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57357

Guidelines for Dasatinib Administration

Starting Dasatinib:

- Correct hypokalemia and hypomagnesemia prior to (and during) dasatinib therapy.
- For Ph +ve ALL patients, start Dasatinib 80mg/m2/day (max 140 mg) on Day 15 induction, and continue until end of therapy and continue until end of therapy. The dose will be given as 40 mg/m2 q 12hr (80 mg/m2 once daily can still be considered for dose rounding causes).
- For patients with poor early response (e.g., persisting blasts with high white cell counts), dasatinib may be started earlier than Day 15 after consulting to PI.

During Consolidation:

- Dasatinib (as well as imatinib) will be withheld for 24-hour prior to HDMTX and until it is cleared during consolidation therapy.

During Re-intensification:

- Tyrosine kinase inhibitors will not be used in Re-intensification treatment

Dasatinib Dose Adjustments for Toxicity:

1. **Hematologic Toxicity:**
   - Consider holding dasatinib during periods of myelosuppression, until ANC > 300/mm^3 and platelet count > 50 x 10^9/L.

   - Consider reducing dasatinib dose to 60 mg/m^2 daily if myelosuppression interferes with the ability to administer therapy without interruption. Dose can be escalated back to 40 mg/m^2 q12hr if tolerated. Consider replacing with imatinib 340 mg/m2 if toxicity persist at reduced dosage. All modifications should be discussed with the PI.

2. **Effusions:**
   - Dasatinib may cause fluid retention, including **pleural and pericardial effusions**, pulmonary hypertension, and generalized or superficial edema. A prompt chest x-ray (or other appropriate diagnostic imaging) is recommended for symptoms suggestive of effusion (new or worsening dyspnea on exertion or at rest, pleuritic chest pain, or dry cough). Fluid retention may be managed with supportive care (diuretics or corticosteroids); thoracentesis and oxygen therapy may be necessary for severe fluid retention. **Utilizing once-daily dosing is associated with a decreased frequency of fluid retention.**

   - If pleural effusion occurs or other non-hematological toxicity interferes with the ability to administer it continuously with chemotherapy, resume at reduced (60 mg/m2 daily). Dosecan be escalated back to 40 mg/m2 b.i.d. if well tolerated. Consider replacing with imatinib 340 mg/m2 daily if toxicity persists at reduced dosage. All modifications should be discussed with PI.

3. **Cardiac Dysfunction:**
    a. **QT Prolongation**
        - Use caution in patients at risk for QT prolongation, including:
            - patients taking potassium-wasting diuretics (i.e. furosemide)
            - patients with long QT syndrome.
            - patients with cumulative high-dose anthracycline therapy.
            - Patients with conditions which cause hypokalemia or hypomagnesemia. **Correct hypokalemia and hypomagnesemia during dasatinib therapy.**

        - **Avoid concurrent use of drugs that are generally accepted to have a risk of causing Torsade's de Pointes** (including: erythromycin, pseudoephedrine).
          Class IA (e.g. quinidine, disopyramide, procainamide), Class III (e.g. amiodarone, sotalol, ibutilide), or Class IC (e.g. flecainide), antiarrhythmic medicinal products, antipsychotics (e.g. chlorpromazine, haloperidol, pimozide), opioids (e.g. methadone), macrolide antibiotics (e.g. erythromycin, clarithromycin, azithromycin); quinolone antibiotics (e.g. ciprofloxacin, moxifloxacin), antimalarials (e.g. chloroquine), GI stimulants or others (e.g. domperidone, droperidol).

        - Dasatinib should not be administered to patients with **≥ Grade 2 prolonged QTc.** If patient has ≥ Grade 2 QTc interval (CTCv4: Grade 2 QTc 481 - 500 ms) during treatment, hold dasatinib and consult cardiology. Avoid other medications known to cause prolonged QTc during treatment if the QTc becomes prolonged. Dasatinib may be resumed if prolongation of QTc resolves to ≤ Grade 1 (CTCv4 Grade 1: QTc 450 - 480 ms). Patients whose prolonged QTc does not resolve to ≤ Grade 1 will be excluded from dasatinib treatment.

    b. **Pulmonary Arterial Hypertension (PAH)**
        - Evaluate for underlying cardiopulmonary disease **prior to therapy initiation and during therapy**; evaluate and rule out alternative etiologies in patients with symptoms suggestive of PAH (eg, dyspnea, fatigue, hypoxia, fluid retention) and interrupt therapy if symptoms are severe.
        - Discontinue permanently with confirmed PAH diagnosis (may be reversible upon discontinuation).

4. **Dermatologic toxicity**
    - Discontinue dasatinib if severe mucocutaneous reaction (including Stevens-Johnson syndrome and erythema multiforme) occurs and other etiologies have been ruled out.

5. **Drug Interactions:**
   - **CYP3A4 Inhibitors** (e.g. **voriconazole**, **posaconazole,** itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, lopinavir, grapefruit juice)
     - **Avoid coadministration of strong CYP3A4 inhibitors**. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended.
     - If concomitant administration with a strong CYP3A inhibitor cannot be avoided, dose reduction and monitoring for toxicity is required. Dasatinib dose will be reduced from 80 mg/m2 once daily (max 140mg) to 20 mg/m2 once daily (max 40mg) or, when patient is receiving reduced dose, from 60 mg/m2 once daily (max 100mg) to 10 mg/m2 once daily (max 20mg), with careful monitoring.
     - If reduced dose is not tolerated, the strong CYP3A4 inhibitor must be discontinued or dasatinib therapy temporarily held until concomitant inhibitor use has ceased.
     - **When a strong CYP3A4 inhibitor is discontinued, allow a washout period (~1 week) prior to adjusting dasatinib dose upward.**

   - **Antacids, H2 Antagonists, and proton pump inhibitors**
     - It is recommended to avoid **Antacids, H2 Antagonists, and proton pump inhibitors** with dasatinib as they may decrease dasatinib blood levels.
     - Aluminum hydroxide/magnesium hydroxide products (i.e. Epicogel) may be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib.

   - **Anticoagulants and medications that inhibit platelet function**
     - **Avoid using medications that inhibit platelet function or anticoagulants with dasatinib;** due to the possibility of gastrointestinal, cardiac, and cutaneous hemorrhage.

LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

Known Risk of TdP	Possible Risk of TdP	Conditional Risk of TdP
Amiodarone (KR)	Aripiprazole (PR)	Amitriptyline (CR)
Azithromycin (KR)	Dextromethorphan/Quinidine (PR)	Amphotericin B (CR)
Ciprofloxacin (KR)	Granisetron (PR)	Chloral hydrate (CR)
Clarithromycin (KR)	Hydrocodone - ER (PR)	Diphenhydramine (CR)
Domperidone (KR)	Palonosetron (PR)	Esomeprazole (CR)
Donepezil (KR)	Tacrolimus (PR)	Furosemide (frusemide) (CR)
Erythromycin (KR)	Tizanidine (PR)	Hydrochlorothiazide (CR)
Escitalopram (KR)	Tramadol (PR)	Itraconazole (CR)
Fluconazole (KR)	Venlafaxine (PR)	Ketoconazole (CR)
Haloperidol (KR)		Olanzapine (CR)
Ondansetron (KR)		Omeprazole (CR)
Pentamidine (KR)		Pantoprazole (CR)
Propofol (KR)		Piperacillin/Tazobactam (CR)
Voriconazole (CR)		Posaconazole (CR)
		Quetiapine (CR)
		Risperidone (CR)
		Sertraline (CR)

Known Risk of TdP: These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended.

Possible Risk of TdP: These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.

Conditional Risk of TdP: These drugs are associated with TdP BUT only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP.)