ASCO GI Conference Review

Making Education Easy GI Cancers Symposium, January 2008, Florida, USA

In this issue:

Welcome

to the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium Conference Review, a locally focused summary of some of the newest strategies in prevention, screening, and treatment of gastrointestinal cancers presented in January 2008.

This Review has been created to allow those unable to attend to access a summary of conference highlights dealing with gastrointestinal cancer treatments that are likely to affect current practice. Selection and review of the research has been carried out independently by Associate Professor David Perez, who attended the Gastrointestinal Cancers Symposium in Orlando, Florida.

I hope you find the conference review stimulating and I look forward to your feedback.

Kind Regards

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Efficacy of adjuvant imatinib mesylate following complete resection of localized, primary gastrointestinal stromal tumor (GIST) at high risk of recurrence: The U.S. Intergroup phase II trial ACOSOG Z9000

Authors: DeMatteo RP et al

Summary: This single-arm, phase II multicentre study investigated the efficacy of open-label imatinib mesylate administered at a daily oral dose of 400 mg for 1 year, following the resection of a KIT-expressing primary gastrointestinal stromal tumour (GIST) that was at high risk of recurrence (tumour size >10 cm, tumour rupture, or <5 peritoneal metastases). Data were evaluable from 107 patients (median age 58 years). The median tumour size was 13 cm, with 50% of tumours originating from the stomach and 42% from the small intestine. At a median 4-year follow-up, the 1, 2, and 3 year overall survival rates were 99, 97, and 97%, respectively; corresponding values for the 1, 2, and 3 year recurrence-free survival rates were 94, 73, and 61%, respectively. Imatinib therapy was well tolerated.

Comment: This report presents data from a phase 2 study of adjuvant imatinib for resected, poor prognosis GIST tumours. The 3-year overall survival for 107 patients was 97% compared to historical figures of around 50%. These data reflect the results of the phase 3 study in standard prognosis patients which was halted after 14 months because of a clear difference in disease-free survival of 3 versus 17%. Longer follow-up of these cohorts is required but adjuvant imatinib is developing an impressive track record.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 8

About Research Review

Research Review is an independent publisher producing electronic journals to help make education easier for the NZ medical community.

Barrett's esophagus: Prevalence of central adiposity, metabolic syndrome, and a pro-inflammatory state

Authors: Power DG et all

Summary: Detailed metabolic and nutritional assessments in 102 patients with Barrett's oesophagus and 78 patients with non-Barrett's acid reflux (GORD) were performed to screen for the metabolic syndrome and to measure adipokines and cytokines, to determine their relevance to inflammation and development of oesophageal adenocarcinoma. BMI measurements revealed that 78% of Barrett's patients and 75% of GORD patients were overweight or obese. The metabolic syndrome was diagnosed in 46% of Barrett's patients and 32% of GORD patients and the Barrett's population had a significantly higher number of features of metabolic syndrome. Among Barrett's patients, the metabolic syndrome was significantly associated with an adverse metabolic profile including increased trunk fat, a ≥10 cm waistline, elevated CRP, leptin, insulin resistance, hypertension, and decreased adiponectin. Moreover, compared with short-segment metaplasia (<3 cm), long-segment Barrett's (>3 cm) was associated with significantly more patients with the metabolic syndrome (60% vs 92%) and patients who were centrally obese (23.8% vs 62%). IL-6 levels were also significantly higher in long-segment Barrett's compared with short-segment Barrett's (4 vs 0.56).

Comment: The rising incidence of Barrett's oesophagus is a concern to oncologists because of its association with oesophageal adenocarcinoma. This study reports a strong association between Barrett's oesophagus, central obesity and the metabolic syndrome. The latter is associated with an elevated serum leptin. Leptin has a modulating effect on cellular differentiation and may therefore contribute to the evolution of oesophageal metaplasia. This adds impetus to the importance of lifestyle factors in the prevention of oesophageal cancer.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 2

Long term results of the MRC OEO2 randomized trial of surgery with or without preoperative chemotherapy in resectable esophageal cancer

Authors: Allum WH et al

Summary: The initial results of the OEO2 trial (a randomised controlled trial of preoperative chemotherapy in patients undergoing radical surgery for oesophageal cancer) demonstrated a statistically significant survival advantage for both disease-free survival (DFS) and overall survival (OS) in 400 patients treated with two cycles of combination cisplatin and 5-fluorouracil before surgery (CS), compared with 402 patients undergoing surgery alone (S), with a median 3-year follow-up and 596 deaths (see Lancet 2002; 359: 1727-33). The present analysis reports 6-year median follow-up data. Of 655 deaths (335=S and 320=CS), 77.6% have been cancer related; (S) 78.5% and (CS) 76.6%. DFS and OS remain significantly longer in the CS arm; DFS hazard ratio (HR) = 0.82 (95% CI, 0.71 to 0.95; p=0.008); Survival HR=0.84 (95% CI, 0.72 to 0.98; p=0.03) with 5-year survival rates of 23% in (CS) compared with 17% in (S). The difference in survival in favour of CS remains consistent in both patients with adenocarcinoma (HR=0.86) and squamous cell carcinoma (HR=0.81).

Comment: These 6-year follow-up data from the MRC OEO2 neo-adjuvant oesophageal cancer study show an encouraging 6% survival advantage. This compares with a 9% advantage at 2 years. The benefits were similar for both squamous cell carcinoma and adenocarcinomas. These data are in keeping with meta-analyses of neo-adjuvant chemotherapy.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 9

A randomized trial of postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus neoadjuvant chemotherapy for localized squamous cell carcinoma of the thoracic esophagus (JCOG 9907)

Authors: Ando N et all

Summary: This phase III trial compared adjuvant chemotherapy with neoadjuvant chemotherapy, to determine the perioperative optimal timing for chemotherapy in patients with clinical stage II and III (excluding T4Nany) oesophageal squamous cell carcinoma (ESCC). In arm A, patients received two courses of chemotherapy of cisplatin (80 mg/m^2, divided dose day 1) plus 5-FU (800 mg/m^2, continuous infusion days 1–5) following transthoracic esophagectomy with lymphadenectomy surgery. In arm B, the same two courses of chemotherapy as arm A were given before surgery. 330 patients were randomised between May 2000 and May 2006 and followed-up for a median 22.6 months. No between-group differences were seen for toxicity during chemotherapy and surgical complications. An analysis conducted in March 2007 revealed a hazard ratio (HR) for progression-free survival of 0.76 in favour of arm B and an HR for OS of 0.64 also in favour of arm B, which was highly significant (p=0.014). The JCOG Data and Safety Monitoring Committee recommended early termination of the study and publication of the results.

Comment: This report compares neo-adjuvant versus adjuvant cisplatin and 5-FU in stage 2/3 squamous carcinoma of the oesophagus. In 330 patients the 5-year overall survival was 60% versus 38.4% in favour of the neo-adjuvant approach. Fewer adjuvant patients completed the treatment programme. This lends strong support to the neo-adjuvant approach when surgery is intended.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 10

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Independent commentary by Associate Professor David Perez, Medical Oncologist, Dunedin Hospital.

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ASCO GI Conference Review

Microscopic margins and patterns of treatment failure in resected pancreas adenocarcinoma

Authors: Gnerlich JL et al

Summary: Data were retrospectively analysed from 100 patients who had undergone standard or pylorus-sparing pancreaticoduodenectomy (PD), 27 of whom had ≥1 positive microscopic margins on surgical pathology (uncinate 16%, portal vein groove 8%, pancreatic neck 6%, and posterior margin 4%), to determine the correlation of microscopic margin status with survival and local control. First site of failure included local recurrence (LR) in 5 patients, LR + distal recurrence (DR) in 23 patients, and DR only in 32 patients. Of 28 patients with local failure, 16 (57%) had negative microscopic margins. The presence of any positive microscopic margin correlated with LR (p=0.02) and with overall survival (p=0.04). A subset analysis of the four margin sites revealed that only positive posterior pancreatic margin correlated with LR (p=0.03).

Comment: The utility of radiation or chemoradiation for resected pancreatic cancer with positive microscopic margins is not resolved. This retrospective study of 100 patients treated in a major centre revealed 27 with positive margins. Across the whole cohort first relapse confined to the local region was rare [5%], compared to distant [32%] and local/distant [23%]. This provides indirect evidence that adjuvant radiation is unlikely to impact on survival.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 199

Panitumumab (pmab) efficacy and patient-reported outcomes (PRO) in metastatic colorectal cancer (mCRC) patients (pts) with wild-type (WT) KRAS tumor status

Authors: Amado RG et al

Summary: To determine whether panitumumab shows greater efficacy in progression-free survival (PFS) according to wild-type (WT) or mutant (MT) KRAS tumour status, 463 patients with chemorefractory metastatic colorectal cancer (mCRC) received panitumumab (6mg/kg every two weeks) plus best supportive care (BSC) or BSC alone. Of 427 patients with available KRAS data, 43% had MT KRAS. The hazard ratios (HRs) for PFS (comparing panitumumab:BSC) were 0.45 (95% CI, 0.34 to 0.59) in the WT KRAS group and 0.99 (95% CI, 0.73 to 1.36) in the MT KRAS group (p<0.0001), favouring panitumumab over BSC. Median PFS values were 12.3 weeks for panitumumab patients with WT KRAS and 7.4 weeks for MT KRAS; corresponding values for BSC patients were 7.3 weeks in both KRAS groups. Of panitumumab patients with WT KRAS, 17% responded and 34% had stable disease, versus 0% and 12%, respectively, in the MT KRAS group. When treatment arms were combined, overall survival was prolonged for WT KRAS versus MT KRAS (HR = 0.67, 95% CI, 0.55 to 0.82). In a pro analysis of 363 patients (188 panitumumab; 175 BSC), CRC symptoms and numerical differences in health-related quality of life scores significantly favoured panitumumab in WT KRAS tumours; no such differences were observed for MT KRAS.

Comment: This report highlights the predictive value of KRAS status for benefit from panitumumab in metastatic colorectal cancer. Of 427 patients, 43% had mutant KRAS and this predicted for inferior response, progression-free survival and quality of life. Similar data are also emerging for cetuximab, in which wild-type KRAS predicts superior outcomes. Predictive assays of this type will greatly assist in the rational use of these expensive agents.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 278

Two-stage hepatectomy for irresectable colorectal cancer liver metastases: A 14-year experience

Authors: Adam R et al

Summary: The feasibility, risks, and outcomes of two-stage hepatectomy were assessed in 51 patients with irresectable colorectal liver metastases (CLM), in whom single resection could not achieve a complete treatment. Two-stage hepatectomy was feasible for 35 of the patients (69%); at diagnosis, they had a mean number of 9.6 metastases with a mean maximum diameter of 50.2 mm. Preoperative chemotherapy was administered to 34/35 patients; 27 of whom continued chemotherapy between the two procedures and 26 also received postoperative chemotherapy. The mean delay between the two liver resections was 4.3 months. Postoperative mortality within 2 months was 0% after the first hepatectomy and 11% after the second; morbidity rates were also higher after the second hepatectomy (63% vs 23%, p<0.01). At a median 26 months' follow-up from the time of first hepatectomy, overall 3- and 5-year survivals were 57% and 39%, respectively.

Comment: This single institution, open study from France once again highlights the rapid advances in hepatic resection for colorectal metastases. Two-stage hepatectomy was feasible in 35 of 51 patients with unresectable metastases. The mean period between resections was 4.3 months. Virtually all patients received neo-adjuvant chemotherapy and most received adjuvant as well. At a median follow-up of 26 months the survival data seem to reflect standard hepatectomy results but longer term data will clearly be needed.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 283

Timing of liver surgery for synchronous colorectal metastases: A case-matched study

Authors: de Haas R et al

Summary: To determine the optimal surgical strategy for patients with synchronous colorectal liver metastases (CLM) undergoing a limited (<3 segments) hepatectomy, this study reviewed data from 228 such patients, of whom 55 were treated with a simultaneous colorectal and hepatic resection (S group) and 173 were treated with a delayed hepatectomy (D group). Postoperative mortality within 2 months was similar between the S group and the D group (0% vs 1%), but significantly less morbidity was experienced by the S group (9% vs 24%, p=0.02). Five-year overall survival (OS) and disease-free survival (DFS) rates were 47% and 24% in the S group, respectively, compared with 52% and 27% in the D group; the between-group comparisons were not significant. Case-matching of 26 patients in each group (similar in terms of number, size, and distribution of CLM) confirmed these results. Multivariate analysis revealed 3 poor prognostic factors of survival: female gender, >3 CLM at diagnosis, and maximum size of CLM at diagnosis >30 mm.

Comment: The patient with synchronous liver metastases always poses a dilemma concerning the appropriate timing of primary tumour resection and liver resection. This retrospective, single institution study suggests that simultaneous resection of primary and liver metastases is both safe and associated with less morbidity. A selection bias was likely to exist but multivariate analysis suggested the best outcome was in those with less than 3 liver metastases with diameters less than 30mm.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 451

To view the full abstracts in this Review please go to:

http://www.asco.org/portal/site/ASCO/menuitem

Systemic or hepatic arterial chemotherapy is useful after curative resection of liver metastases from colorectal cancer. A meta-analysis of randomized controlled trials

Authors: Uzzan B et al

Summary: Data were reviewed from 9 randomised clinical trials (involving 1147 patients) to determine whether the addition of adjuvant systemic or hepatic arterial chemotherapy (CT) (5-FU) to curative R0 surgery for liver metastases from colorectal cancer improves survival (overall survival [OS] or relapse-free survival [RFS]). A fixed-effect meta-analysis revealed significant improvements in OS and RFS after the addition of adjuvant or neoadjuvant CT to surgery: hazard ratio (HR) OS = 0.81 (95% CI, 0.67 to 0.99; p=0.04) and HR RFS = 0.77 (95% CI, 0.67 to 0.89; p=0.001). Results of 5 RCTs (443 patients) that used intra-arterial CT yielded similar results to those of the 2 larger randomised controlled trials assessing systemic CT. The most recent multicentre randomised clinical trial (Nordlinger, 2007) used systemic CT (FOLFOX 4) and showed a trend towards a better RFS after surgery + CT (35.4% vs 28.1%; HR RFS = 0.79 [95% CI, 0.62 to 1.02; p=0.058]). Similarly, a second recent RCT using 5-FU IV bolus (Portier 2006) showed that CT significantly improved RFS (but not OS).

Comment: The recently reported EORTC study of neoadjuvant plus adjuvant FOLFOX with hepatic metastectomy provided encouraging disease-free survival data but the greatest interest awaits the availability of overall survival data. This small meta-analysis of 9 randomised studies reports improved disease-free and overall survival for those patients receiving some form of adjuvant chemotherapy. The case for adjuvant chemotherapy is strengthening but the optimal timing and mode of delivery remain unclear.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 467

Disparities in access to adjuvant chemotherapy affect outcomes for rectal cancer

Authors: Cheung WY et al

Summary: These researchers investigated the effect of adjuvant chemotherapy (AC) timing on rectal cancer outcomes, explored clinical factors accounting for treatment delays, and examined the relative impact of (a) postsurgical morbidity and (b) accessibility to care in causing these delays by analysing postoperative hospital stay (POHS) and established access to care with neoadjuvant chemotherapy. The SEER-Medicare database revealed two cohorts of patients with stage II and III rectal cancer: patients with known contact with a medical oncologist because of prior neoadjuvant chemotherapy (group A; n=442) and patients without such demonstrated access to care (group B; n=5617). The median interval between surgery and AC was 46 days in group A and 42 days in group B (p=0.02). While only 17% and 11% of pts in groups A and B, respectively, waited ≥3 months for AC, their median overall survival values were significantly shorter than for patients who waited <3 months: 33 vs 71 months in group A (p=<0.01) and 44 vs 80 months in group B (p=<0.01). Length of POHS predicted for AC delays in both groups. Further analyses revealed 3 factors predicted for AC delays only for patients in group B: advanced age (p=<0.01), Black race (p=<0.01), and low socioeconomic status (p=0.03).

Comment: The time window for initiation of adjuvant chemotherapy for rectal cancer has been ill-defined. These data on more than 6000 patients derived retrospectively from the SEER database show a major reduction in median survival of 44 versus 80 months for those who wait more than 3 months to initiate adjuvant therapy. Since prospective investigations of this question will not be feasible on ethical grounds this analysis offers a reasonable guideline.

Reference: ASCO Gastrointestinal Cancers Symposium; Abstr 455

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