ESMO Conference Review

Colorectal Oncology

Summarising Significant Global Medicine ESMO, Istanbul 2006

In this issue:

Welcome

to a review of the ESMO conference. This is a focused summary of some of the most exciting clinical research on colorectal oncology presented at the European Society of Oncology Congress in 2006.

This Review has been created to allow those unable to attend, but with a keen professional interest in colorectal oncology, to access a summary of significant clinical studies presented that potentially affect current practice. Selection and review of the research is carried out independently by Dr David Porter, who recently attended the ESMO Congress in Turkey and Dr Shaun Holt. Wherever relevant the Review also provides website links to key studies in the field.

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

Kind regards,

Dr Shaun Holt
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First efficacy and safety results from XELOX-1/NO16966, a randomised 2x2 factorial phase 3 trial of XELOX vs. FOLFOX4 + bevacizumab or placebo in first-line metastatic colorectal cancer (MCRC)

Authors: Cassidy J et al

Summary: This study was established to build on previous phase 2 research exploring the comparable efficacy of XELOX with data already available on the efficacy of FOLFOX4. Phase 2 involved previously untreated patients with metastatic colorectal cancer and showed XELOX had similar efficacy to existing data on FOLFOX4. The addition of bevacizumab to XELOX treatment in the original study showed improvements in progression free survival. 1401 additional patients were recruited for the amended trial which was a 2-arm non-inferiority study exploring the potential improvements to progression free survival of adding bevacizumab to XELOX or FOLFOX4. Secondary endpoints included overall survival, overall response rate, time to failure, time and duration of response and safety. The results showed the primary endpoint of non-inferiority was met in terms of progression free survival. Also the addition of bevacizumab to XELOX or FOLFOX4 significantly improved progression free survival when compared with XELOX or FOLFOX4 plus placebo. As the median follow-up time was 18.6 months, overall survival data is not mature.

Comment: This large trial is important for 2 reasons. It demonstrates that the oral 5FU prodrug, capecitabine, is as effective as 48 hour infusions of 5FU when combined with oxaliplatin. The greater convenience and reduced resource utilisation involved with the oral therapy should make this the regimen of choice. Targeting the tumour vasculature with bevacizumab is also shown to help delay disease progression in these combinations, as it has with irinotecan/5FU combination.

Single-agent cetuximab as first-line treatment for elderly patients with advanced colorectal cancer, preliminary results of a TTD Phase 3 study

Authors: Sastre, J et al

Summary: This study was undertaken to explore the activity of cetuximab as a single therapy first-line treatment for elderly patients over 70. The authors acknowledged the importance of this special age group because of co-morbidities, altered drug metabolism and loss of functional capacity. 41 patients were included with a median age of 76 and 27% had undergone previous adjuvant chemotherapy. Patients received an initial dose of 400mg/m2 and 250 mg/m2 each week afterwards. 2 patients required dose reduction and 12 required a one week dose delay giving a median relative dose intensity of 80%. Toxicities were similar to other studies of cetuximab including rash, nail toxicities and infusion related toxicities. The overall response rate of those evaluable for effectiveness was 15.4% with tumour growth control of 54%. The authors concluded first-line treatment as a single agent was feasible in elderly patients.

Comment: The effectiveness of first line therapy with cetuximab in this trial in elderly patients does not seem greatly different to that demonstrated in other studies. The high cost of this agent, combined with the problematic skin rash it causes, make it an unattractive choice in this population.

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Cetuximab dose-escalation study in patients with metastatic colorectal cancer (MCRC) with no or slight skin reactions on cetuximab standard dose treatment (Everest): Preliminary PK and efficacy data of a randomised study

Authors: Van Cutsem, E et al

Summary: This randomised study explored the correlation between cetuximab dose escalation on epidermal growth factor receptor (EGFR) expression and later signalling in skin/tumour biopsies in people with EGFR-expressing metastatic colorectal cancer. Patients were recruited with at least one lesion suitable for biopsy and randomised to either a standard dose arm, an escalating dose arm, or those not randomised remained on the standard regimen. Patients in the escalating dose arm displayed significantly greater response rates than the randomised standard dose arm, over half reaching the maximum dose with no safety concerns. The escalating dose arm displayed similar rates of grade 3/4 skin reactions as the non-randomised arm with the standard dose arm showing 0% grade 3/4 skin reactions. The authors concluded those who exhibit mild or no reaction to standard cetuximab treatment have better tumour response rates through dose escalation.

Comment: Skin rash is common in therapies acting via the EGF receptor and is dose dependent. It is associated with better treatment outcomes in colorectal cancer patients treated with cetuximab. In this trial, treatment with escalating doses until the development of skin toxicity is superior to fixed dose administration. This approach should now be considered for all patients undergoing therapy with cetuximab for colorectal cancer.

Prediction of response to 1: ST line palliative chemotherapy by sequential F-18-fluorodeoxyglucose positron emission tomography in patients with advanced-stage colorectal cancer

Authors: Bystrom, P et al

Summary: This study was undertaken to explore whether the addition of fluoro-18-deoxyglucose positron emission tomography (FDG-PET) to standard CT/MRI scanning early in treatment can more accurately predict response to palliative chemotherapy. 57 patients received combination irinotecan with 5FU and folinic acid in a randomised trial using the Nordic schedule or de Gramont schedule. FDG-PET of the abdomen and thorax was carried out before treatment and after the second chemotherapy cycle. Variations in tumour FDG uptake were compared with best radiological response as a reference. The results showed a close relationship between metabolic response and best objective therapy response according to RECIST criteria. Time to progression and overall survival were longer for metabolic responders with a significant correlation apparent for overall survival. The authors concluded reduced metabolic activity after 2 therapy cycles correlated with best overall response.

Comment: This is a carefully performed trial that offers the prospect that PET scanning early in a course of chemotherapy will determine the benefit of therapy sooner than may be possible with conventional CT scanning. In this way patients destined to not respond may be spared additional chemotherapy related toxicity, while at the same time reducing ineffective healthcare expenditure. PET also offers the prospect of improved selection of candidates for liver resection. These are valuable messages at a time when the introduction of PET scanning to New Zealand is under active consideration.

Irinotecan in first line therapy of elderly patients with metastatic colorectal cancer: metaanalysis of four trials

Authors: Folprecht, G et al

Summary: This metaanalysis was undertaken to identify the differences in benefits and common side effects displayed according to the age of patients when using irinotecan in combination as first-line therapy. First line therapy of irinotecan has shown improved response rates and progression free survival in three previous randomised studies. The trials analysed were Saltz 2000, Douillard 2000 and Kohne 2005 together with one phase 2 trial Sastre 2005. Results from 303 patients over 70 and 1181 under 70 were included producing overall response rates of 39.5% and 33.1% respectively. Progression free survival was 6.7 and 5.7 months respectively and overall survival 15.9 and 15.4 months. Both neutropenia grade 3/4 and stomatitis grade 3/4 were more common in elderly patients. The authors concluded neutropenia and stomatitis were moderately increased in elderly patients but that they benefited from irinotecan/5-FU in a similar way to younger patients. They suggest (fit) elderly patients should be offered irinotecan therapy in the same way younger patients were.

Comment: There is often hesitance or reluctance to use irinotecan based chemotherapy combinations in those over 70 because of concerns about the consequence of side effects such as diarrhoea in this age group. This analysis of four major trials suggest that a rethink is required, at least in those who would meet the eligibility criteria for these trials. The toxicity profile in this age group is not momentously different to that seen in those aged less than 70, and the benefit of therapy is identical. Care should continue to be exerted in less fit candidates.

Randomised phase 3 trial comparing irinotecan plus capecitabine (Xeliri regimen) vs. irinotecan, 5-FU and folinic acid (Saltz regimen) as first-line treatment in patients with metastatic colorectal cancer

Authors: Munoz, A et al

Summary: The focus of this study was to compare the safety and efficacy of the Xeliri and Saltz regimens for metastatic colorectal cancer. The authors rationale was with the Saltz regimen traditionally the standard first-line treatment, the Xeliri combination would offer a potentially more convenient option if it produced comparable safety and efficacy. Target recruitment for the study was almost 350 patients but recruitment was stopped after low rates producing only 61 patients. Enrolled patients received Xeliri combination every 3 weeks or Saltz every 6 weeks. Treatment was maintained until disease progression, unacceptable toxicity or withdrawal of consent. Overall response rates for Xeliri and Saltz were 39% and 27% respectively, median time to progression 8.2 vs. 4.3 months and 1-year survival 72% vs. 60%. The analysis of grade 3/4 toxicities produced no statistically significant differences and the conclusions were the Xeliri regimen was at least as effective as Saltz and better tolerated with Xeliri.

Comment: It's a great shame that recruitment targets in this trial were not met. Nonetheless treatment with the Xeliri regimen appears to be at least as effective as the Irinotecan and 5FU combination. This is achieved without any appreciable change in the side effect profile. The greater convenience and reduced resource utilisation associated with Xeliri make it a better choice for the treatment of metastatic colorectal cancer than the Saltz regimen.

Two doses of oxaliplatin plus capecitabine as first-line treatment for advanced colorectal cancer patients

Authors: Ibeas, R et al

Summary: This study was undertaken to explore the activity and tolerability of an oxaliplatin plus capecitabine (OX/CAP) combination in advanced colorectal cancer. The first half of patients received OX 130mg/m2, 3-hour IV, day 1 plus CAP 1000mg/m2 twice daily from day 2 to 15 (3 week cycle). The authors conducted an interim analysis which indicated one third of patients needed a reduction in OX dose because of neurotoxicity. The second half of patients were therefore started on a dose of OX 85mg/m2, 2-3hour IV, day 1 with the same dose of CAP. Results led the authors to conclude that, for advanced colorectal cancer patients, lower dose oxaliplatin in combination with capecitabine provided similar effectiveness data as the same combination with higher dose oxaliplatin and with lower toxicity.

Comment: A poke in the eye for the concept of relative dose intensity, at least with oxaliplatin. Toxicity was much reduced in the group receiving the lower (85mg/m2) dose of oxaliplatin, particularly the troublesome problem of neurotoxicity. In spite of the reduced actual dose intensity in this group, the efficacy was not less than in the higher dose arm.

Independent commentary by Dr David Porter

Research Review publications are intended for New Zealand health professionals

Capecitabine vs. bolus 5-FU/LV as adjuvant therapy for patients with Dukes' C colon cancer: Pharmaco-economic evaluation of X-ACT trial data from a Czech perspective

Authors: Jiraskova, L et al

Summary: According to previously published data, capecitabine use as an adjuvant treatment for colon cancer produces at least equivalent disease free survival and improved safety profile when compared with bolus 5FU/LV (Twelves et al. NEMJ 2005;352:2696-704). It also showed improved relapse free survival and improved covariate-adjusted overall survival. In this study, the authors have used this previous study data to evaluate the cost-effectiveness from a Czech perspective including drug costs, administration/secondary care costs and also the cost to patients/society of travel and time commitments for patients. Despite the higher initial drug costs, this was offset by reduced administration costs and improved outcomes leading to lower costs of ongoing care. Inclusion of the societal costs showed the oral therapy capecitabine provided a significant cost saving over bolus 5FU/LV. The authors concluded the pharmacoeconomic analysis supported the replacement of bolus 5FU/LV with oral capecitabine for adjuvant treatment of colon cancer in the Czech Republic.

Comment: This report reinforces the critically important message that more than drug acquisition costs should be considered when new therapies are being purchased or false economies may result. Capecitabine is at least as effective as 5FU in adjuvant therapy for colorectal cancer, but drug costs are more expensive for the newer agent. These are offset by the reduced nursing and building space requirements for oral therapy. Capecitabine is a particularly attractive option for those living in rural areas, where weekly trips over several months to remote hospitals for chemotherapy are not always feasible.

Results of an interim analysis of a multinational randomised, double-blind, phase 3 study in patients with previously treated metastatic colorectal cancer (MCRC) receiving FOLFOX4 and PTK787/ZK or placebo

Authors: Koehne, C-H et al

Summary: This study involved 855 patients with metastatic colorectal cancer and the use of a novel oral therapy PTK787/ZK or placebo in addition to FOLFOX4 treatment. PTK787/ZK is intended to inhibit tyrosine kinase signalling of all known VEGF receptors. The interim results showed overall survival in the PTK787/ZK arm was 12.1 months vs. 11.8 for placebo. The authors suggest there is a low probability of the mature data indicating a significant difference in overall survival. Response rates were similar in each arm and progression free survival was longer in the PTK787/ZK arm (5.5 months vs. 4.1 months). Those with high LDH showed increased progression free survival when using PTK787/ZK (5.6 months vs. 3.8 months) and improved overall survival (9.6 vs. 7.5 months). The primary endpoint of overall survival was not met but progression free survival was improved in the general population and particularly for those with high LDH.

Comment: This is a surprisingly disappointing outcome with the addition of PTK787/ZK to standard chemotherapy. This small molecule targets the VEGF receptor, so a benefit from its use was anticipated, considering the activity of bevacizumab when combined with similar chemotherapy regimens.

Phase 2 clinical trial of weekly oxaliplatin concurrent with capecitabine plus pre-operative radiotherapy in locally advanced resectable cancer, Spanish cooperative group for gastrointestinal tumour therapy

Authors: Majem, M et al

Summary: This study aimed to assess the effectiveness of the preoperative use of oxaliplatin with capecitabine and radiation therapy for patients with locally advanced resectable rectal cancer. 43 patients underwent preoperative treatment and these interim results included 30 patients. Patients had surgery after 6-8 weeks of treatment. The primary endpoint was the pathalogic complete response. Secondary endpoints were toxicity, rate of complete resection, local and distant relapse rate and overall survival. Of the patient data examined at the time of presentation the overall response rate was 83.3% with a pathologic complete response rate of 16.7%. Interim conclusions were that this approach appeared to be effective for locally advanced resectable rectal cancer and the safety profile was favourable.

Comment: The logic of replacing prolonged infusions of 5FU with capecitabine and adding oxaliplatin to a combined chemoradiation protocol in rectal cancer is immediately obvious. The results of this trial are highly encouraging, but further evaluation in Phase III trials is needed to prove whether this is a genuine step forward in the treatment of rectal cancer.

Full abstracts featured in this Conference Review are available at: http://annonc.oxfordjournals.org/content/vol17/suppl_9/index.dtl?etoc