failed to show increased toxicity on human myeloid stem cells. Likewise several early studies (24, 41, 42) using the calcium channel blocker verapamil in combination with several anti-cancer agents in humans has failed to document enhanced toxicity of these agents.

NAV1.954476.004

2.0 OBJECTIVES OF THE STUDY

2.1 To determine the toxicity of adding a calcium channel blocker to the cis Platin and 5-Fluorouracil regimen.

2.2 To determine the response rate of patients with colorectal cancer to a regimen consisting of cis Platin and 5-Fluorouracil and the calcium channel blocker diltiazem.

3.0 SELECTION OF PATIENT

3.1 Eligibility

Patients with advanced colorectal cancer that is incurable by surgery, radiation or chemotherapy

3.2 Entrance requirements

a. Measurable disease by routine radiologic studies or physical examination

b. ECOG performance of 0-2

c. Estimated survival of at least 3 months

d. Hemoglobin $\geq$9.0, WBC $\geq$4,000, platelet count $\geq$100,000, Cr cl $\geq$40ml/min

e. Ability to give informed consent

3.3 Exclusions

a. Prior history of congestive heart failure or cardiac arrhythmias

b. Concomitent treatment with Beta blockers or digoxin

c. EKG findings consistant with first, second or third degree heart block or sinus bradycardia (HR <60)

d. Left ventricular ejection fraction $\leq$45%

e. Prior treatment with Ardiamycin at a dose $\geq$350mg/m^2

f. Prior history of renal disease (serum cr $\geq$2.0)

g. Chemotherapy administration within 4 weeks of treatment (6 weeks for nitrosourea)

h. Radiation therapy administered to a signal lesion within 6 weeks of treatment

3.4 Pre-Treatment Testing

Prior to entering the study, all patients will undergo physical examination, CBC/Diff/Plts., SMA 6-12, appropriate radiographic study of signal lesion(s) (CXR, CT scan etc), EKG, MUGA scan, Cr Cl, and CEA

4.0 DETAILED DESCRIPTION OF STUDY

Patients entered on protocol will begin taking Diltiazem 2 days prior to admission to allow for adequate levels at the start of chemotherapy. The initial starting dose will be 30mg by mouth every 6 hours. This dose will be escalated by 30mg in sequential sets of 5 patients assuming no untoward effects are noted at the previous dose level. A maximum dose of 90mg by mouth every 6 hours will be attempted. Diltiazem will be continued at the same dose until 24° after completion of chemotherapy.

ENCLOSURE(49)