Sorafenib Guidelines

Dosing:

- During conventional chemotherapy regimen (200 mg/m2/dose/day, rounded to accommodate tablet size), the maximum dose will be 400 mg
- During Maintenance (100 mg/m2/dose/day, rounded to accommodate tablet size), the maximum dose will be 200 mg.

Administration:

- Sorafenib tablets should be taken:
    - At least 1 hour before or 2 hours after food.
    - With food (moderate to low fat meal)
    - With clear liquids (approximately 2 to 4 ounces for children < 12 years and 4 to 8 ounces for ≥ 12 years).
- Tablets should not be crushed, but should be swallowed whole.
- Grapefruit and its juice should be avoided for the duration of treatment with sorafenib.
- If dose is skipped or missed, **do not** replace it. Wait for the next dose schedule to take the drug

Requirements to Start Each Sorafenib Course

Patients must meet the following parameters before starting sorafenib in any course.

- Shortening fraction ≥ 27%
- BP less than the 95th percentile for age, height and gender (antihypertensive therapy is allowed)
- No concomitant treatment with CYP3A4 inducers/inhibitors
- Normal renal function as defined by: Creatinine clearance or radioisotope GFR > 70mL/min/1.73 m2

When to start and duration of therapy

- Sorafenib therapy will start on **Day 11** of Induction I and continue until **Day 28**.

- On subsequent courses, sorafenib therapy will commence the day following completion of conventional chemotherapy and continue for a total of **28** days.
- Maintenance dose and duration----- Combined Clinic

Contraindications:

- Uncontrolled hypertension for 14 days after use of anti-hypertensives
- Shortening fraction <27 %
- Gastrointestinal perforation

Use with Caution:

- Use with caution in patients with underlying or poorly-controlled hypertension and in patients with cardiac disease.
- Temporary interruption of therapy is recommended in patients undergoing major surgical procedures for precautionary reasons related to wound healing.

Major Side Effects

- **Cardiac:** cardiotoxicity
- **General fatigue** (33-40%, severe 6%)
- **Skin erythema** (>10%) - hand-foot skin reaction (25-35%, severe 6-8%)
- Rash yellow skin discoloration/desquamation (27-40%, severe <1%)
- Hand-foot skin reaction and rash are the most common side effects of sorafenib and **generally appear during the first six weeks of treatment**.
- **Hypertension** (17%, severe 4%), is usually mild to moderate **occurs early in the course** of treatment (**especially in the first six weeks)**
- Gastrointestinal perforation

Sorafenib Dose limiting toxicity:

Dose limiting toxicities (DLT) were defined as any side effects that prevented continued administration of the prescribed dosing and prompted either drug cessation or dose reduction.

Dose De-escalation

- If a patient experiences dose-limiting toxicity that is possibly, probably, or definitively related to sorafenib in any course while receiving **sorafenib at 200 mg/m2 once daily, the sorafenib dose should be decreased to 100 mg/m2 daily.**
- If the patient experiences dose-limiting toxicity at a dose of **100 mg/m2 once a day, then sorafenib should be discontinued.** These patients will continue to receive standard chemotherapy per protocol.
- Patients who require sorafenib dose reduction may not have a subsequent sorafenib dose increase.
- Sorafenib doses held for toxicity will not be made up.

Dose Limiting Toxicity	**Management**
Hematologic Failure of marrow recovery ▪ 40 days after 1st and 2nd induction ▪ 40 days after Intensification I ▪ 75 days after Capizzi	Reduce dose to 100 mg/m2/day
Skin Rash ▪ Grade I ▪ Grade II-III	No modifications Hold Sorafenib until Grade I skin rash then continue on 100m/m2/day Topical steroids and antihistamines
Cardiotoxicity ▪ FS < 27%	Hold sorafenib until FS >27% then continue on 100mg/m2/day
Hypertension	Start amlodipine/nifedipine according to algorithm
Gastrointestinal perforation	Discontinue sorafenib