OTHER AGENTS

BEXAROTENE
(TARGRETIN®)

I. MECHANISM OF ACTION

Bexarotene is a selective retinoid X receptor (RXR) ligand. Activation of the RXR pathway leads to the induction of programmed cell death (apoptosis) and other cellular activities.

II. PHARMACOKINETICS

A 10-fold or greater increase in bioavailability is seen with the micronized formulation compared to conventional soft gelatin capsules Administration of bexarotene 300 mg/m^2 after a fat-containing meal resulted in a 35% increase in AUC and a 48% increase in peak plasma concentrations when compared with these values following administration of bexarotene with a glucose solution. Cytochrome P450 3A4 is suggested by in vitro studies to be the major cytochrome P450 responsible for formation of the oxidative metabolites. Oxidative metabolites may be glucuronidated. Elimination half-life is 7 hours Cmax: 2 to 4 hours. Bexarotene and its metabolites are eliminated primarily through the hepatobiliary system. Less than 1% of the dose is excreted in the urine unchanged. No specific studies have been performed in patients with renal or hepatic impairment. Although renal elimination is insignificant, protein binding changes due to renal impairment may alter the pharmacokinetics of bexarotene in patients with renal insufficiency. Hepatic impairment though to greatly decrease the clearance of bexarotene.

III. DOSAGE AND ADMINISTRATION

A) Oral bexarotene should be taken with fat-containing meals and the capsules should be protected from light.

B) Do not apply the gel near mucosal areas of the body. Sufficient gel should be applied to cover the lesion with a generous coating. The gel should be allowed to dry before covering with clothing. Do not use occlusive dressings with bexarotene gel. Avoid application of the gel to normal skin around the lesions to prevent irritation. Wait 20 minutes after showering or bathing before applying the gel. Avoid bathing, showering, or swimming for at least 3 hours after any application, if possible. Protect gel from light.

IV. TOXICITY

A) Hyperlipidemia has been reported frequently, as a dose-limiting toxicity, following therapeutic administration of bexarotene. Hyperlipidemia, including elevated triglyceride (64%) and cholesterol levels (51%) were reported in patients (n=94) who received oral bexarotene during a phase II/III clinical trial. Hyperlipimic effects are reversible upon discontinuation of bexarotene therapy and can be controlled by reducing the dose of bexarotene or adding antilipemic therapy. Fasting blood lipid determinations should be performed prior to starting bexarotene therapy and weekly until the lipid response to bexarotene is established, usually within 2—4 weeks, and then at 8-week intervals. Due to a potential drug interaction, gemfibrozil is not recommended for use with bexarotene.

B) Pancreatitis has been reported in several patients following administration of bexarotene at doses of greater than 300 mg/m^2/day. The occurrence of pancreatitis appears to be associated with the development of hypertriglyceridemia. Patients who have risk factors

for pancreatitis, including prior pancreatitis, uncontrolled hyperlipidemia, alcoholism, uncontrolled diabetes mellitus, biliary tract disease, and treatment with medications known to increase triglycerides or to be associated with pancreatitis, should generally not be treated with oral bexarotene.

C) Central hypothyroidism was reported in 39.7% of patients with refractory or persistent early-stage cutaneous T-cell lymphoma (CTCL; n=58) and 29% of patients with refractory advanced-stage CTCL (n=94) treated with oral bexarotene. TSH is not a good screening test for the development of hypothyroidism in these patients.

D) Dry skin, dermatitis, dermal pain, pruritus, photosensitivity, and rashes may occur following oral administration of bexarotene capsules or topical application of bexarotene gel.

E) Elevated hepatic enzymes have been observed in 5% patients receiving an initial dose of 300 mg/m^2/day PO of bexarotene. The incidence is higher in patients receiving initial bexarotene doses more than 300 mg/m^2/day PO. In clinical trials, elevations of hepatic enzymes resolved within one month in 80% of patients following a decrease in dose or discontinuation of therapy. Baseline liver function tests (LFTs) should be obtained, and LFTs should be carefully monitored one, two and four weeks after initiating systemic therapy, and if stable, at least every 8 weeks thereafter during treatment. Discontinuation of systemic bexarotene therapy should be considered if LFTs reach more than 3-times the upper limit of normal values for SGOT/AST, SGPT/ALT, or bilirubin.

F) Reversible leukopenia (1 - 2.99 x 10^9/L WBC) occurred in 18% of patient with cutaneous T cell lymphoma (CTCL) receiving an initial oral bexarotene dose of 300 mg/m^2/day. Patients receiving an initial oral bexarotene dose more than 300 mg/m^2/day had an incidence of leukopenia of 43%. No patient with CTCL developed leukopenia of $< 1 \times 10^9$/L WBC. The time to onset of leukopenia was about 4—8 weeks. In patients receiving 300 mg/m^2/day the incidence of grade 3 or 4 neutropenia was 12% and 4%, respectively. The leukopenia and neutropenia resolved within 30 days of dose reduction or discontinuation of bexarotene therapy in 93% of patients with CTCL and 82% of patients with non-CTCL cancers.

BORTEZOMIB
(VELCADE®)

I. MECHANISM OF ACTION

The proteasome is a multicatalytic enzyme complex that degrades numerous types of proteins, many of, which are regulatory proteins that control the cell cycle or play a role in survival pathways. The expression and degradation of these proteins is essential for normal cellular function. Therefore the proteasome plays an important role in up- or down-regulation of growth signaling pathways by removing key signals via protein degradation. Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in cells. The 26S proteasome degrades ubiquinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins and therefore maintaining homeostasis within cells.

II. PHARMACOKINETICS

Mean elimination half-life is 9 – 15 hours. It is distributed into tissues, kidneys, bone marrow and urine. It does not cross the blood brain barrier or penetrate the eye. It is 82% protein bound. There is a decrease in clearance and increase in elimination half-life over cycles, but there is no clinically significant accumulation. The drug is metabolized by the CYP 450 enzyme system, primarily via 3A4, 2D6, 2C19, and 1A2. Drug interactions are likely with competitive drugs. The clinical trials allowed enrollment with CrCL to 10 mL/minute. There are no specific dose recommendations, rather that patient with CrCL < 13 mL/minute and those receiving hemodialysis be more closely monitored for toxicity during treatment. There are no PK data in hepatic impairment so no dosing recommendations can be made at this time.

III. DOSAGE AND ADMINISTRATION

The recommended dose of bortezomib for multiple myeloma is 1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 10- day rest period (days 12-21). This 3-week period is considered as 1 treatment cycle. At least 72 hours should elapse between consecutive doses of bortezomib.

IV. TOXICITY

A) Peripheral neuropathy: The neuropathy is predominately sensory, although cases of mixed sensori-motor neuropathy have been reported. Patients who present for bortezomib treatment with pre-existing symptoms and/or signs of peripheral neuropathy may experience worsening of symptoms during treatment with bortezomib. If neuropathic pain and/or peripheral sensory neuropathy occur, follow the recommended dose modification schedule below:

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib to 1mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7mg/m^2 and change treatment schedule to once per week
Grade 4 (permanent sensory loss that interferes with function)	Discontinue bortezomib

Peripheral neuropathy, peripheral sensory neuropathy, and peripheral neuropathy aggravated occurred in 37% patients. Grade 3 neurotoxicity occurred in 14% patients, and there were no grade 4 events.

B) Hypotension: occurs in 12% patients, and is orthostatic or postural hypotension. Patients with a history of syncope or receiving antihypertensives or who are dehydrated are at greater risk for developing this side effect. Pre-hydration with 500 mL to 1000 mL sodium chloride 0.9% may prevent this from occurring in susceptible individuals.

C) Gastrointestinal: nausea, vomiting, diarrhea and constipation requiring treatment may occur.

D) Hematologic toxicity: Grade 3 and 4 hematologic toxicity occurs in a small percentage of the population (and the trials were performed in heavily pretreated patients, with up to 66% having undergone a prior HSCT). Thrombocytopenia: 27% Grade 3 and 3% Grade 4. 4% patients discontinued treatment due to thrombocytopenia of any grade. Neutropenia: Grade 3 13%, Grade 4 less than 1%.

E) Pulmonary: There are emerging reports of pulmonary toxicity with bortezomib. The reports to date have occurred in Japanese patients and African American patients [Reference: Miyakoshi S, et al. *Blood* 2006; 2006;107:3492 - 4].

V. CLINICAL MONITORING

CBC with differential and platelets; regular neurological examination and observation for peripheral neuropathy; evaluate patient's medications prior to Rx (i.e. any antihypertensives – suggest holding them until after the dose)

VI. DRUG INTERACTIONS

No formal drug interaction studies have been conducted with bortezomib. Bortezomib is a substrate of cytochrome P450 3A4, 2D6, 2C19, and 1A2. Patients who are on bortezomib and drugs that are inducers or inhibitors of cytochrome P450 3A4 should be closely monitored for toxicity or reduced efficacy.

Drug Interactions			
Bortezomib Drug Interactions			
Precipitant drug	**Object drug***		**Description**
CYP450 inducers or inhibitors	Bortezomib	↑↓	Bortezomib is a substrate for cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Closely monitor patients for toxicities or reduced efficacy when bortezomib is co-administered with drugs that are inducers/inhibitors of cytochrome P450 3A4.
Bortezomib	CYP450 2C19 substrates	↑	Bortezomib may inhibit 2C19 isoenzyme activity and increase exposure to drugs that are substrates for this isoenzyme.
Bortezomib	Oral hypoglycemic agents	↑↓	Co-administration has resulted in hypo- and hyperglycemia. Closely monitor blood glucose levels and adjust dose of antidiabetic medication if necessary.

* ↑ = Object drug increased. ↓ = Object drug decreased.

Reference: Facts and Comparisons, on-line 2007; accessed January 4, 2007.

DASATINIB
(SPRYCEL™; BMS354825)

I. MECHANISM OF ACTION

Is a dual BCR-ABL inhibitor and SRC inhibitor. It is active in Imatinib resistant cell lines. It has a 2-log greater potency than Imatinib. It retained activity against 14/15 imatinib-resistant BCR-ABL mutants in pre-clinical studies. BMS 354825 competes with ATP for the ATP-binding site in the kinase domain of selected protein tyrosine kinases and has been shown to inhibit at least 5 protein kinases/kinase families: SRC family kinases; BCR-ABL; c-KIT; EPHA2; and the PDGR β receptors. Comparative potency of BMS 354825 are as follows:

Kinase	Fold more potent than Imatinib (based in IC_{50})
BCR-ABL	260
c-KIT	8
PDGFβ	60
SRC	> 1000

II. PHARMACOKINETCS

Unknown at present. Serum levels well above the concentration required to block CML proliferation *in vitro* were readily achieved in clinical trials without side effects. Pharmacodynamic studies demonstrated more than 50% inhibition of phosphorylation of the BCR-ABL substrate CRKL and the Src kinases Lyn. The oral bioavailability varies according to species studied. The oral bioavailability ranged from 15% in monkeys to 34% in dogs, with the average bioavailability in mice and rats being 16 and 27% respectively. Distribution: BMS 354825 is highly bound to proteins, and the blood to plasma ration in humans is 1.8. There is extensive extravascular distribution. Metabolism: incubation with recombinant human cytochrome P450 isoenzymes suggests that dasatinib is primarily metabolized by the CYP3A4 isoenzyme. Many other enzymes appear capable of metabolizing the drug, including CYP1A1, 2C9, 2E1, FMO3, 1B1, 2B6, 2A6, 2C8, and 4A1. It is unknown currently what contributions these enzymes may have to the total metabolic clearance of BMS 354825. Elimination: very little is eliminated in the urine and bile. This suggests that the major route of elimination is by metabolism. Preliminary PK data in human subjects suggests that the PK of a dose of 70 mg PO BID is comparable to that of 140 mg PO QD.

III. DOSAGE AND ADMINISTRATION

The FDA approved dose in patients with CML refractory or intolerant to imatinib is 140 mg PO QD administered as 70 mg PO BID with or without a meal. In clinical trials the dose was escalated to 90 mg PO BID in patients with chronic phase CML who did not achieve a hematologic or cytogenetic response at 70 mg PO BID and to 100 mg PO BID in patients with advanced phase CML or Philadelphia chromosome positive ALL.

There are currently no clinical studies with dasatinib in patients with impaired liver function (clinical trials excluded patients with ALT and/or AST of greater than 2.5 x ULN). Dasatinib is primarily metabolized hepatically. Caution is recommended in patients with hepatic dysfunction.

Similarly there are no clinical trials evaluating dasatinib in patients with renal impairment (patients on the clinical trials were excluded if the SCr was greater than 1,5 mg/dL. Minimal dasatinib and metabolites area excreted via the kidney, therefore no renal clearance is expected and no dose modification would be anticipated.

Dose adjustments for neutropenia and thrombocytopenia:

PHASE	HEMATOLOGICAL INDICES	ACTION
Chronic Phase CML (starting dose 70 mg PO BID)	ANC < 0.5 x 10^9/L and/or platelets < 50 x 10^9/L	1. Stop dasatinib until ANC ≥ 1 x 10^9/L and platelets ≥ 50 x 109/L. 2. Resume treatment with dasatinib at the original starting dose. 3. If platelets < 25 x 10^9/L and/or recurrence of ANC < 0.5 x 10^9/L for greater than 7 days, repeat Step 1 and resume dasatinib at a reduced dose of 50 mg PO BID (2nd episode) or 40 mg PO BID (3rd episode).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 70 mg PO BID)	ANC < 0.5 x 10^9/L and/or platelets < 10 x 10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop dasatinib until ANC ≥ 1 x 10^9/L and platelets ≥ 20 x 10^9/L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume dasatinib at a reduced dose of 50 gm PO BID (2nd episode) or 40 mg PO BID (3rd episode). 4. If cytopenia is related to leukemia, consider dose escalation to 100 mg PO BID.

IV. TOXICITY

Doses are well tolerated up to 180 mg PO QD (and for up to 9 months of therapy). Principal drug-related toxicities were manifested as gastrointestinal, hematopoietic, and lymphopoietic. One case of prolonged QTc interval has been reported.

(a) Hematological toxicity: myelosuppression is a hallmark of CML and also a characteristic side effect of chemotherapy. Therefore when evaluating hematological toxicity it is important to consider this in the analysis. Hematological toxicity was one of the main reasons for dose reductions and interruptions in the clinical trials. Grade 3 and 4 hematological toxicity seen is reported below:

Grade 3 and Grade 4 Hematological Toxicity with Dasatinib

% Of Subjects experiencing Grade 3 or 4 Hematological Toxicity					
	Chronic Phase (n = 208)	Accelerated Phase (n=118)	Myeloid Blast Phase (n=97)	Lymphoid Blast Phase/Ph+ ALL (n = 88)	Total (n = 511)
Thrombocytopenia	45	79	82	81	66
Neutropenia	44	71	79	75	62
Anemia	16	67	70	50	44
Leukopenia	22	57	66	68	46

Myelosuppression generally recovered after a brief (2 – 4 weeks) interruption of therapy. Non-clinical studies suggested that dasatinib inhibits collagen-induced platelet aggregation in humans (and animals). Patients enrolled in the clinical trials were closely evaluated for bleeding evens. Approximately 33% of patients on clinical trial had a bleeding event and of those, half were consider study drug related. Gastrointestinal hemorrhage occurred in 8% subjects, and was more common in more advanced stages of leukemia. Most patients had dasatinib therapy interrupted at this time, but no patient discontinued therapy due to GI bleeding. Three cases of CNS hemorrhage were identified among the 511 safety analysis patients. Two of these occurred in advanced stage leukemia patients and could be due to the underlying advanced stage of the disease.

(b) Non-hematological toxicity: Side effects occurring in more than 10% of patients on clinical trials included: gastrointestinal disorders – diarrhea, nausea and vomiting; pyrexia; peripheral edema; asthenia; rash; dyspnea; pleural effusion; and headache. Drug-related edema was reported in 24% of patients. The incidence of edema was similar across all phases of CML treatment with dasatinib. Superficial edema was more common than generalized edema. All of the episodes of edema were Grade 1 or 2, with the exception of 2 patients. No patient discontinued dasatinib treatment as a consequence of treatment-related edema. Overall 14% patients developed drug-related pleural effusions. This was more common in myeloid blast crisis patients (22%). Most pleural effusions were Grade 1 or 2. Other forms of fluid retention were uncommon. Ascites occurred infrequently. Cardiomyopathy occurred in 9 patients on clinical trials resulting in treatment discontinuation in 7 cases. Clinical trials evaluated the effect of dasatinib on the QTc interval. Dasatinib therapy resulted in a mean change in the QTcF of 3 – 6 milliseconds. Approximately 1% of patients had prolongation of the QTc interval to greater than 500 msec.

Toxicity	Frequent	Infrequent
GI disorders	Upper abdominal pain, flatulence, constipation, abdominal distension, dyspepsia, colitis, mouth ulcerations	Gastritis, dry mouth, tongue ulceration, anal fissure, gingivitis, GERD, gingival hyperplasia, gingival swelling, neutropenic colitis.
General & administration	Chills, chest pain, pain, mucosal inflammation	Chest discomfort, facial pain, flu-like illness, malaise, axillary pain.
Skin and subcutaneous tissue disorders	Alopecia, erythema, acne, dry skin, dermatitis acneform, skin exfoliation, urticaria.	Acute neutrophilic dermatitis, erythema nodosum, dermatitis, eczema, generalized erythema, hyperhydrosis, PPE, photosensitivity skin reaction, pigmentation disorder, pyoderma gangrenosum.
Respiratory, thoracic and mediastinal disorders	Dyspnea (exertional), lung infiltration.	Hypoxia, pneumonitis, pulmonary hypertension, pharyngolaryngeal pain, dysphonia, wheezing, ARDS, atelectasis, interstitial lung disease.

CNS	Dizziness, paresthesia	Neuropathy, tremor, peripheral neuropathy, syncope, cerebral hemorrhage, dyskinesia, hypoaesthesia, neuralgia, migraine, somnolence.
Musculoskeletal	Muscle spasms, back pain.	Muscular weakness, musculoskkleletal pain, neck pain, shoulder pain
Cardiac	Palpitations, AF, CCF	Tachycardia, AML, SCT, congestive cardiomyopathy, MI, ventricular arrhythmias, ventricular tachycardia.
Eye disorders	Conjunctivitis	Blurred vision, eye pain, diplopia, and visual disturbance.
Vascular disorders	Flushing	Hot flush, hypertension, peripheral ischemia, thrombosis, phlebitis, vasculitis.
Psychiatric disorders	Insomnia, depression, confused state, agitation, disorientation, irritability, restlessness.	
Reproductive system and breast disorders	Breast pain, breast tenderness, erectile dysfunction, and irregular menstruation.	
Hepatobiliary	Hyperbilirubinemia, cholestasis, cholecystitis, jaundice.	
Renal and urinary disorders	Renal failure, dysuria, urethral stricture, urinary retentions.	
Neoplasms benign, malignant and unspecified		Tumor lysis syndrome.

V. CLINICAL MONITORING

CBC + differential.

VI. DRUG INTERACTIONS

Dasatinib is an inhibitor of CYP 3A4 but not an inducer of CYP3A4. Dasatinib may decrease the clearance of drugs that are significantly metabolized by CYP3A4. Dasatinib is extensively metabolized in humans and the CYP 3A4 plays a major role in this drugs metabolism. Dasatinib does not induce CYP1A2, 2B6, 2C9, or 3A4 isoenzymes.

A number of drug interaction studies have been performed including simvastatin, rifampin, and antacids (Maalox® and H_2 antagonists). Dasatinib co administered with simvastatin results in modest increases in simvastatin concentrations. Ketoconazole results in an increased C_{max} and AUC by 4- and 5-fold, respectively. Substances that inhibit CYP3A4 activity e.g., ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin) may decrease metabolism and increase concentrations of dasatinib. When co-administered with rifampin the magnitude of the drug interactions is much greater. The C_{max} and AUC of dasatinib were decreased by

more than 81% when a single dose of dasatinib was administered following 8 days of continuous dosing with rifampin.

Concomitant administration of dasatinib with potent enzyme inducers (e.g., phenobarbital, carbamazepine, phenytoin, etc) is contraindicated. Administration of dasatinib with *Hypericum perforatum* (St John's Wort) may decrease dasatinib plasma concentrations unpredictably. Patients receiving dasatinib should not take St John's Wort.

Simultaneous co-administration of dasatinib with an aluminum hydroxide/magnesium hydroxide containing antacid resulted in a 55% decrease in exposure (AUC) of dasatinib. When the administration of dasatinib and aluminum hydroxide/magnesium hydroxide antacids was separated by 2 hours there was no effect on exposure. Therefore these agents must be separated by 2 hours (2 hours prior to or 2 hours after the dose of dasatinib). Administration of famotidine 10 hours prior to and dasatinib reduced exposure to dasatinib by 61%, therefore H_2 antagonists should be avoided in patients receiving dasatinib.

Dasatinib is a time-dependent inhibhitor of CYP3A4. Therefore CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine A, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids should be administered with caution in patients receiving dasatinib.

DENILEUKIN DIFTITOX
(ONTAK®)

I. MECHANISM OF ACTION

A) A recombinant DNA-derived cytotoxic protein designed to direct the cytocidal action of diphtheria toxin to cells, which express the IL-2 receptor.

B) The human IL-2 receptor exists in low (CD25), intermediate (CD122/CD132), and high (CD25/CD122/CD132) affinity. The high affinity form of this receptor is usually found only on activated T lymphocytes, B-lymphocytes and macrophages. Some leukemias and lymphomas express one or more of the subunits of the IL-2 receptor. Ex vivo studies suggest that ONTAK interacts with the high affinity IL-2 receptor on the cell surface and inhibits cellular protein synthesis, resulting in cell death within hours.

II. PHARMACOKINETICS

A) Radiolabeled denileukin diftitox was evaluated in rats – the liver and kidneys were the primary sites of distribution and accumulation of radiolabeled material.

B) Metabolism- Proteolytic degradation.

III. DOSAGE AND ADMINISTRATION

A) 9 or 18 mcg/kg/day IV for five consecutive days every 21 days. Infused over at least 15 minutes.

B) For GVHD doses are 9 micrograms/kg on days 1, 3, 5, 15, 17, and 19.

IV. TOXICITY

A) Hypersensitivity- acute hypersensitivity reactions during or within 24 hours of denileukin diftitox infusion. Premed with Prednisone 20 mg PO QD beginning one day prior to cycle 1 and 2 and continuing for 1 day after the last infusion, Tylenol® 650 mg, and Benadryl® 50 mg.

B) Vascular leak syndrome- onset of symptoms is usually delayed, occurring within the first two weeks of infusion and may persist or worsen after the cessation of denileukin diftitox. Weight, edema, blood pressure, and albumin should be monitored as an outpatient.

C) Hypoalbuminemia- nadir occurs one to two weeks after denileukin diftitox. Serum albumin should be monitored prior to the initiation of each treatment course. Delay denileukin diftitox until albumin level is at least 3 g/dL.

D) Infectious- lymphocyte counts drop and returns to normal by day 15.

E) Visual Loss: Changes in visual acuity and/or visual field defects ranging from blurred vision to blindness can occur. Loss of color vision with or without retinal pigment mottling has been reported following administration of denileukin. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment.
[Reference: http://www.fda.gov/cder/Offices/OODP/whatsnew/denileukin.htm].

F) Cardiovascular: ventricular arrhythmias have been reported occurring within 2 – 7 days of initiation of treatment.

G) Others- flu-like syndrome within several hours to days after denileukin; diarrhea; rash.

V. CLINICAL MONITORING

A) Prior to administration test of CD25 expression.

B) Labs- BUN/SCr, LFTs, CBC with differential, albumin.

ERLOTINIB
(TARCEVA®)

I. MECHANISM OF ACTION

Erlotinib is an orally available epidermal growth factor receptor (HER-1/EGFR) tyrosine kinase (TK) inhibitor. It is a quinazoline derivative that binds competitively to the adenosine triphosphate binding site at the EGFR intracellular TK domain and therefore inhibits EGFR autophosphorylation.

II. PHARMACOKINETICS

A) Absorption- oral bioavailability about 80%.
B) Distribution- highly protein bound (92% to 95%).
C) Metabolism- erlotinib undergoes metabolic alteration, which occurs predominantly in the liver. It is metabolized to several metabolites including principle metabolite, OSI-420, which is also responsible for inhibiting tumorigenesis and contributing to the overall antitumor effect.
D) Approximately 80% of the metabolism of erlotinib occurs via cytochrome CYP3A4. Potent inhibitors (e.g. ketoconazole, voriconazole, erythromycin, grapefruit juice, itraconazole, fluconazole, verapamil, dilitazem, etc) or inducers (e.g. rifampin, phenytoin, carbamazepine, St. John's Wort, barbiturates, etc) can significantly affect the metabolism of erlotinib, altering the plasma exposure and, potentially, efficacy and tolerability. Studies have shown that cytochrome P450 1A2, 2C8, 2C9, 2C19, and 2D6 do not appear to be involved.
E) Elimination- following multiple dosing of 150 mg, elimination half-life is 18.18 +/- 9.74 hours; the predominant metabolite of erlotinib, OSI-420, is eliminated primarily in the bile.
F) No data on dosage adjustment in patients with renal and hepatic dysfunction. However, dose reduction may need to be considered in patients with severe hyperbilirubinemia.

III. DOSAGE/ADMINISTRATION

Administered orally. Available as 25 mg, 100 mg, and 150 mg tablets.

IV. TOXICITY

A) Cutaneous acneiform rash (74-91% overall) dose limiting; which preferentially affect the face, upper trunk areas. It usually appears at the end of the first week of dosing, reaches peak intensity during the second week, and progressively resolves. Treatment with topical or systemic tetracycline-type antibiotics has been reported to accelerate the resolution of the rash in some patients.
B) Diarrhea (31-37%)-dose-limiting; characterized by mild to moderate watery diarrhea with median time to the first occurrence on day 12. Diarrhea was reported to be controllable with aggressive use of loperamide.
C) Mild to moderate nausea/vomiting (17%).
D) Fatigue (14%).
E) Pruritis (20%).
F) Stomatitis (17%).

V. CLINICAL MONITORING

Dose reduction of the drug should only be considered in patients who develop significant grade 4 skin toxicity.

VI. DRUG INTERACTIONS:

Clinically significant drug interactions with potent CYP 3A4 inhibitors or inducers. Erlotinib is metabolized primarily by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP1A2. Drugs that are inducers of CYP3A4 activity will decrease the plasma concentrations of erlotinib. Concomitant administration of rifampicin with erlotinib results in a two-third decrease in erlotinib AUC. In patients receiving potent inducers of CYP3A4, alternate treatments lacking CYP3A4 inducing activity should be considered. If an alternative treatment is unavailable, an erlotinib dose greater than 150 mg/day should be considered in the absence of severe adverse reactions, and the clinical response should be carefully monitored. If the erlotinib dose is adjusted upward, the dose must be reduced upon discontinuation of the inducer. Inducers of CYP3A4 include: barbiturates, bosentan, carbamazepine, dexamethasone, nevirapine, oxcarbazepine, phenobarbital, phenytoin or fosphenytoin (and possibly ethotoin), rifampin, rifabutin, rifapentine, and St. John's Wort, Hypericum perforatum. This list may not be inclusive of all agents that may induce CYP3A4. Substances that are potent inhibitors of cytochrome P450 (CYP) 3A4 activity decrease the metabolism of erlotinib and increase erlotinib concentrations. This increase may be clinically relevant as adverse reactions to erlotinib are related to dose and exposure; therefore caution should be used when administering CYP3A4 inhibitors with erlotinib. Concomitant administration of ketoconazole with erlotinib increases mean erlotinib AUC by two-thirds. The following are drugs that may inhibit CYP3A4: amiodarone, anti-retroviral protease inhibitors, cimetidine, clarithromycin, dalfopristin; quinupristin, delavirdine, diltiazem, efavirenz (induces or inhibits), erythromycin, fluvoxamine, fluoxetine, grapefruit juice, imatinib, STI-571, itraconazole, mifepristone, RU-486, nefazodone, telithromycin, troleandomycin, verapamil and voriconazole. This list may not be inclusive of all agents that may inhibit CYP3A4 [Reference: Clinical Pharmacology Online, Accessed 03/30/05].

GEFITINIB
(IRESSA®)

I. MECHANISM OF ACTION
A) Gefitinib is an orally active, low-molecular-weight anilinoquinazoline derivative.
B) Is a selective epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, which reversibly binds to the ATP-binding site of the tyrosine kinase receptor and completely inhibits autophosphorylation by EGFR-TK. This results in blockage of downstream EGFR signal transduction pathways, cell cycle arrest, and inhibition of angiogenesis.

II. PHARMACOKINETICS
A) Absorption- oral bioavailability about 50%.
B) Distribution- extensive tissue distribution.
C) Metabolism- Metabolic pathway have not been determined.
D) Elimination- terminal half-life 46 hours; <0.5% renally excreted; mostly excreted via bile.

III. DOSAGE AND ADMINISTRATION
A) Approved dose is 250 mg/day taken orally with or without food. Higher doses do not give a better response and cause increased toxicity.
B) Patients with poorly tolerated diarrhea or skin adverse reactions may be successfully managed by briefly interrupting therapy for up to 14 days and then restarting the 250 mg/day dose.
C) Available as 250 mg oral tablets.
D) Gefitinib is subject to a limited distribution program. The following patients are eligible to receive gefitinib: (a) patients currently receiving and benefiting from gefitinib; (b) patients who have previously received and benefited from gefitinib; and (c) previously enrolled patients or new patients in non-investigational new drug (IND) clinical trials approved by an IRB prior to June 17th, 2005. New patients may also be able to obtain gefitinib if AstraZeneca decides to make it available under IND and the patients meet the criteria for enrollment under the IND.

IV. TOXICITIES
A) Dermatologic- acne-like follicular skin rash (dose limiting); usually appears from 2—14 days of beginning treatment. Higher doses have been associated with a more rapid onset of rash.
B) Gastrointestinal- diarrhea (dos-limiting), nausea, vomiting.
C) Myelosuppression- not common; usually only mild (grade 1 to 2).
D) Pulmonary- interstitial pneumonia (1%) and one third of the cases were fatal. In the event of acute onset or worsening of pulmonary symptoms (dyspnea, cough, fever), gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately.
E) Others: eye pain, corneal erosion/ulcer, asthenia, and fatigue.

V. CLINICAL MONITORING
A) Periodic CBC, LFTs.
B) Physical exam (persistent diarrhea, facial acne-like rash).

INTERFERON ALFA
(ROFERON-A®: IFN ALFA-2a; INTRON A®: IFN ALFA-2B)

I. MECHANISM OF ACTION

A) Interferon alfa is made by recombinant DNA technology using *E. coli*. There are two forms, designated interferon alfa 2a (Roferon®) and interferon alfa 2b (Intron A®).
B) Part of the body's natural system to control malignant processes when they start is Killer cells and Natural Killer cells. Interferon alfa activates these cells to become cytotoxic. Tumor surveillance is heightened.
C) Interferon alfa also inhibits the expression of certain oncogenes.
D) Induces tumor cells to express surface antigens that may serve as targets for cytotoxic monoclonal antibodies.
E) Inhibits the growth of early hematopoietic progenitor cells of the granulocyte, erythrocyte, megakaryocyte, and macrophage hematopoietic cell lines.

II. PHARMACOKINETICS

A) Given IM, SC, or IV.
B) Bioavailability from the IM or SC route is 80% of the IV route.
C) Does not cross the blood-brain barrier.
D) Metabolized in the kidney.

III. DOSAGE AND ADMINISTRATION: See relevant regimens in next section.

IV. TOXICITY

A) Flu-like symptoms - 100% of patients. Fever, chills, rigors, tachycardia, malaise, arthralgias, headache, nasal congestion, sinus drainage, urinary urgency, dizziness. The fever occurs within 6 hr of administration. Most frequent with doses over 18mu, patients over age 65, doses given IV.
B) Fatigue - 50 - 100% of patients. Common with doses over 20mu, older patients, and patients with poor performance status.
C) Anorexia - 30 - 50% of patients.
D) Mental status changes/confusion.
E) Depression/ psychiatric [Reference: Trask PC, et al. *J Clin Oncol* 2000; 18:2316 - 36].
F) Neutropenia in 40 - 60% of patients.
G) Metallic or salty taste in 13 - 25% of patients.
H) Proteinuria in 15 - 20% of patients.
I) Alopecia. Excessive growth of eyelashes.
J) Dyspnea/nonproductive cough in 34% of patients.
K) Thyroid abnormalities - monitor baseline TFT's and then periodically throughout treatment.

V. CLINICAL MONITORING

A) Monitor CBC, electrolytes, LFTs, thyroid function tests, mental status, and vital signs.
B) Teach patient that full effect of drug may take up to 6 months to be seen.

IMATINIB MESYLATE
(GLEEVEC®)

I. MECHANISM OF ACTION

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia. It acts to inhibit proliferation and induces apoptosis in bcr-abl positive cell lines as well as fresh leukemic cells from Ph chromosome positive CML. In vitro studies have also shown that imatinib is not entirely selective against bcr-abl, and also inhibits the tyrosine kinase receptor for platelet-derived growth factor, stem cell factor, c-kit, and inhibits PDGF- and SCF-mediated cellular events.

II. PHARMACOKINETICS

It is well absorbed (98%). Peak concentrations achieved 2 – 4 hours after a dose. The elimination half-life of imatinib and its major active metabolite are 18 and 40 hours respectively. The mean AUC increases proportionally with increasing doses of imatinib (over the dose range of 25 – 1000mg). The drug is highly protein bound (95%), predominantly to albumin and α_1-acid glycoprotein. Imatinib is metabolized by the Cytochrome P450 3A4 isoenzyme system. Other Cytochrome P450 enzymes such as CYP1A2, CYP2D6, CYP2C9 and CYP2C19 also play a minor role in its metabolism. Elimination is predominantly in the feces, mostly as metabolites (see section VI for Drug Interactions). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces).

III. ADMINISTRATION

Oral capsule 100 mg and oral tablet 400 mg (not scored). The recommended dose is 400 mg orally daily for patients in chronic phase of CML, and 600 mg orally daily for those patients in accelerated phase or blast crisis. GIST patients should receive 400 – 800 mg PO QD.

IV. TOXICITY:

A) Fluid retention and edema: edema is most frequently periorbital or in lower limbs. It is best managed with diuretics, other supportive measures, or by reducing the dose of imatinib. The frequency of severe edema was 1 – 5%.
B) Gastrointestinal irritation: take with food and a large glass of water.
C) Hematologic toxicity: predominantly neutropenia and thrombocytopenia. These side effects are more commonly seen with advanced disease (i.e. accelerated phase/ blast crisis).
D) Hepatotoxicity: severe elevations of transaminases or bilirubin occurred in 1.1 – 3.5% patients and can be managed by reduction in the dose of imatinib. Monitor LFT's prior to therapy and then periodically as clinically indicated.
E) Cardiovascular: A recent report has shown that 10 imatinib treated patients developed severe CHF and LV dysfunction. Pre-imatinib therapy all patients had NYHA functional class 1 and normal LVEF. All patients had preexisting conditions including HTN, diabetes and CAD. Preclinical studies also show that imatinib treated mice develop LV contractile dysfunction. The labeling of the drug has been amended to the following "severe CHF and LV dysfunction have occasionally been reported in patients taking imatinib. In the IRIS study in newly diagnosed CML-CP patients, severe cardiac failure and LV dysfunction was observed in 0.7% patients taking imatinib compared to 0.9% in the IFN-ara-C arm. [Reference: FDA Medwatch Letter, October 19, 2006].

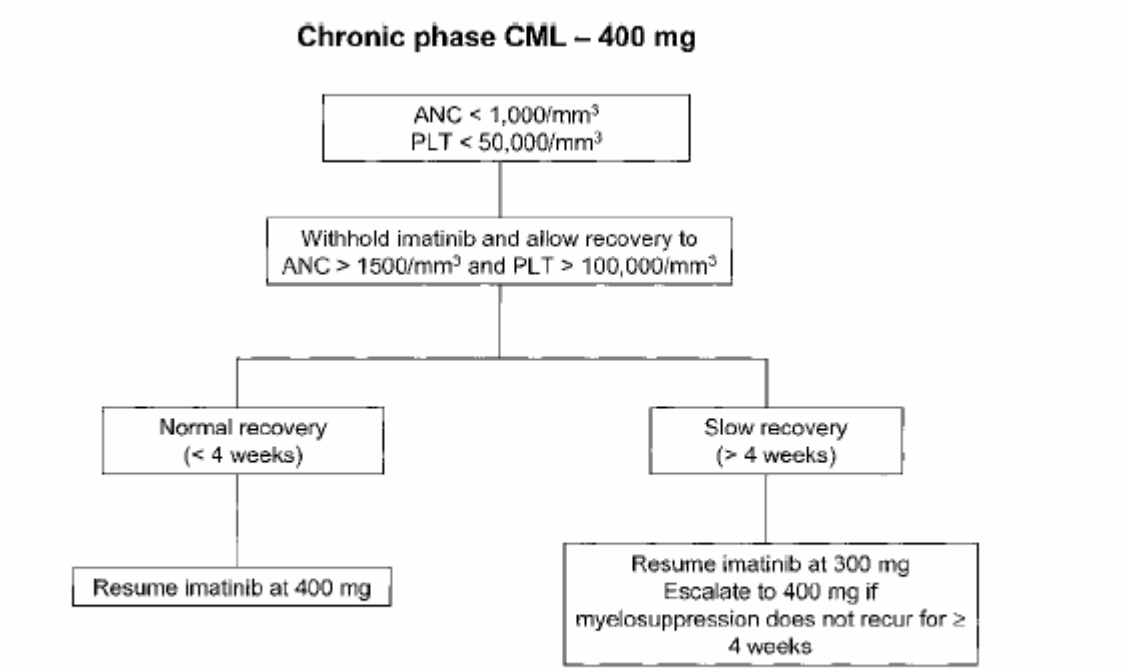

Fig 2. Management of myelosuppression in chronic phase. ANC, absolute neutrophil count; PLT, platelet count.

Patients with cardiac disease or risk factors should be monitored carefully and any pts with signs and symptoms consistent with cardiac failure should be evaluated and treated.

Reference: Deininger MW, et al. *J Clin Oncol* 2003;21:1637 – 47.

DOSAGE ADJUSTMENT GUIDELINES FOR MARROW SUPPRESSION WITH IMATANIB (per Package Insert)

Phase of Disease	Neutropenic/ Thrombocytopenia	Recommendation
Chronic Phase CML (starting dose 400 mg/day)	ANC $< 1.0 \times 10^9$/L and/or platelets $< 50 \times 10^9$/L.	1. Stop imatinib until ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L. 2. Resume treatment with imatinib at a dose of 400mg. 3. If recurrence of ANC $< 1 \times 10^9$/L and/or platelets $< 50 \times 10^9$/L, repeat step 1 and resume imatinib at a reduced dose of 300 mg.
Accelerated Phase CML and Blast Crisis (starting dose 600 mg/day)	ANC $< 0.5 \times 10^9$/L and/or platelets $< 10 \times 10^9$/L (note these values occurring after at least 1 month of therapy.	1. Check if cytopenia is related to leukemia (BM aspirate/biopsy). 2. If cytopenia is unrelated to leukemia, reduce dose of imatinib to 400 mg. 3. If cytopenia persist 2 weeks, reduce further to 300mg/day. 4. If cytopenia persist 4 weeks and is still unrelated to leukemia, stop imatinib until ANC $\geq 1 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L and then resume treatment at 300 mg/day.

Reference: Deininger MW, et al. *J Clin Oncol* 2003;21:1637 – 47.

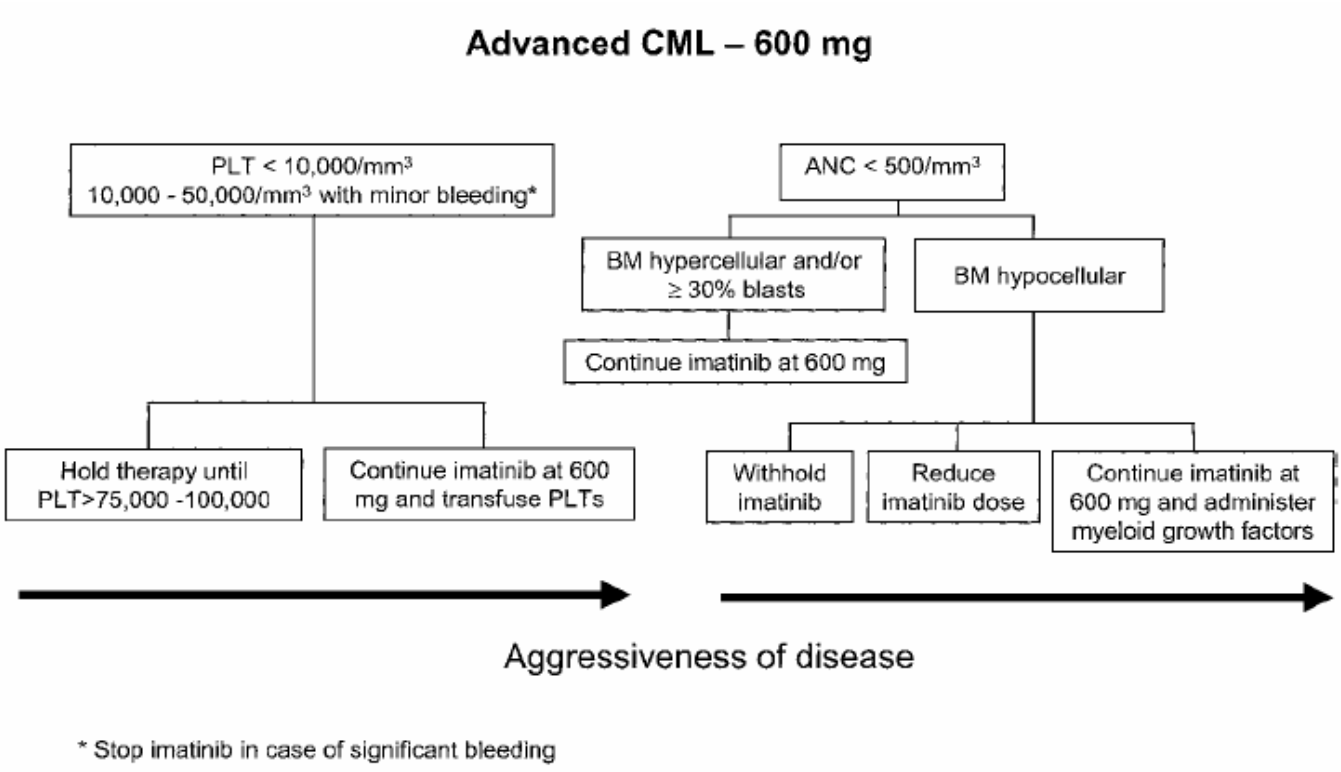

Fig 3. Management of myelosuppression in advanced phase. ANC, absolute neutrophil count; PLT, platelet count; BM, bone marrow.

Reference: Deininger MW, et al. *J Clin Oncol* 2003;21:1637 – 47.

V. CLINICAL MONITORING

Routine monitoring of blood counts should occur as follows: a CBC should be performed weekly for the 1st month, biweekly for the 2nd month, and periodically thereafter as clinically indicated. These side effects are more commonly seen with advanced disease (i.e. accelerated phase/ blast crisis).

VI. DRUG INTERACTIONS:

The following drugs may alter imatinib plasma concentrations:

Drugs that may increase imatinib plasma concentrations

Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations e.g. ketoconazole, itraconazole, erythromycin, clarithromycin; amiodarone, delaviridine, diltiazem, fluoxetine, grapefruit juice, nefazodone, nevirapine, quinupristin-dalfopristin, ritonavir, saquinavir, verapamil, zarfiruclast, and zileuton.

Drugs that may decrease imatinib plasma concentrations

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 may reduce exposure to imatinib e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital, St John's Wort.

Drugs that may have their plasma concentration altered by imatinib

Imatinib increases the C_{max} and AUC of simvastatin 2- and 3.5-fold respectively. Imatinib will increase plasma concentrations of other CYP3A4 metabolized drugs.

ALDESLEUKIN, IL-2
(PROLUEKIN®)

I. MECHANISM OF ACTION

A) The exact mechanism by which aldesleukin mediates antitumor activity is unknown. Aldesleukin's effects are essentially identical to those of endogenous interleukin-2.
B) Aldesleukin interacts with the high-affinity IL-2 receptor expressed on cells of the immune system and stimulates a cytokine cascade involving various interferons, interleukins, and tumor necrosis factors.
C) Aldesleukin along with other cytokines induce proliferation and differentiation of B and T-cells, monocytes, macrophages, and cytotoxic lymphocytes which include natural killer (NK) cells, cytotoxic T-cells, tumor-infiltrating lymphocytes (TIL), and lymphokine-activated killer (LAK) cells.
D) Aldesleukin's antitumor activity is believed to result from activation of cytotoxic lymphocytes, however, the exact mechanism is unknown.
E) Whether aldesleukin acts directly or through second messengers is also unclear, however, aldesleukin does elevate production of interleukin-1, tumor necrosis factors alpha and beta, interferon gamma, and interleukin-6.

II. PHARMACOKINETICS

A) Following a short IV infusion, the drug is rapidly distributed to the extravascular and extracellular space as well as to the liver, spleen, kidneys, and lungs. Approximately 30% of an administered dose is distributed within the plasma.
B) The pharmacokinetics of IL-2 may be affected by sodium dodecyl sulfate, the solubilizing agent in the commercial formulation. In addition, subcutaneous administration with albumin produces slightly higher and more prolonged serum levels of aldesleukin.
C) Following distribution, aldesleukin is cleared from the systemic circulation by the kidneys through both glomerular filtration and peritubular extraction. The drug is then metabolized to amino acids by renal cells lining the proximal convoluted tubules. Very little drug is excreted unchanged in the urine.
D) Following a 5 minute IV infusion, the serum distribution and elimination half-life in cancer patients was 13 and 85 minutes, respectively.

III. DOSAGE AND ADMINISTRATION

A) Aldesleukin is administered by rapid IV infusion, continuous IV infusion, or by subcutaneous injection. IV bolus is better tolerated than IV continuous infusion.
B) Treatment dosages vary depending on types of cancer or different diseases.

IV. TOXICITY

A) Myelosuppression: leukopenia (16%); anemia (29%); thrombocytopenia (all grades: 37%; grade 4: 1 %).
B) Flu-like symptoms: fever and/or chills and flu-like symptoms are common with aldesleukin therapy. Fever is manageable with prophylactic administration of acetaminophen or indomethacin. Meperidine may be administered to control chills and rigors.
C) Cardiovascular:
    - Capillary leak syndrome may begin immediately following initiation of aldesleukin therapy.
    - Hypotension (all grade 71%; grade IV: 4%) seen in high dose IL-2.

- Arrhythmias (most commonly atrial tachyarrhythmias and occasionally ventricular arrhythmias).
- Bradycardia and complete heart block.
- Ischemic heart disease, myocardial infarction, angina pectoris, sudden death, dilated cardiomyopathy, and myocarditis.

D) Gastrointestinal:

Anorexia, diarrhea, nausea, and vomiting are dose-related. Other adverse effects include stomatitis, GI hemorrhage, constipation, esophagitis, sialorrhea, and tracheoesophageal fistulas.

H_2 blocker may be used for prophylaxis of GI irritation and bleeding.

Nausea/vomiting and diarrhea can be manageable with prophylactic administration of antiemetics and antidiarrheals.

E) Renal: Therapy with aldesleukin is associated with varying degrees of renal impairment. Abnormalities include elevated serum creatinine as well as oliguria and anuria. In many patients azotemia occurs in the presence of hypotension. The incidence and degree of renal abnormality correlates with dose and duration of aldesleukin treatment. There is no evidence of cumulative renal toxicity with repeated cycles.

F) Dermatologic: Macular erythematous skin rash was reported in 100% of patients receiving high-dose aldesleukin and characterized by burning and pruritus beginning 2 to 3 days after initiation of therapy. Eruptions were usually localized to the head and neck, occasionally progressing to generalized erythroderma. Resolution with desquamation occurred within 48 to 72 hours after discontinuation of therapy.

G) Others: Weight gain and peripheral edema are almost always seen with high-dose aldesleukin therapy due to capillary leak syndrome.

V. CLINICAL MONITORING/PRECAUTION

A) Concomitant administration of aldesleukin and glucocorticoids may reduce the antitumor effectiveness of aldesleukin and should be avoided.

B) Vital signs especially blood pressure as high dose aldesleukin may produce significant hypotension and may require resuscitation with fluid and/or pressor agents. ICU monitoring typically required.

C) CBC, differential and platelet counts (prior to and daily during aldesleukin therapy).

D) Blood chemistries: electrolytes, renal and hepatic function tests (prior to and daily during aldesleukin therapy).

E) Chest X-rays (prior to and daily during aldesleukin therapy).

F) Renal function: Serum creatinine should be less than or equal to 1.5 mg/dL before starting treatment.

L-ASPARAGINASE
(ELSPAR®)

I. MECHANISM OF ACTION

L-asparaginase converts L-asparagine to L-aspartic acid, which is taken up by normal cells and converted to L-asparagine again. Sensitive tumor cells lack the machinery to convert L-aspartic acid to L-asparagine and must obtain L-asparagine from the environment. By giving L-asparaginase the tumor cell is deprived of L-asparagine, a necessary building block of DNA. Resistance is due to increased endogenous asparagine synthetase activity.

II. PHARMACOKINETICS

L-asparaginase remains mostly intravascular but does penetrate into CSF. Otherwise, the pharmacokinetics is poorly described.

III. DOSAGE AND ADMINISTRATION

L-asparaginase is ordered in units. It is usually given IM because the IV route causes more allergic reactions.

- A test dose of 2 units of *E. coli* asparaginase is usually given ID prior to the initial dose.
- If PEG-asparaginase is used, the dose is 82.5 units/kg every 14 days or 2500 units/m^2 every 14 days.

IV. TOXICITY

A) Hypersensitivity - Urticaria, hypotension, laryngospasm, serum sickness, arthralgias, proteinuria, fever. Occurring in fewer than 10% of patients, it is related to dose (> 6000 u/m^2/day), route (more common IV), and bacterial source. Skin testing is not foolproof but a test dose can still help.

B) Impaired protein synthesis - Depletion of the L-asparagine pool leads to poor protein synthesis by the liver. There is a fall in albumin, Factors II, V, IX, X, XI, and XIII; plasminogen, antithrombin III, proteins C & S. Fibrinogen falls and PT/PTT rise. Bleeding and thrombosis are possible as a result of the disrupted clotting system; Follow fibronigen and supplement when necessary (less than 100 - 125).

C) Neurologic - confusion, stupor, coma.

D) Pancreatitis - 15% patients. Sometimes the amylase is normal.

E) Nausea, vomiting and chills.

F) Renal - elevated BUN and excessive calcium and phosphorus elimination.

Toxicity of Asparaginase	
REACTION	**%**
Immediate reaction	70%
Nausea, vomiting, fever, chills	
Hypersensitivity reactions	<10%
Urticaria/ Bronchospasm/ Hypotension	
Decreased protein syntheses	100%
Albumin/ Insulin	
Clotting factors II, V, VII, VIII, IX, X	
Serum lipoproteins	
Antithrombin III	
Cerebral dysfunction	33%
Disorientation/Coma/ Seizures	
Organ toxicities	
Pancreatitis	15%
Liver function test abnormalities	100%
Azotemia (? increased nitrogen load)	68%
From Ohnuma T. Holland JF. Sinks LF. Biochemical and pharmacological studies with L-asparaginase in man. *Cancer Res* 1970;30;2297 - 305.	

V. CLINICAL MONITORING

A) Check the route of administration carefully.
B) A skin test should be ordered.
C) There are two natural sources of L-asparaginase, one from *E. coli* and the other from *Erwinia* bacteria. Changing from one source to another may circumvent any adverse reactions. A third form is PEG-asparaginase (Oncospar®), which uses polyethylene glycol to mask the immunogenicity of *E.coli* asparaginase. Note that PEG-asparaginase is only given once every 2 weeks.
D) Be prepared to treat anaphylaxis.
E) Be aware of any possible coagulopathies that may occur. Prior to administering asparaginase as part of leukemia protocols, baseline fibrinogen should be checked, and again at regular intervals. Administer cryoprecipitate if fibrinogen less than 100.

LENALIDOMIDE
(REVLIMID®)

I. MECHANISM OF ACTION

A) Lenalidomide is a novel 4-amino-glutarimide analogue of thalidomide that is more potent but does not have the neurotoxic and teratogenic effects of thalidomide.
B) In MDS (particularly those with -5q31.1), it may restore red-cell production in part by eliminating ineffective myelodysplastic clones but does not extinguish the myelodysplastic syndrome-initiating stem cell.
C) Enhances cell-mediated immunity by potentiating the production of interleukin-2 and interferon-gamma and increasing the responses of cytolytic T cells and natural killer cells in experiments in animals.
D) Suppresses TNF-alpha, IL-1beta, and IL-6 production.
E) Increases IL-10 secretion.

II. PHARMACOKINETICS

In healthy volunteers, lenalidomide is rapidly absorbed following oral administration, with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Coadministration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. Lenalidomide exhibits linear pharmacokinetics, with increases in AUC and Cmax occurring proportionately with increased in dose. Accumulation is not seen with multiple dosing at the recommended dose.

Pharmacokinetics in MDS patients have not been evaluated. In multiple myeloma patients, C_{max} was reached between 0.5 and 4 hours post-dose on days 1 and 28 of therapy. Exposure (AUC) in myeloma patients was 57% higher than that seen in normal volunteers. Lenalidomide is approximately 30% bound to plasma proteins *in vitro*.

In healthy volunteers, approximately 67% of a dose is excreted unchanged via urinary excretion. It appears to be actively excreted by the kidneys, as urinary excretion exceeds GFR. The elimination half-life is approximately 3 hours.

In myeloma patients with mild renal impairment, the AUC of lenalidomide is 56% greater than in those with normal renal function. The pharmacokinetics in patients with hepatic impairment have not been studied. The effects of age, gender, or race on the pharmacokinetics of lenalidomide have not been studied, and there is no data available in patients under 18 years of age.

III. DOSAGE AND ADMINISTRATION

******NOTE DIFFERENT DOSES FOR DIFFERENT INDICATIONS******

A) MDS: 10 mg PO daily, 10 mg PO daily x 21 days every 4 weeks.
B) Myeloma: 25 mg PO per day for 21 out of every 28 days.

Dose modifications in the MULTIPLE MYELOMA clinical trials are as follows:

NCI Toxicity Grade	Day 1 of Cycle
Neutropenia (ANC $< 1 \times 10^9$/L	• Hold dose and start G-CSF. • Follow CBC weekly. • Restart at a dose of 25 mg daily dose when neutropenia has resolved to an ANC of $> 1 \times 10^9$/L (if neutropenia is the only toxicity present requiring dose reduction). • Restart at a dose of 15 mg daily dose when neutropenia has resolved to an ANC of $> 1 \times 10^9$/L (if other toxicities in conjunction with neutropenia occur). • For each subsequent drop of ANC to $< 1 \times 10^9$/L interrupt lenalidomide therapy. Once ANC recovers to 1×10^9/L and greater resume lenalidomide at 5 mg /day less than the previous dose. Do not dose below 5 mg PO daily.
Thrombocytopenia (platelet count less than 30×10^9/L)	• Hold dose. • Follow CBC weekly. • Restart at 15 mg daily when platelet count has increased to $\geq 30 \times 10^9$/L without evidence of hemostatic failure (i.e., bleeding or petechiae). • For each subsequent drop to $< 30 \times 10^9$/L interrupt treatment. Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg PO daily.

Dose modification for MYELODYSPLASTIC SYNDROME:

Dosage Adjustments during Lenalidomide Therapy in Patients with MDS

PLATELET COUNTS	
If thrombocytopenia develops WITHIN 4 weeks of beginning therapy at 10 mg/day	
BL over 100 x 10^9/L and falls to below 50 x 10^9/L	Interrupt therapy
When returns to 50 x 10^9/L or above	Resume at 5 mg daily
BL less than 100 x 10^9/L and falls to 50% of baseline	Interrupt therapy
If BL is over 60 x 10^9/L and returns to 50 x 10^9/L or above	Resume at 5 mg daily
If BL below 60 x 10^9/L and returns to 30 x 10^9/L or above	Resume at 5 mg daily
If thrombocytopenia develops AFTER 4 weeks of therapy at 10 mg/day	
Falls to less than 30 x 10^9/L (or 50 x 10^9/L and needs transfusions)	Interrupt therapy
Returns to 30 x 10^9/L or above	Resume at 5 mg/daily
If thrombocytopenia develops on 5 mg/day	
Falls to less than 30 x 10^9/L (or 50 x 10^9/L and needs transfusions)	Interrupt
Returns to 30 x 10^9/L or above	Resume at 5 mg QOD
NEUTROPHIL COUNTS (ANC)	
If neutropenia develops WITHIN 4 weeks of beginning therapy at 10 mg/day	
Baseline over 1 x 10^9/L and falls to below 0.75 x 10^9/L	Interrupt therapy
When returns to 1 x 10^9/L or above	Resume at 5 mg daily
Baseline less than 1 x 10^9/L and falls to less than 0.5 x 10^9/L	Interrupt therapy
When returns to 0.5 x 10^9/L or above	Resume at 5 mg daily
If neutropenia develops AFTER 4 weeks of therapy at 10 mg/day	
Falls to less than 0.5 x 10^9/L for 7 or more days OR Falls to less than 0.5 x 10^9/L and associated with fever	Interrupt therapy
When returns to 0.5 x 10^9/L or above	Resume at 5 mg daily
If neutropenia develops on 5 mg/day	
Falls to less than 0.5 x 10^9/L for 7 or more days *OR* Falls to less than 0.5 x 10^9/L and associated with fever	Interrupt therapy
When returns to 0.5 x 10^9/L or above	Resume at 5 mg QOD

IV. TOXICITY

A) Most common: neutropenia, thrombocytopenia. Severe myelosuppression was dose-dependent in a recently published, single-center trial in patients with MDS.
B) Other common side effects: pruritis in first week (28%), transient urticaria (14%), diarrhea.
C) Less common but severe: pneumonia (3%), autoimmune hemolytic anemia (2%).
D) Infrequent: fatigue, bone pain, edema, myalgias.
E) Thromboembolic complications have been reported. They are more frequent in patients with multiple myeloma, particularly those patients who are receiving concomitant dexamethasone.

The results of trials evaluating thromboembolic prophylaxis with lenalidomide in multiple myeloma patients are outlined in the table below:

Studies evaluating antithrombotic prophylaxis with lenalidomide

Author	Regimen	Newly diagnosed (ND) or relapsed/refractory (RR)	N	VTE Prophylaxis	VTE incidence (%)
Zonder et al (2005)	Lenalidomide	ND	12	None	75
			26	Aspirin 326 mg/day	15
Dimopoulos et al (2005)	Lenalidomide	ND	351	None	8.5
	Dexamethasone			None	4.5
Richardson et al (2006)	Lenalidomide ± dexamethasone	RR	70	Nil	2.9 (only if dex added)

Reference: Hussein MA. *Thromb Hemost* 2006;95:924 – 30.

V. CLINICAL MONITORING – CBC with differential.

VI. DRUG INTERACTIONS

To date, no drug interactions involving lenalidomide have been identified.
Lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P-450 pathway, and therefore is unlikely to be involved in P-450-based drug interactions in humans. In single-dose pharmacokinetic studies, no interaction with warfarin was demonstrated.

THALIDOMIDE
(THALOMID®)

I. MECHANISM OF ACTION

A) The complete mechanism of action of thalidomide is not completely understood.
B) Thalidomide inhibits angiogenesis by interrupting processes mediated by bFGF and/or vascular endothelial growth factor (VEGF).
C) *In vitro* and *in vivo* studies show that thalidomide selectively reduces levels of tumor necrosis factor alpha (TNF-α) by accelerating the degradation of TNF-alpha mRNA encoding protein. Thalidomide reduces the half-life of the TNF-α mRNA protein from 30 minutes to about 17 minutes. Thalidomide does not affect mRNA levels of interleukin (IL)—1 or IL—6. TNF-alpha has been associated with the pathology and symptoms of many different diseases including ENL, AIDS, cancers, graft-versus-host disease, tuberculosis and malaria.
D) Thalidomide also co-stimulates human T cells, including cell proliferation mainly of the CD8+ subset, and stimulates IL-2 and IFN-γ production. It augments NK-like activity, and inhibit IL—12 production.

II. PHARMACOKINETICS

A) Thalidomide is administered orally and is slowly absorbed from the GI tract. The exact bioavailability has not been determined due to poor aqueous solubility of thalidomide.
B) The PK differ in patients treated with thalidomide. In patients with Hansen's disease, following thalidomide 400 mg the Cmax was 3.44 mcg/ml with a Tmax of 5.7 hours and AUC 46.4 mcg•hr/mL and in HIV-positive patients following thalidomide 300 mg the Cmax was 3.47 mcg/ mL with a Tmax of 3.4 hours and AUC 40.11 mcg•hr/mL.
C) Patients with aphthous ulcers or other conditions affecting the GI tract may have different pharmacokinetic profiles due to potential differences in absorption. Administration of thalidomide with a high fat meal causes minor changes in the AUC and Cmax but increases the Tmax to about 6 hours in healthy volunteers.

D) Thalidomide is 55—66% protein bound. In a study of HIV-positive males, thalidomide was detected in the semen.
E) Thalidomide appears to undergo non-enzymatic hydrolysis in the plasma and is not hepatically metabolized.
F) The half-life seems to be similar in all groups studied with an average half-life of 6—7 hours. Less than 0.7% of the dose is excreted in the urine as unchanged drug and thalidomide is undetectable in the urine 48 hours after a single dose. In addition, only a small amount of thalidomide metabolites may be detected in the urine 12—24 hours after dosing. The pharmacokinetics of thalidomide in patients with renal or hepatic insufficiency has not been determined.

III. DOSAGE AND ADMINISTRATION

A) 50-1200 mg PO once daily depending on indication of the disease.
B) For treatment of advanced or refractory multiple myeloma, the initial dosage was 200 mg/day PO with doses increased by 200 mg/day PO every 2 weeks to tolerance or a maximum dose of 800 mg/day.

IV. TOXICITY

A) Peripheral nervous system: numbness, paresthesia, pain in the extremities, and burning sensation (30%).
B) Central nervous system: Hangover feeling, nervousness, tremor (10%), confusion, aural buzzing, fatigue (20-50%), depression (5-20%), dizziness, somnolence (>50%), headache, sedation, fluctuation of blood pressure (5%), bradycardia (5%).
C) Gastrointestinal: Constipation (>50%), nausea (5-20%), increased appetite, xerostomia (10%).
D) Hematological: Deep vein thrombosis (5-30%) - see table below; neutropenia (<5%); granulocytopenia (<5%).
E) Skin: Red palms, skin rash (25%), toxic epidermal necrolysis (1%), brittle fingernails, pruritis (20-50%).
F) Genital system: teratogenicity, phocomelia, menstrual irregularities, decreased libido
G) Endocrine: Hypothyroidism (5-20%), edema (5-20%).

Incidence of venous thromboembolism (VTE) in multiple myeloma patients treated with thalidomide-containing regimens without VTE prophylaxis

STUDY	STUDY DESIGN	REGIMEN	N	VTE INCIDENCE (%)
NEWLY DIAGNOSED MULTIPLE MYELOMA (MM)				
Single agent thalidomide				
Rajkumar et al 2003	Single arm phase 2 trial	T	31	3
Thalidomide plus chemotherapy				
Zangari et al 2002	Randomized comparative trial	CCT + T	50	28
		CCT	50	4
Zangari et al 2003	Retrospective comparative study	DTPACE	192	16
		DCEP + T	40	2.5
Osman et al 2001	Retrospective analysis of two single arm phase 2 trials	TAD	15	27
		TD	45	7
Facon et al 2005	Randomized controlled trial	MP	191	5
		MPT	124	12
		MEL 100	121	6.5
Thalidomide plus dexamethasone				
Cavo et al 2003	Single arm phase 2 trial	TD	19	26
Rajkumar et al 2002	Single arm phase 2 trial	TD	50	12
Weber et al 2003	Non-randomized comparative trial	TD	40	15
		T	28	4
Rajkumar et al 2006	Randomized controlled trial	TD	103	17
		D	104	3

PREVIOUSLY TREATED/RELAPSED/REFRACTORY				
Single Agent Thalidomide				
Barlogie et al 2001	Single arm phase 2 trial	T	169	<2
Thalidomide plus chemotherapy				
Camba et al 2001	Non-randomized study	Various chemotherapy + T	18	27.8
Urbauer ete al 2002	Single arm phase 2 trial	T + DCEP	14	21
Lee et al 2003	Randomized comparative trial	DTPACE	236	15
Minnema et al 2003	Retrospective study	Various chemotherapy + T	20	35
Thalidomide plus dexamethasone				
Anagnostopoulos et al 2002	Single arm phase 2 trial	TD	47	8

CT=chemotherapy; T=thalidomide; L=lenalidomide; CCT=combination chemotherapy; D=dexamethasone; DCEP=dexamethasone, cyclophosphamide, etoposide, cisplatin; MP=melphalan, prednisone; MPT=melphalan, prednisone, thalidomide; TAD=thalidomide, dexamethasone, doxorubicin; TD=thalidomide, dexamethasone.

Reference: Hussein MA. *Thromb Hemost* 2006;95:924 – 30.

Studies evaluating antithrombotic prophylaxis with thalidomide

Author	Regimen	Newly diagnosed (ND) or relapsed/refractory (RR)	N	VTE Prophylaxis	VTE incidence (%)
Warfarin					
Cavo et al 2002	TD	ND	19	None	26
Cavo et al 2004			52	Warfarin (1.25 mg/day)	13
Chanan-Khan et al 2004	VAD-t	ND	16	Warfarin (1-2 mg/day)	12
Low molecular weight heparin (LMWH)					
Palumbo et al 2006	MPT	ND	65	None	16.9
			64	LMWH (SQ enoxaparin 40mg/day x 4 months)	3.1
Minnema et al 2004	VAD	ND	201	None	5
	TAD	ND	211	LMWH (SQ nadroparin 2850 IU anti-Xa)	9
Zangari et al 2004	Chemotherapy	ND	134	None	8.6
	Chemotherapy + T	ND	87	None	34.5
	Chemotherapy + T	ND	35	Warfarin (1mg/day)	31.4
	Chemotherapy	ND	68	None	14.5
	Chemotherapy + T	ND	62	LMWH (SQ enoxaparin 40 mg/day)	14.7
Zangari et al 2004	DTPACE	RR	98	LMWH (SQ enoxaparin 40 mg/day)	10
	VDTPACE	RR	69	LMWH (SQ enoxaparin 40 mg/day)	0
Aspirin					
Hassoun et al 2004	AD followed by TD	ND	31	Aspirin PO 81 mg/day	9.6
Baz et al 2004	DVd-T	ND and RR	19	None	57.8
			84	Aspirin 81 mg/day	17.8
Hussein et al 2004	DVd-R	RR	21	Aspirin 81 mg/day	5
Baz et al 2005	DVd-R	RR	58	Aspirin 81 mg/day	9
Palumbo et al 2005	MPR	ND	38	Aspirin 81 mg/day	2.6

AD=doxorubicin, dexamethasone; DTPACE=dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide; DVd-R=pegylated doxorubicin, vincristine, reduced frequency dexamethasone and revlimid (lenalidomide); DVd-T=pegylated doxorubicin, vincristine, reduced frequency dexamethasone, thalidomide; LMWH=low molecular weight heparin; MPR=melphalan, prednisone, and revlimid (lenalidomide); MPT = melphalan, prednisone and thalidomide; ND=newly diagnosed; RR=relapsed/refractory; T=thalidomide; TAD=thalidomide, dexamethasone, doxorubicin; TD=thalidomide, dexamethasone; VAD=vincristine, doxorubicin, dexamethasone; VAD-t=vincristine, doxorubicin, dexamethasone and low dose thalidomide; VDTPACE=Bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide.

Reference: Hussein MA. *Thromb Hemost* 2006;95:924 - 30.

VI. CLINICAL MONITORING

A) Thalidomide is the most heavily regulated drugs in the US and may only be obtained through approved physicians and pharmacies registered in the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) Program.
B) CBC.
C) Plasma HIV RNA: HIV positive patients only.
D) Pregnancy testing.

SORAFENIB
(NEXAVAR™; BAY 43-9006)

I. MECHANISM OF ACTION

BAY 43-9006 is an investigational oral compound known as a Raf kinase inhibitor. It inhibits the RAF/MEK/ERK signaling pathway (part of the Ras oncogene pathway), thus, preventing cell proliferation. BAY 43-9006 also prevents tumor angiogenesis via effects on the VEGFR-2/PDGFR-β pathway.

II. PHARMACOKINETICS

The mean bioavailability of sorafenib tablets is 38-49% when compared to an oral solution. The mean elimination half-life of sorafenib is approximately 25-48 hours. Steady-state plasma sorafenib concentrations are achieved within 7 days with multiple dosing of Sorafenib. Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a high-fat meal, sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that sorafenib be administered without food (at least 1 hour before or 2 hours after eating)

Sorafenib is 99.5% highly protein bound to human plasma proteins. Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine N-oxide, shows *in vitro* potency similar to that of sorafenib.

Following oral administration of a 100 mg dose of a solution formulation of sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

Dosing adjustment is not required in patients with mild to moderate hepatic Impairment or renal insuffiency. The pharmacokinetics of sorafenib has not been studied in patients with severe hepatic impairment (Child Pugh C) or severe renal impairment (CrCL <30 mL/min) or in patients undergoing dialysis. No dosage modification is necessary for Child-Pugh A or B liver impairment.

III. DOSAGE AND ADMINISTRATION

The recommended dose is 400 mg (2 x 200 mg tablets) twice daily taken either 1 hour before or 2 hours after meals. Adverse events were accommodated by temporary dose interruptions or reductions to 400 mg once daily or 400 mg every other day.

Dosage modifications for skin toxicity:

SKIN TOXICITY GRADE	OCCURRENCE	SUGGESTED DOSE MODIFICATION
Grade 1: numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema, or discomfort of the hands or feet that does not disrupt normal activities	Any occurrence	Continue treatment and consider topical therapy for symptomatic relief.
Grade 2: painful erythema and swelling of the hands or feet and/or discomfort affecting normal activities	First occurrence	Continue treatment and consider topical therapy for symptomatic relief. If no improvement within 7 days see below.
	No improvement within 7 days or second or third occurrence	Interrupt treatment until toxicity resolves to grade 0 to 1. When resuming treatment, decrease dose by one dose level (400 mg daily or 400 mg every other day)
	Fourth occurrence	Discontinue sofafenib
Grade 3: Moist desquamation, ulceration, blistering, or severe pain of the hands or feet, or severe discomfort that causes inability to work or perform activities of daily living	First or second occurrence	Interrupt treatment until toxicity resolves to grade 0 to 1. When resuming treatment, decrease dose by one dose level (400 mg daily or 400 mg every other day).
	Third occurrence	Discontinue sofafenib

Reference: Drug Facts and Comparisons 2006 online; accessed 7/20/06.

IV. TOXICITY

Sorafenib toxicities (based on an updated phase 3 study database of 902 patients) included reversible skin rashes in 40% and hand-foot skin reaction in 30%. Diarrhea was reported in 43%, treatment-emergent hypertension in 17%, and sensory neuropathic changes in 13%. Alopecia, oral mucositis, and hemorrhage also were reported more commonly on the sorafenib arm. The incidence of treatment-emergent cardiac ischemia/infarction events was higher in the sorafenib group (2.9%) compared with the placebo group (0.4%). Grade 3 and 4 adverse events were unusual; only hand-foot skin reaction occurred at 5% or greater frequency in the sorafenib arm.

Despite exclusion of patients with unstable coronary artery disease or recent myocardial infarction from the study, sorafenib was linked to an increased incidence of cardiac ischemia/infarction, relative to placebo (2.9% vs 0.4%). Consideration should be given to temporary or permanent discontinuation of therapy in patients who develop these conditions. Laboratory findings included asymptomatic hypophosphatemia in 45% versus 12% and serum lipase elevations in 41% versus 30% of sorafenib versus placebo patients, respectively. Grade 4 pancreatitis was reported in 2 sorafenib patients, although both patients subsequently resumed sorafenib, one at full dose.

V. CLINICAL MONITORING

Weekly monitoring of blood pressure is recommended during the first 6 weeks of treatment. Because sorafenib may also be linked to an increased risk for bleeding, patients receiving concomitant warfarin therapy should be monitored regularly.

VI. DRUG INTERACTIONS

Sorafenib metabolism is principally hepatic via CYP3A4 and UGT1A9 pathways. Sorafenib is an inhibitor of UGT1A1. Caution is recommended when administering sorafenib with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan) Concomitant treatment with sorafenib resulted in a 21% increase in the AUC of doxorubicin. Caution is recommended when administering doxorubicin with sorafenib. Sorafenib inhibits CYP2B6 and CYP2C8 *in vitro* with Ki values of 6 and 1-2 μM, respectively. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when co-administered with sorafenib. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with sorafenib.

SUNITINIB
(SUTENT™)

I. MECHANISM OF ACTION

Sunitinib is a small-molecule tyrosine kinase inhibitor that has direct antitumor activity and anti-angiogenic action. Its main targets are the receptors for VEGF (VEGFR), Kit and Flt-3, and PDGFR, in addition to binding bone metastases [Reference: Sakamoto KM. *Curr Opin Invest Drugs* 2004;5:1329 - 39].

II. PHARMACOKINETICS

Sunitinib is metabolized primarily by the cytochrome P-450 enzymes, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23% to 37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of ^{14}C sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4%, and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance ranged from 34 to 62 L/h with an interpatient variability of 40%.

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9 to 101 ng/mL. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested (Reference: Facts and Comparisons 2006).

III. DOSAGE AND ADMINISTRATION (Reference: Facts and Comparisons 2006)

The recommended dose for GIST and advanced RCC is one 50 mg oral dose taken once daily on a schedule of 4 weeks on treatment followed by 2 weeks off. It may be taken with or without food.

Dose modification: Dose increase or reduction of 12.5 mg increments is recommended based on individual safety and tolerability.

Concomitant therapy:
Selection of an alternative concomitant medication with no or minimal enzyme induction potential is recommended. A dosage increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be coadministered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity. Selection of an alternative concomitant medication with no or minimal enzyme inhibition potential is recommended. A dosage reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be coadministered with strong CYP3A4 inhibitors. If dosage is increased, monitor carefully for toxicity.

Renal Function Impairment -
No clinical studies were conducted in patients with impaired renal function. Studies that were conducted excluded patients with serum creatinine greater than 2 times the upper limits of normal (ULN). Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42 to 347 mL/min.

Hepatic Impairment -
No clinical studies were conducted in patients with impaired hepatic function. Studies that were conducted excluded patients with ALT or AST greater than 2.5 times ULN or, if due to underlying disease, greater than 5 times ULN.

IV. TOXICITY

In general it is well tolerated. In clinical trials in solid tumor patients, the most common side effects were diarrhea, vomiting, fatigue, thrombocytopenia, and neutropenia. Other Grade 3/4 toxicities seen in patients treated with greater than 50 mg/day maximum tolerated dose) were asymptomatic transient increases in lipase ± amylase, uncomplicated neutropenia, hypertension and diarrhea.

V. CLINICAL MONITORING

CBC + differential; If symptoms of pancreatitis - amylase and lipase.
Perform complete blood counts (CBCs) with platelet count and serum chemistries including phosphate at the beginning of each treatment cycle for patients receiving treatment with sunitinib.
Monitor for clinical signs and symptoms of congestive heart failure (CHF). Consider baseline and periodic evaluations of left ventricular ejection fraction (LVEF). Monitor for hypertension and myelosuppression regularly. Monitor for adrenal insufficiency in patients who experience stress such as trauma, surgery, or severe infection. Monitor thyroid function in patients with symptoms suggestive of hypothyroidism. In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. Interrupt and/or reduced the dose of sunitinib in patients without clinical evidence of CHF but with an ejection fraction less than 50% and greater than 20% below baseline.
Advise patients that possible skin discoloration is due to the drug color (yellow), which occurs in approximately one third of patients. Advise patients that depigmentation of the hair or skin may occur during treatment with sunitinib. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister, or rash on the palms of the hands and soles of the feet.

VI. DRUG INTERACTIONS

The drug interaction between sunitinib and ketoconazole has been characterized. Following a 10 mg oral dose of sunitinib in combination with ketoconazole (400 mg PO QD for 7 days),the combination resulted in a less than 2-fold increase in sunitinib exposure (C_{max} increased from 4.8 to 7.6 ng/mL and AUC increased from 268 to 454 ng.h/mL). This increase was greater in patients of Asian descent compared to Caucasians. Ketoconazole also caused a small decrease in exposure to the metabolite SU-12662 (C_{max} decreased from 0.59 to 0.42 ng/mL and AUC decreased from 77 to 67 ng.h/mL). The half-life of sunitinib and metabolite (SU-12662) were not altered by ketoconazole co-administration, indicating that the CYP3A4 inhibition by ketoconazole has greater impact on presystemic elimination than on systemic clearance of sunitinib. Where possible to co-administration of ketoconazole and sunitinib should be avoided. Grapefruit juice may also increase sunitinib concentrations.

VORINOSTAT
(ZOLINZA™)

I. MECHANISM OF ACTION

Vorinostat is histone deacetylase (HDAC) inhibitor, that acts to inhibit enzymatic activity of HDAC1, HDAC2, HDAC3 (class I), and HDAC 6 (Class II). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, there is an over expression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation.

II. PHARMACOKINETICS

Absorption is greatest following the ingestion of a high fat meal (33% higher), although these changes are not thought to be clinically meaningful. Vorinostat is 71% bound to human plasma proteins. The major metabolic pathways of Vorinostat include glucuronidation and hydrolysis followed by β-oxidation. Two metabolites are produced – O-glucuronide and 4-anilino-4-oxobutanoic acid, both of which are pharmacologically inactive. Vorinostat is eliminated primarily through metabolism with less than 1% of the dose recovered unchanged in the urine. Age, race, and gender do not appear to have any clinically relevant effects on vorinostat pharmacokinetics.

Vorinostat has not been evaluated in patients with hepatic dysfunction or renal dysfunction. Based on the mode of elimination of vorinostat, renal impairment is not likely to have any effect.

III. DOSAGE AND ADMINISTRATION

The recommended daily dose is 400 mg PO once daily with food. If the patient is intolerant to therapy, the dose may be reduced to 300 mg PO QD with food. The dose may be further reduced to 300mg once daily with food for 5 consecutive days each week, as necessary. The medication is supplied as 100 mg white capsules.

IV. TOXICITIES

The most common drug-related adverse events can be classified into 4 symptom complexes: (a) gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, and constipation); (b) hematologic abnormalities (thrombocytopenia, anemia); (c) taste disorders (dysgeusia, dry mouth). Grade 3 – 5 toxicities occurring with a frequency of more than 2% include: thrombocytopenia (5.8%), fatigue (3.5%), nausea (3.5%), anorexia (2.3%), muscle spasms (2.3%), and anemia (2.3%). The most serious adverse events in CTCL trials were pulmonary embolism in 4.7% of patients.

Laboratory abnormalities were reported as follows: hyperglycemia in 69%. Transient increases in serum creatinine were detected in 46.5%. Proteinuria was reported in 51% patients, the clinical significance of this abnormality is unknown.

V. CLINICAL MONITORING

Serum glucose, protein (urinalysis), CBC.

VI. DRUG INTERACTIONS

Vorinostat is not an inhibitor of CYP drug metabolizing enzymes. Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by vorinostat at higher concentrations that are pharmacologically relevant. Therefore vorinostat is not likely to affect the PK of many other drugs. No formal clinical trials have been conducted to test for drug interactions.

Coumarin-derivative anticoagulants: prolongation of prothrombin time and the International Normalized Ratio have been observed in a recipient of vorinostat and coumarin-derivative anticoagulants. Carefully monitor PT and INR in patients receiving concurrent vorinostat and coumarin-derivative anticoagulants.

Other histone-deacetylase inhibitors: severe thrombocytopenia and gastrointestinal bleeding have been reported with concomitant use of vorinostat and HDAC inhibitors (e.g., valproic acid). Monitor platelet count every 2 weeks for the first 2 months.

Prescribing information available at: http://www.fda.gov/cder/foi/label/2006/021991lbl.pdf.