salivary gland. It has been reported to NOT be present on cells of the hematopoietic lineage.

II. PHARMACOKINETICS

A) Concentrations decrease rapidly in the first 30 minutes post-dose. A slight increase or plateau in concentration occurred at ~1 - 4 hours, followed by a terminal decline phase.
B) Distribution – exhibits linear pharmacokinetics with extravascular distribution.
C) Metabolism and elimination – half-life was 4.5 hours with range between (3.3-5.7 hours). No accumulation occurred after 3 consecutive doses of 60 mcg/kg in cancer patients.
D) PK profile in patients with renal or hepatic sufficiency has not been assessed.

III. DOSAGE AND ADMINISTRATION

A) Recommended dosage is 60 micrograms/kg/day, administered as an IV bolus injection for 3 consecutive days BEFORE and AFTER myelotoxic therapy as part of HSCT conditioning for a total of 6 doses.
B) Pre-HSCT myelotoxic therapy: The first 3 doses should be administered prior to HSCT myelotoxic therapy, with the third dose 24 to 48 hours before HSCT myelotoxic therapy.
C) Post-HSCT myelotoxic therapy: The last 3 doses should be administered post-HSCT myelotoxic therapy; the first of these should be administered after, but NOT on the same day of hematopoietic stem cell infusion and at least 4 days after most recent administration of palifermin.
D) Vials contain 6.25 mg of palifermin. Reconstitute with WFI. The reconstituted solution can be refrigerated for 24 hours. Do not freeze the reconstituted solution.

IV. TOXICITY

A) Skin toxicities: rash, erythema, edema, pruritus.
B) Oral toxicities: dysesthesia, tongue discoloration/thickening, alteration of taste.
C) Musculoskeletal: pain arthralgias.
D) Other – the effects of palifermin on stimulation of KGF receptor expressing, non-hematopoietic tumors in patients are not known. Palifermin has been shown to enhance the growth of human epithelial tumor cell line growth in a human carcinoma xenograft model.

V. CLINICAL MONITORING: Monitor oral mucosa; examine skin daily for rash.

VI. DRUG INTERACTIONS

No formal drug-drug interaction studies have been performed. However, it has been shown to bind to heparin in vitro, therefore if heparin is used to maintain an IV line, saline should be used to rinse the line prior to and after palifermin administration.
Palifermin should NOT be administered within 24 hours before, during infusion of, or within 24 hours after administration of chemotherapy.

PAMIDRONATE
(AREDIA®)

I. MECHANISM OF ACTION

A) Pamidronate is a second-generation bisphosphonate, which is indicated for treating hypercalcemia, Paget's disease, and osteolytic bone lesions of multiple myeloma and breast cancer. Of note, pamidronate failed to demonstrate a significant overall treatment benefit compared with placebo in palliation of bone pain or reduction of SREs [Reference: Small EJ, et al. *J Clin Oncol* 2003;21:4277 - 84].

B) Pamidronate inhibits bone resorption by actions on osteoclasts; they may interfere with osteoclast recruitment and cellular activity, and can induce osteoclast apoptosis; this latter effect may be mediated through osteoblasts.

C) One study suggested that the concentration of parathyroid hormone-related protein (PTHrP) can be used to predict the response of tumor-inducing hypercalcemia to pamidronate. When the PTHrP was undetectable (less than 2 pmol/L) the response was good in all 7 treatments. PTHrP in the range 2 to 12 pmol/L was associated with a good response in 10 of 14 treatments, while PTHrP greater than 12 pmol/L was associated with a poor response in all 11 treatments. Good response was determined to be normocalcemia for greater than 14 days post-treatment.
[Reference: Gurney et al. *Lancet* 1993;341:1611 - 3].

D) It has also been suggested that bisphosphonates also inhibit the ability of breast and prostate cancer cells to adhere to and invade the extracellular matrix, and may have antiangiogenic effects *in vivo*.

II. PHARMACOKINETICS

A) Oral absorption is poor and oral from is not available.

B) Onset of action for hypercalcemia of malignancy: initial response 1-2 days; peak response: 6 days.

C) Distribution – 22% protein bound.

D) Metabolism- does not undergo biotransformation.

E) Elimination- 95% of the drug primarily excreted unchanged by kidneys; terminal half-life about 28 hours.

III. DOSAGE AND ADMINISTRATION

A) For treatment of hypercalcemia associated malignancy:

- Moderate hypercalcemia (corrected serum calcium of 12 to 13.5 mg/dL): 60 to 90 mg as a single intravenous (IV) infusion over at least 2 to 24 hours, with adequate hydration;
- Severe hypercalcemia (corrected calcium greater than 13.5 mg/dL): 90 mg as a single IV infusion over at least 2 to 24 hours.

Retreatment may be considered with recurrence; however, it is recommended that a minimum of 7 days elapse (expected time to reach nadir level in serum calcium) before a second course of therapy. Infusions greater than 2 hours may reduce the risk of for renal toxicity.

B) For treatment of osteolytic bone lesions due to metastatic breast cancer and multiple myeloma: Dose: 90 mg IV over 2 to 4 hours every 3 to 4 weeks.
Note: Patients who receive pamidronate should have serum creatinine assessed prior to each treatment. Treatment should be withheld for renal deterioration defined as follows:
- For patients with normal baseline creatinine, increase of 0.5 mg/dL
- For patients with abnormal baseline creatinine, increase of 1 mg/dL

It is suggested treatment with pamidronate be resumed only when the creatinine returns to within 10% of the baseline value.

C) For treatment of moderate to severe Paget's disease:
Dose: 30 mg IV over 4 hours for 3 consecutive days (total dose 90 mg).

IV. TOXICITY

A) Generally well tolerated.
B) Flu-like symptoms (fever with or without rigors), hypocalcemia, hypomagnesemia, hypophosphatemia, skeletal pain, nausea, constipation.
C) Thrombophlebitis and soft tissue symptoms (18%), which is characterized by redness, swelling, pain.
D) Renal failure (increase SCr, albuminuria, azotemia). It is suggested that the mechanism of renal failure is most commonly associated with focal collapsing segmental glomerulosclerosis; in other words, deterioration in kidney function is often preceded by albuminuria.
E) Cases of osteonecrosis of the jaw have been reported in cancer patients during post-marketing experience. Many of the patients were also receiving chemotherapy and corticosteroids and the majority of the cases were associated with dental procedures. Dental surgery may exacerbate the condition in patients who develop osteonecrosis of the jaw while on bisphosphonate therapy.

V. CLINICAL MONITORING

A) Serum calcium, phosphate, magnesium, and potassium following initiation of therapy.
B) Patients should have serum creatinine assessed prior to each treatment and treatment should be withheld for renal deterioration (increase of 0.5 mg/dL) in patients with normal baseline creatinine and an increase of 1 mg/dL in patients with abnormal baseline creatinine).
C) An expert panel from the American Society of Clinical Oncology recommends intermittent evaluation every 3 to 6 months of all patients receiving chronic pamidronate therapy for the presence of albuminuria and azotemia. Discontinuation of zoledronic acid is warranted in cases of unexplained albuminuria (greater than 500 mg/24 hours of urinary albumin) or azotemia (an increase of 0.5 mg/dL) or more in serum creatinine or an absolute value of greater than 1.4 mg/dL among patients with normal baseline serum creatinine levels). Patients should be reassessed every 3 to 4 weeks.
D) Dental examination with appropriate preventive dentistry prior to treatment with bisphosphonates and signs of toxicity (e.g., fever, increased bone pain, flu-like symptoms, and ocular symptoms) while on treatment.

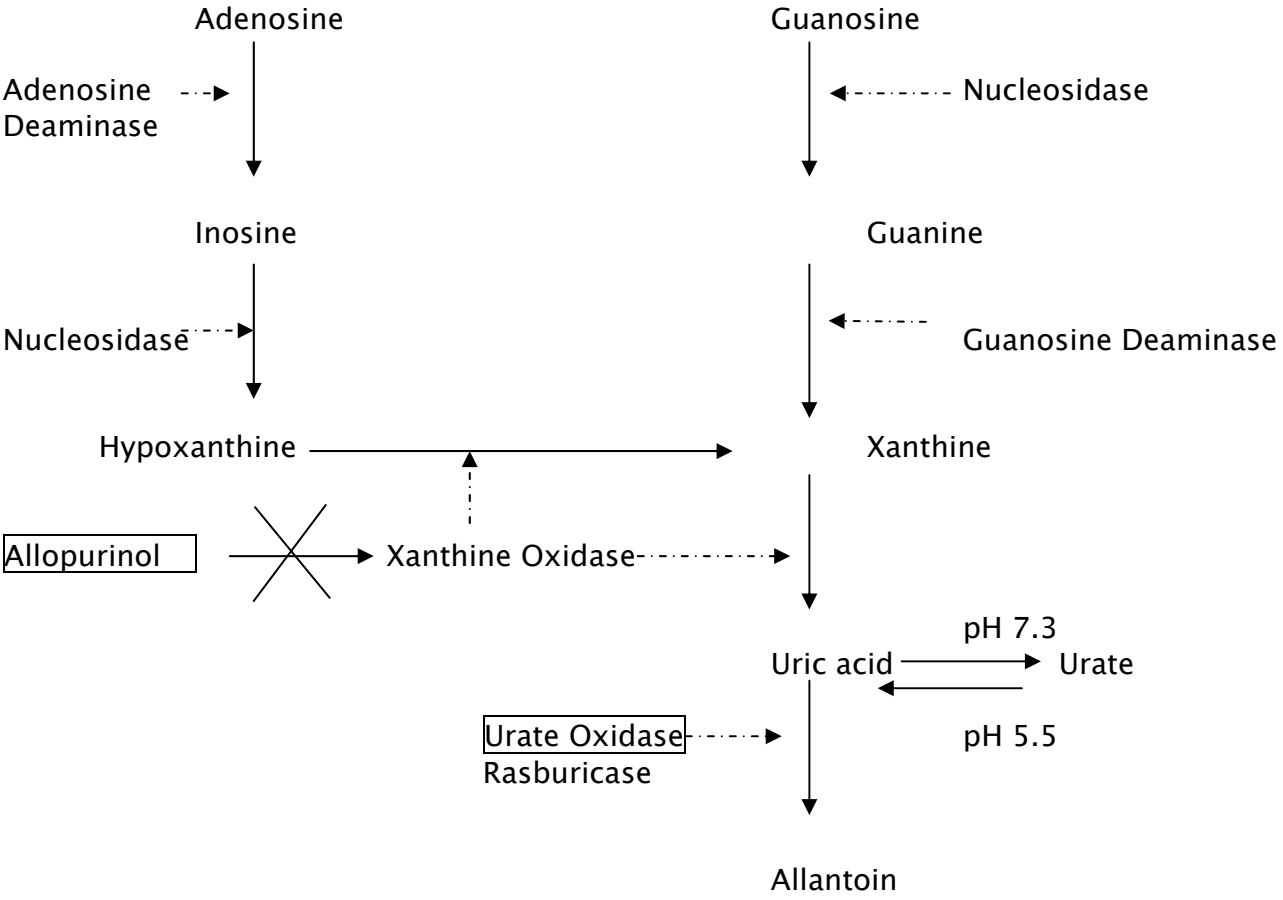
VI. DRUG INTERACTIONS

Not reported.

RASBURICASE
(ELITEK®)

I. MECHANISM OF ACTION

Tumor lysis syndrome (TLS) is a metabolic disorder characterized by a variety of electrolyte disturbances resulting from the release of intracellular substances after tumor cell lysis. It usually occurs within the first 24 – 48 hours after initiating effective treatment and may persist for 5 – 7 days post-therapy. The release of intracellular contents can be so massive that the body's excretory and cellular buffering mechanisms and pathways are overwhelmed, resulting in severe hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia (secondary to hyperphosphatemia). The concentration of uric acid or calcium phosphate may exceed the limits of solubility and precipitation of these compounds can result in renal failure that further exacerbates the metabolic abnormalities. Hyperuricemia is caused by rapid breakdown of nucleic acids. As renal excretory capabilities are overloaded, uric acid nephropathy may develop, with precipitation of uric acid crystals. The purine metabolic pathway is depicted below:



Reference: Jeha S. *Semin Hematol* 2001;38:4 – 8.

In the liver, xanthine oxidase catalyzes the conversion of hypoxanthine and xanthine to uric acid. Uric acid has a pK_a of 5.7 and is poorly soluble in acidic urine, but relatively soluble in plasma. As plasma uric acid concentrations increase, so does the potential for precipitation of uric acid crystals in the renal tubules. Uric acid is further oxidized by urate oxidase to allantoin. As allantoin is approximately 10-fold more soluble than uric acid, the problem of allantoin crystal precipitation does not occur. Rasburicase is the newest agent available to prevent TLS. Urate oxidase is an enzyme that catalyzes the conversion of uric acid into allantoin the more soluble end product (see diagram). Allantoin is rapidly eliminated via the kidneys and degrades the existing uric acid, leading to a faster onset of action. Rasburicase is a recombinant urate oxidase product.

II. PHARMACOKINETICS

The AUC_{0-24hr} and C_{max} increase linearly with doses over a limited dose range (0.15 to 0.2 mg/kg). C_{max} and AUC do not increase from Day 1 of therapy to Day 5 of therapy, indicating a lack of accumulation of rasburicase. The mean plasma terminal half-life was 16 hours $\pm$ 6.3 (SD) at the dose of 0.15 mg/kg and 21.1 $\pm$ 12 hours in patients treated at 0.2 mg/kg. The elimination half-life is 18 hours. No studies of interactions with other drugs have been conducted in humans. Rasburicase does not affect the activity of CYP1A, CYP 2A, CYP2B, CYP2C, CYP2E or CYP3A, therefore induction or inhibitory potential would not be anticipated.

III. DOSAGE AND ADMINISTRATION

Rasburicase is reconstituted with the diluent provided. It is further diluter to a total volume of 50 mL with NS. This medication is not to be administered as a bolus infusion, and is to be infused over 30 minutes. The solution should not be filtered. The reconstituted solution can be stored for up to 24 hours at 2^{o}C to 8^{o}C.

IV. TOXICITY

Rasburicase has been reported to cause severe hypersensitivity reactions, including anaphylaxis. Rasburicase has been reported to cause hemolysis in those patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. High-risk patients (i.e., patients of African or Mediterranean ancestry) should be screened for G6PD deficiency prior to starting rasburicase. In patients developing hemolysis on rasburicase, treatment should be stopped immediately. Rasburicase has also been associated with methemoglobinemia, and as such should be immediately discontinued in those individuals developing methemoglobinemia.

V. CLINICAL MONITORING

At room temperature, rasburicase causes enzymatic degradation of uric acid in blood, plasma, and serum samples. This can results in spuriously low uric acid levels. In order to prevent this from occurring, the following procedure for the handling of uric acid samples must be followed:

- Uric acid must be analyzed in plasma.
- Blood must be collected in pre-chilled tubes containing heparin anticoagulant
- Samples must be immersed immediately in an ice-water bath.
- Plasma samples must be prepared by centrifugation in a pre-cooled centrifuge (4^{o}C)
- The plasma must be maintained in an ice-water bath and analyzed for uric acid within 4 hours of collection.

ZOLEDRONIC ACID
(ZOMETA®)

I. MECHANISM OF ACTION

A) Zoledronic acid is a heterocyclic imidazole bisphosphonate and it is up to 840 times as potent as pamidronate.
B) It inhibits bone resorption by actions on osteoclasts; they may interfere with osteoclast recruitment and cellular activity, and can induce osteoclast apoptosis; this latter effect may be mediated through osteoblasts.
C) Bisphosphonates inhibit proliferation and induce apoptosis of a variety of human tumor cell lines *in vitro*, including breast, myeloma, melanoma, and prostate cell lines. Zoledronic acid appears to have the ability to suppress bone turnover for long periods of time (up to one year in one clinical trial). This long-term effect may be due to its effects on the basic multicellular units in bone. Exposure of the multicellular units to the bisphosphonate inhibits the activity of that unit for its entire life span (approximately 3 months), and defines the duration of action of the drug.
D) It has also been suggested that bisphosphonates also inhibit the ability of breast and prostate cancer cells to adhere to and invade the extracellular matrix, and may have antiangiogenic effects *in vivo*.
E) Clinical evidence also suggests that zoledronic acid may inhibit the progression of established bone lesions in patients with multiple myeloma.

II. PHARMACOKINETICS

A) Human oral absorption data for zoledronic acid are unavailable.
B) Distribution – 22% protein bound.
C) Metabolism- does not undergo biotransformation.
D) Elimination- 95% of the drug primarily excreted unchanged by kidneys; terminal half-life about 167 hours.

III. DOSAGE AND ADMINISTRATION

A) For treatment of hypercalcemia-associated malignancy: Dose: 4 mg IV over at least 15 minutes every 3 to 4 weeks.
B) For multiple myeloma and metastatic bone lesions from solid tumors: (a) Creatinine clearance >60 mL/min: 4 mg infused over no less than 15 minutes every 3 to 4 weeks. The optimal duration of therapy is not known; (b) Upon treatment initiation, the recommended doses of zoledronic acid for patients with reduced renal function (mild and moderate renal impairment) are listed in the following.

Baseline Creatinine Clearance (mL/min)	Recommended Dose*
> 60	4 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3 mg

*Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl=75 mL/min)

These doses are calculated to achieve the same AUC as that achieved in patients with a CrCL of 75 mL/min. Creatinine clearance is calculated using Cockcroft-Gault formula. During treatment, serum creatinine should be measured before each dose and

treatment should be withheld for renal deterioration. In clinical studies, renal deterioration was defined as follows:
- For patients with normal baseline creatinine, increase of 0.5 mg/dL.
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL.
In the clinical studies, zoledronic acid treatment was resumed only when the creatinine returned to within 10% of the baseline value. The drug should be re-initiated at the same dose as that prior to treatment interruption.

IV. TOXICITY

A) Generally well tolerated.
B) Flu-like symptoms (fever with or without rigors), hypocalcemia, hypomagnesemia, hypophosphatemia, skeletal pain, nausea, constipation.
C) Renal failure (increase SCr, albuminuria, azotemia). It is suggested that the mechanism of renal failure is most commonly associated with tubular dysfunction and interstitial nephritis; in other words, albuminuria is less likely to be seen.
D) Cases of osteonecrosis of the jaw have been reported in cancer patients during post-marketing experience. Many of the patients were also receiving chemotherapy and corticosteroids and the majority of the cases were associated with dental procedures. Dental surgery may exacerbate the condition in patients who develop osteonecrosis of the jaw while on bisphosphonate therapy.

V. CLINICAL MONITORING

A) Serum calcium, phosphate, magnesium, and potassium following initiation of therapy.
B) Patients should have serum creatinine assessed prior to each treatment and treatment should be withheld for renal deterioration (increase of 0.5 milligram/deciliter (mg/dL) in patients with normal baseline creatinine and an increase of 1 mg/dL in patients with abnormal baseline creatinine).
C) An expert panel from the American Society of Clinical Oncology recommends intermittent evaluation every 3 to 6 months of all patients receiving chronic zoledronic acid therapy for the presence of albuminuria and azotemia. Discontinuation of zoledronic acid is warranted in cases of unexplained albuminuria (greater than 500 mg/24 hours of urinary albumin) or azotemia (an increase of 0.5 mg/dL) or more in serum creatinine or an absolute value of greater than 1.4 mg/dL among patients with normal baseline serum creatinine levels). Patients should be reassessed every 3 to 4 weeks.
D) Dental examination with appropriate preventive dentistry prior to treatment with bisphosphonates and signs of toxicity (e.g., fever, increased bone pain, flu-like symptoms, and ocular symptoms) while on treatment.

VI. DRUG INTERACTIONS

Thalidomide: the risk of renal dysfunction may be increased when zoledronic acid is used in combination with thalidomide in multiple myeloma patients.