GI Cancer Conference Review

Making Education Easy GI Cancer World Congress, June 2007, Spain

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Welcome to the Gastrointestinal Cancer World Congress Conference Review

Conference Review, a locally focused summary of some of the most exciting clinical research on GI Cancer presented last month.

This Review has been created to allow those unable to attend, but with a keen professional interest in GI cancer treatments, to access a summary of significant clinical studies presented that are likely to affect current practice. Selection and review of the research is carried out independently by Dr Dragan Damianovich, Medical Oncologist, Auckland City Hospital, who attended the 9th World Congress in Barcelona, Spain.

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

Kind Regards

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Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) in the first-line treatment of MCRC: OPUS, a phase II study

Authors: Schuch G et al

Summary: This multicentre European phase II trial explored the antitumour activity of first-line cetuximab in combination with FOLFOX-4 in 337 patients with epidermal growth factor receptor-expressing metastatic colorectal cancer, stratified by ECOG performance status (PS) (0–1 and 2) and randomised to receive FOLFOX-4 alone (controls) or in combination with cetuximab (400 mg/m2 initial dose, then 250 mg/m2/week). Approximately 90% of patients had good performance status (0–1) and more patients in the control arm had adjuvant chemotherapy. The best confirmed overall response rate was significantly better with combination treatment than with FOLFOX-4 alone (45.6% vs 35.7%; odds ratio 1.648). Progression-free survival and overall survival data were not available at the time of presentation. Most commonly observed grade 3/4 toxicities included neutropenia (31.5% of controls vs 27.6% of combination treatment recipients), diarrhoea (6.0% vs 7.1%, respectively), leucopenia (5.4% vs 7.1%, respectively) and rash (9.4% of combination treatment recipients only).

Comment: The response rate observed for the cetuximab and chemotherapy combination is slightly lower than in similar phase II studies. However, an approximate 10% difference in favour of combination of chemotherapy with a biological agent has been a constant finding. Neutropenia is the most common problem with combination of cetuximab with oxaliplatin-based chemotherapy, rather than diarrhoea observed with combination of cetuximab with irinotecan-based treatment regimens.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii18 (Abstr O-0022)

Changes to toxicity with the addition of cetuximab or substitution of capecitabine in FOLFOX: preliminary safety report for the first 804 patients from the MRC COIN (CR10) trial

Authors: Maughan T et al

Summary: This study reports preliminary toxicity data for a 3-arm trial comparing continuous chemotherapy (CT) plus cetuximab or intermittent CT with standard continuous CT (oxaliplatin + fluoropyrimidine; OxFp) in the first-line treatment of advanced colorectal cancer. All chemotherapy-naïve patients (PS 0–2) with measurable and inoperable disease receive (A) (OxFp) (FOLFOX every 2 weeks or oxaliplatin + capecitabine every 3 weeks, according to patient or investigator's preference), (B) OxFp plus weekly cetuximab, (C) intermittent OxFp. Treatment is given in arms A and B until disease progression, cumulative toxicity or patient choice, while treatment in arm C is stopped after 12 weeks in stable/responding patients and reintroduced at disease progression. Of a total of 804 randomised patients, 12-week toxicity data were available for 85%. Two-thirds of patients received oxaliplatin + capecitabine and one-third FOLFOX. Rates of grade 3/4 toxicity were similar between oxaliplatin + capecitabine and FOLFOX (31% and 33%, respectively), but were significantly increased with the addition of cetuximab to each chemotherapy regimen (53% and 54%, respectively). Gastrointestinal toxicity (nausea, vomiting and diarrhoea) was more common with oxaliplatin + capecitabine and neutropenia more common with FOLFOX. The rate of grade 3/4 gastrointestinal toxicity was significantly higher with addition of cetuximab to oxaliplatin + capecitabine (nausea and vomiting 14% vs 7%, diarrhoea 23% vs 13%). Lethargy, skin rash and hypersensitivity reactions were also increased with use of cetuximab.

Comment: This is another trial showing comparability of overall toxicity of capecitabine + oxaliplatin combination to a FOLFOX regimen. The increased rate of gastrointestinal toxicity, especially diarrhoea, might be an issue with addition of cetuximab to capecitabine-based regimens due to overlapping toxicities.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii18 (Abstr O-0023)

A large phase IV study of first-line bevacizumab plus irinotecan and infusional 5-FU/LV in metastatic CRC: AVIRI

Authors: Sobrero A et al

Summary: This multinational open-label trial evaluated the efficacy and safety of first-line bevacizumab (BEV) in combination with irinotecan and infusional 5-FU. Between April and November 2005, 209 patients received ≥6 cycles of first-line BEV (5 mg/kg given on day 1) together with irinotecan and infusional 5-FU (classical FOLFIRI, simplified FOLFIRI and weekly regimen, all allowed). Two-thirds of patients had good ECOG Performance Status (0–1). Approximately 30% of patients received adjuvant chemotherapy and only 4% adjuvant FOLFOX4. Median time from completion of adjuvant treatment to relapse was 1 year. A preliminary efficacy analysis revealed an objective response rate of 44% and an estimated 6-month progression-free survival of 82%. Toxicities included grade 3/4 neutropenia (30% of patients), diarrhoea (12%), bleeding (3.8%), hypertension (3.8%), arterial thromboembolism (4.8%), GI perforation (2.4%) and problems with wound healing (0.5%).

Comment: Although non-randomised, this is the largest clinical trial to date to report the results for first-line BEV in combination with irinotecan and infusional 5-FU. The safety profile appears consistent with that observed in other BEV trials in mCRC, while preliminary results suggest at least similar efficacy to the now obsolete bolus IFL regimen.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii 18 (Abstr O-0024)

Preliminary efficacy of bevacizumab with first-line FOLFOX, XELOX, FOLFIRI and monotherapy for MCRC: First BEAT Trial

Authors: Rivera F et al

Summary: This trial evaluated the efficacy and safety of first-line bevacizumab (BEV) in combination with most common chemotherapy (CT) regimens and involved 1927 patients with metastatic colorectal cancer in 41 countries between June 2004 and February 2006. Eligible patients received BEV 5 mg/kg in combination with two-weekly (5-FU-based) and 7.5 mg/kg with three-weekly (capecitabine-based) CT regimens until disease progression. The median age was 59 years (33%, ≥65 years). Patients with ECOG Performance Status (PS) ≥2 were excluded. Among patients receiving 5-FU or capecitabine monotherapy with BEV, prognosis appeared poorer with respect to age ≥65 years, PS and 60-day mortality rate (6.6%) compared with those receiving doublets. The most commonly used regimens with BEV were FOLFOX (28%) and FOLFIRI (26%) followed by XELOX (18%) and capecitabine or 5-FU (15%). Grade 3 to 5 serious adverse events associated with BEV included hypertension (4.6%), bleeding (2.6%), GI perforation (1.7%), arterial thromboembolism (1.1%), wound healing complications (1.0%) and proteinuria (0.7%). Median progression-free survival durations were 10.5 months for FOLFOX, 10.3 months for XELOX, 11.1 months for FOLFIRI and 9.1 months for patients receiving 5-FU or capecitabine with BEV.

Comment: This is the largest community-based study on the first-line use of BEV in metastatic colorectal cancer. The results seem consistent with the ones reported in randomised clinical trials.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii19 (Abstr O-0025)

Conference Reviews are prepared with independent commentary from relevant specialists. To become a reviewer or to commission a conference review contact ***admin@researchreview.co.nz***

Independent commentary by Dr Dragan Damianovich, Medical Oncologist, Auckland City Hospital.

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Survival and response results from XELOX-1/NO16966: a randomised phase III trial of XELOX versus FOLFOX4 as first-line treatment for patients with metastatic colorectal cancer (MCRC)

Authors: Cassidy J et al

Summary: This equivalence phase III trial was originally designed to compare first-line XELOX with first-line FOLFOX-4 in metastatic colorectal cancer (mCRC). Following observed benefits in progression-free survival and overall survival associated with bevacizumab (BEV) in combination with IFL (Hurwitz H et al. N Engl J Med 2004; 350: 2335-2342), the trial design was amended to 2x2 partially blinded study evaluating the addition of BEV to either XELOX or FOLFOX4 (see the next study below). Patients were randomised to receive XELOX (Ox 130 mg/m2 + cap 1000 mg/m2 bid oral d1-14, q3w) or standard FOLFOX4 (ox+5-FU+LV), and after the amendment, BEV 7.5 mg/kg iv q3w or placebo in combination with XELOX and BEV 5 mg/kg iv q2w or placebo with FOLFOX4. A total of 2034 patients were recruited. The two treatment regimens were equivalent in respect to objective response rate (37.1% vs 39.6%), median progression-free survival (8 vs 8.5 months) and median overall survival (19.8 vs19.6 months). No significant difference in overall survival was observed in either the 2-arm study (n=334) (median 18.8 vs 17.7 months) or with the addition of BEV (2x2 study) (median 21.4 vs 21.2 months) between the two treatment regimens. All-cause 60-day mortality rates were also equivalent (2.3% vs 3.4%). Diarrhoea and hand foot syndrome were more frequent with XELOX, while neutropenia and febrile neutropenia were more frequent with FOLFOX4. There was no between-treatment difference in peripheral neuropathy.

Comment: After two large phase III studies (the current[1] and the TREE study[2]) comparing these two regimens have shown similar results, I don't think there is any doubt now that these two regimens are equally effective and interchangeable for the treatment of mCRC in the first-line settings. However, due to different toxicity profiles, patient co-morbidities, patient preference and availability of biological agents should guide us in our decision as to which regimen to chose. That will also depend on available resources for chemotherapy delivery in an individual oncology centre.

Reference: [1]*Annals of Oncology, 2*007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii 19 (Abstr O-0026). [2]*J Clin Oncol,* 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No.18S (June 20 Supplement), 2006: 3510.

Updated efficacy results from XELOX-1/NO 16966, a randomised phase III trial in first-line metastatic colorectal cancer: analysis of bevacizumab in combination with XELOX or FOLFOX4

Authors: Saltz L et al

Summary: This phase III trial evaluated the combination of first-line bevacizumab (BEV) with oxaliplatin-based chemotherapy (FOLFOX4 or the XELOX regimen), as the follow-on phase of the study described above that showed equivalence between the two chemotherapy regimens. Details of the treatment arms are also outlined above. The addition of BEV to either XELOX or FOLFOX4 was associated with significantly better median progression-free survival (PFS) in all analysed patient categories (general approach 9.4 vs 8.0 months, hazard ratio [HR] 0.83; on treatment approach 10.4 vs 7.9, HR 0.63; based on IRC data 11.1 vs 8.6, HR 0.70). The on treatment approach included only the patients with progressive disease or death within 28 days of the last dose of study treatment including BEV. In the general population, patients who stopped BEV at the same time as chemotherapy due to oxaliplatin-related toxicity or drug holiday and before disease progression were also included in analysis. Compared to other patients, those who continued BEV until disease progression achieved a greater PFS benefit. In patients with liver-only disease, the resectability rate increased from 12.9% to 19.2%. BEV-related grade 3/4 toxicity was slightly higher for BEV plus chemotherapy versus chemotherapy alone: GI perforation (0.6% vs 0.3%), bleeding (1.9% vs 1.2%), arterial thromboembolism (1.7% vs 1.0%), hypertension (3.7% vs. 1.2), proteinuria (0.6% vs 0%) apart from wound healing complications (0.1% vs 0.3%). The all-cause 60-day mortality rate was also slightly higher in the combined modality arm (2.0% vs 1.6%)

Comment: The observation that the patients who received BEV longer had better outcomes than patients stopping BEV earlier raises the importance of using BEV until disease progression. The role of "maintenance" monotherapy with BEV in both adjuvant and advanced settings is currently studied in randomised trials.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii 21 (Abstr O-0032)

Survival after peri-operative chemotherapy with FOLFOX4 and surgery for resectable colorectal cancer liver metastases. Final results of the EORTC Intergroup randomised phase III study 4093

Authors: Nordlinger B et al

Summary: The role of peri-operative chemotherapy was assessed in this trial involving 364 patients with ≤4 resectable liver metastases from colorectal cancer. Patients were randomised to peri-operative FOLFOX-4 (oxaliplatin 85 mg/m2 and LV5FU2, 6 cycles prior and 6 after surgery; CT+S) or surgery (S) alone. Patients in the CT arm received a median of 6 cycles pre-operatively; 114 patients received post-operative CT for a median of 6 cycles. There were no CT-related deaths. Surgery was performed in 85.2% and 92.9% of patients in the CT+S and S arms, respectively; complete resection was achieved in 95.5% and 89.4% of operated patients, respectively. Surgical complications developed in 2.6% and 1.2% of the CT+S and S arms, respectively; post-operative deaths occurred in 1.3% and 0.6% of patients, respectively. The pathological complete remission rate was 3.8%. At 3 years, an absolute progression-free survival difference of 7.2% was observed in all patients (hazard ratio [HR] 0.79) and in 9.2% of resected patients (HR 0.73) in favour of peri-operative chemotherapy. The study concluded that peri-operative chemotherapy should become a standard of care in patients with resectable liver metastases from colorectal cancer.

Comment: After several phase II trials and single-institution reports, this pivotal randomised trial confirms the advantage for use of peri-operative chemotherapy with resection of liver metastases in mCRC. The next step now is to evaluate how to best incorporate biological agents with this chemotherapy backbone and further trials are under way to try to specifically address that issue.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii 20 (Abstr O-0029)

An interim analysis of efficacy and safety from a randomised controlled trial of panitumumab with chemotherapy plus bevacizumab (BEV) in metastatic colorectal cancer (MCRC)

Authors: Hecht J et al

Summary: This interim report of a phase III trial evaluates the addition of panitumumab (a fully human monoclonal antibody that targets the epidermal growth factor receptor) to bevacizumab (BEV) plus chemotherapy (CT) in the first-line treatment of 1054 patients with metastatic colorectal cancer (mCRC). Patients received either q2w 5-FU/Ox (F/Ox, e.g. FOLFOX) or q2w 5-FU/Iri (F/Iri, e.g. FOLFIRI). All patients received a standard dose of BEV. Within each cohort, patients were randomised to receive concomitant panitumumab 6 mg/kg q2w or no additional treatment until disease progression or drug intolerability. For this report, the median follow-up time was 6.85 months. Median progression-free survival was inferior for patients receiving concomitant panitumumab, compared with those receiving CT+BEV alone (8.8 vs 10.5 months, hazard ratio 1.44). Median overall survival was 18.4 months for the panitumumab+CT+BEV arm and not reached for the CT+BEV combination. The toxicity rate was higher for the panitumumab+CT+BEV combination, with more patients in this cohort discontinuing chemotherapy earlier due to toxicity (mainly gastrointestinal) and a higher proportion of patients receiving panitumumab had to discontinue treatment due to disease progression (36% vs 27%).

Comment: These results on concurrent use of two biological agents with CT in first-line settings are clearly disappointing. This raises the question as to whether a sequential approach in regard to incorporating targeted agents in standard treatment of mCRC should be favoured. The results from similar studies that are currently still accruing patients are eagerly awaited

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii 21 (Abstr O-0033)

Cetuximab dose-escalation in MCRC patients with no or slight skin reactions on standard treatment (EVEREST)

Authors: Van Cutsem E et al

Summary: In this randomised phase I/II study, cetuximab dose-escalation was investigated in patients with epidermal growth factor receptor-expressing metastatic colorectal cancer failing irinotecan therapy. Cetuximab was delivered at an initial dose of 400 mg/m2 dose, then 250 mg/m2/w, with irinotecan (180 mg/m2 q2w) for 22 days. Patients who had not experienced >grade 1 skin reaction or any other >grade 2 cetuximab-related adverse event and were tolerant to irinotecan then commenced standard-dose cetuximab (250 mg/m2/w) (Arm A; n=45) or dose-escalation cetuximab (dose increased by 50 mg/m2 q2w, until >grade 2 toxicity, tumour response or maximum dose 500 mg/m2) (Arm B; n=44). Non-randomised patients continued standard-dose cetuximab (Arm C; n=77). Compared with standard-dose cetuximab, dose-escalation cetuximab was associated with a better preliminary response rate (13% vs 30%) and better progression-free survival (3.9 vs 4.8 months).

Comment: Positive correlation between grade of skin toxicity (rash) and the outcome has been previously observed. This is the first trial, however, to test this hypothesis in a more controlled manner. This study also raises the question as to whether this strategy should be incorporated in future studies involving cetuximab. Another option is different scheduling of cetuximab (2 weekly) and with a larger dose.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii 22 (Abstr O-0034)

The role of FDG-PET in the selection of patients with colorectal liver metastases

Authors: Ruers T et al

Summary: The purpose of this study was to evaluate the usefulness of FDG-PET scan in selecting patients for curative resection of liver metastases, using data from 203 patients who were selected for surgical treatment of colorectal liver metastases between 1995 and 2003. Group A comprised 100 consecutive patients who were selected for hepatic surgery by conventional imaging (CT chest and abdomen). Group B comprised 103 patients who had an additional FDG-PET scan with conventional imaging. At laparotomy, a greater proportion of patients in Group A than in Group B were considered inappropriate for further treatment (27.0% vs 20.4%). During surgery, more patients in Group A than in Group B showed extrahepatic abdominal disease (10% vs 1.9%). At 3 years, there was a trend to inferior overall (57.1% vs 60.1%) and disease-free survival (23.0% vs 31.4%) for Group A compared to Group B, but the differences were not statistically significant.

Comment: The study shows that FDG-PET scan in addition to conventional imaging might have a potential for reducing the number of futile laparotomies. However, the size of the effect was not enough to significantly impact on survival in this study. The next step should be to try to incorporate FDG-PET in larger randomised trials involving patients with potentially resectable liver metastases from colorectal cancer. A more important question would be to see whether FDG-PET could identify the patients who are not gaining any benefit from neoadjuvant chemotherapy, so they can proceed to surgery earlier.

Reference: *Annals of Oncology,* 2007 World Congress on Gastrointestinal Cancer, Vol 18 (Supplement 7), 2007: vii 22 (Abstr O-0035)

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