



## ORAL AGENTS IN GASTROINTESTINAL ONCOLOGY

DR. LOWELL ANTHONY

Over the last decade not only have the number of therapeutic agents increased in the management of gastrointestinal neoplasms but also the route of administration has changed. This review will focus on advances over the last 12-24 months with regard to oral agents used in colorectal, gastrointestinal stromal tumor and pancreatic malignancies.

### COLORECTAL CANCER

The 5-FU efficacy-toxicity debate has ranged from intravenous bolus to infusional to combination bolus-infusional regimens. Since 2000, bolus 5-FU daily regimens (Mayo) have decreased in popularity as bolus 5-FU weekly (Roswell Park, FLOX) and combination bolus-infusion (FOLFOX / FOLFIRI) have become preferred. With the approval of capecitabine in the adjuvant (Stage III) as well as in first-line and refractory metastatic colorectal cancer settings, there are even more choices in administering 5-FU. Studies to date support the concept of substituting capecitabine where either infusional 5-FU or infusional 5-FU/leucovorin is used. Potential

advantages to consider oral over intravenous routes of 5-FU administration include patient convenience, comfort and avoiding the complications of infusional therapies. Some of the challenges of capecitabine include copay (especially with Medicare) and compliance issues. Also, there may need to be an increased need for patient education and follow-up with oral therapies. Drug-drug interactions to be aware of and potentially avoid are the capecitabine-warfarin and capecitabine-phenytoin combinations.

### 1) TREE STUDY

Recent data from the TREE2 study (Hochster, H., et al) support the use of CapeOX with bevacizumab in the initial phase setting. The TREE trials were designed with safety or toxicity endpoints. From TREE1 it was learned that 1,000 mg/m<sup>2</sup> BID was excessive and that 850 mg/m<sup>2</sup> BID was tolerated better when combined with oxaliplatin. There were no new safety signals in TREE2 when bevacizumab (bev) was added. The TREE trials enrolled 373 patients (150 TREE1 and 223 TREE2). The arms were balanced except for the FOLFOX arm in TREE1 where more patients who had received adjuvant therapy (45%) were accrued vs bFOL (16%) vs

CapeOX (27%), respectively. All grades 3 and 4 adverse events (range) in TREE2 occurring in the first 3 months were: CapeOX + bev of 58% (46-70); bFOL + bev of 60% (48-72); mFOLFOX + bev of 65% (53-76). The incidence of any Grade 3/4 events during TREE2 was: 76% CapeOX + bev vs 85% mFOLFOX + bev vs 74% bFOL + bev with N ranging from 70-72 patients on each arm. Even though efficacy criteria were secondary endpoints for this trial, the median survival of the CapeOX + bev arm was 27.0 months and compared favorably to mFOLFOX + bev (26.0 mos) and to bFOL + bev (20.7 mos). With the addition of bevacizumab (TREE1 vs TREE2), median survival was increased from 18.2 to 24.4 months.

### 2) BICC-C TRIAL

This trial was similar to the TREE study except irinotecan was substituted for oxaliplatin. The treatment arms for period 1 (pre bev, N = 413) were: FOLFIRI vs mIFL vs CapeIri). When bevacizumab became commercially available in 2004 (period 2, N = 117), the CapeIri arm was dropped because of adverse events. A conclusion from this trial was that capecitabine at 1,000 mg/m<sup>2</sup> BID x 14 days every 21 days is not the optimal dose