ARCTIC Study

AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP

Final results of Australasian Gastro-Intestinal Trials Group (AGITG) ARCTIC Study – An international audit of raltitrexed for patients with cardiac toxicity (CT) induced by Fluoropyrimidines (FP)

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Disclosures

- Timothy Price has participated in research and has been an uncompensated member of advisory boards for;
  - AMGEN
  - MERCK
  - BAYER
  - NOVARTIS
  - ROCHE
  - IPSEN

Background

- Cardiac toxicity of FP is a potentially lethal toxicity
- Incidence ranges from 1.2% to 18%
- Capecitabine also causes cardiotoxicity in 3-6.2%
- Bolus 5FU has the lowest rate (2.2-2.4%)
- Asymptomatic ECG changes may occur in up to 88% of patients
- Coronary vasospasm is the most common form, although direct myocardial toxicity is also reported
- Risk factors are: higher doses of FP; prior chest radiation; history of cardiovascular disease; prior cardiotoxic agents.

J Cancer Res Clin Oncol (2008) 134:75-82, IMJ (2010) 4: 303-7, JCO (1989) 7: 509-14

Background (2)

- The majority of cardiac events occur in the first cycle
- Cardiotoxicity is generally reversible after cessation of 5FU therapy
- Re-exposure risk is reported to be 20-100%
- Nitrates and calcium blockers are sometimes used in an attempt to prevent cardiotoxicity

Becker et al; Drugs 1999 (57) 475, Jenson; Cancer Chemother Pharmacol 2006 (4) 487,

Raltitrexed

- a direct and specific thymidylate synthase inhibitor with similar activity to 5FU in colorectal cancer in Phase III trials (3 of 4)
- no obvious reported cardiotoxicity in initial Phase II/III trails.
- has been reported as an alternate option for patients with 5FU induced cardiotoxicity in a number of case reports

Lancet 2002 (359) 1556, JCO 1999 (9) 2943, Annals Onc 1996 (7) 961,
Proc Am Soc Clin Oncol 1997, 16 (abstr 801).

ARCTIC Aim

- Primary Aim: To determine if for patients who experienced cardiac toxicity from 5FU or capecitabine, the substitution with raltitrexed resulted in no further cardiac toxicity
- Target population: Male and female patients aged ≥ 18 years old who have experienced cardiac toxicity from 5FU or capecitabine and who were given raltitrexed following the cardiac event

Methods

- Raltitrexed treatment: Between January 2004 to December 2011
- Retrospective case note review of all patients who had cardiotoxicity from FP, and were subsequently switched to raltitrexed
- Baseline cardiac risk factors were documented
  - Dyslipidaemia, hypertension, past smoker, present smoker, diabetes and past history of IHD

Methods (2)

- Rates of cardiac events pre and post raltitrexed treatment were assessed

- Cardiotoxicity was defined as:
  - Angina/typical ischaemic chest pain
  - myocardial infarct (MI)
  - atypical pain with ECG/troponin changes
  - arrhythmia

- A coronary angiogram was not mandatory

Statistical considerations

- Current evidence suggests the rate of cardiac events due to continuing FP after cardiac events is at least 20%
- In 40 patients treated with raltitrexed,
  - If at least 13 events were observed it would suggest the event rate is higher than that of continuing FP
  - If <4 events were observed in 40 patients treated with raltitrexed it would suggest cardiotoxicity is lower in comparison to continuing these patients on FP
- These rates were based on a 95% confidence interval for a true rate of cardiac toxicity of 20%

Results

- 12 institutions in Australia and the UK provided data
- 42 patients were treated with raltitrexed following a cardiac event while on FP during the study period
- Median age 62 years (range 36-81)
- 64% were male
- Prior ischaemic heart disease: 9 of 34 (26%)
- Cardiac risk factors:
  - Nil 5 (12%)
  - One 14 (33%)
  - Two 12 (29%)
  - Three 11 (26%)

Results-demographics

- Cancer Diagnosis
  - Colorectal 93%, Oesophageal 5%, Biliary 2%
- Chemotherapy
  - Fluoropyrimidine (FP) alone 11 (26%)
  - Epirubicin/Cispaltin/FP 1 (2%)
  - Platinum/FP 26 (62%)
  - Irinotecan/FP 4 (10%)
- Fluoropyrimidine
  - FP bolus 7 (17%)
  - FP infusion 26 (62%)
  - Capecitabine 9 (21%)

FP – first cardiac event

- Time to event: median 1 cycle (range 1-11)
- 61% in first cycle
- 83% within two cycles
- 48% (20 patients) typical pain, normal cardiac enzymes and ECG
- 19% (8 patients) typical pain and ECG changes but normal cardiac enzymes
- 29% (12 patients) had a myocardial infarction

FP - second cardiac event

- Following their first event, nine patients were re-challenged with 5FU and had a further cardiac event (angina)
  - 1 calcium antagonist, and 1 nitrate added
  - 1 reduced dose 5FU
  - 1 patients was switched to bolus 5FU
- All patients(100%) had recurrent typical cardiac chest pain, two patients associated with ECG changes
- Two patients had a third cardiac event prior to switching to raltitrexed

Raltitrexed

- Median number of cycles 6 (range 1-21)
- Relevant concomitant medications
  - Aspirin 8pts, calcium antagonist 6pts, nitrate 8pts
- Raltitrexed regimen used
  - Single agent 24%
  - Combination 76%
- No patients had further definitive cardiac events on raltitexed
- Comparing the rate of cardiac events due to continuing FP after cardiac events (~20%) to no cardiac events on raltitrexed:
  - 0 events (95% CI 0-8.4), *P* .001

Possible cardiac event on raltitrexed

- 69 y.o. Male with metastatic colorectal cancer
- Two prior cardiac events (typical chest pain)
  - Cycle 1 on day 3, and cycle 3 on day 1 (6hr post infusion)
- Prior therapy infusion 5FU/oxaliplatin x 3 cycles
- Current event
  - Day 14 after cycle 12 of raltitrexed
  - Undergoing rectal RT
  - Presented acute abdomen, diagnosis of perforation/ peritonitis and SVT and anterior ischaemia clinically/ECG, treated IV/oral metoprolol
  - Patient died 24-48 hours later due to complications of peritonitis.
  - Likely arrhythmia secondary to infection/peritonitis

Conclusions

- This is the largest reported series of patients where raltitrexed substitution has occurred for FP cardiotoxicity
- The majority of FP toxicity reported here would be consistent with reversible coronary spasm
- The majority of events occurred in the first cycle (61%), and 83% within second cycle
- 88% of patients had at least one cardiac risk factor
- 26% of patients had a history of definite IHD
- There was no cases of definite cardiac toxicity attributable to raltitrexed
- Ralitrexed is a safe alternative option when FP cardiotoxicity is diagnosed