X-ACT: An important step on an unfinished journey

The adjuvant chemotherapy treatment of stage III colorectal cancer has saved thousands of lives over the last 20 years since the first evidence of the benefit of 5FU and levamisole was reported [1]. The benefit from 5FU based regimens is risk related. Collated data, analysed by the ACCENT investigators from eight years of follow up for 20,898 patients in 18 randomised trials of 5FU based chemotherapy versus control, showed that the absolute improvement in overall survival was 10% for patients with stage III colorectal cancer [2]. Since those initial studies and the refinement of them to the standard of care in the mid to late 1990s of 6 months therapy with bolus 5FU and leucovorin (5FU/LV) regimens, there have been only two practice changing sets of evidence in this field of practice. The first was the introduction of an oral alternative to the bolus 5FU/LV regimens, using either capecitabine or Uftoral [3,4] and the second the introduction of oxaliplatin [5-7].

In a recent edition of Annals the long term outcomes of the X-ACT trial were reported, which confirm the non-inferiority of the oral 5FU prodrug, capecitabine, in comparison with one of the previous international standards, the Mayo clinic bolus 5FU/LV regimen in the adjuvant treatment of stage III colorectal cancer [8]. The X-ACT trial recruited about 2000 patients from many countries internationally, between 1998 and 2001 and has now been extensively reported. The characteristics of the patients in the study were well balanced, with if anything slightly worse prognostic factors in the capecitabine group, though with no statistically significant differences. Elevated CEA was present in 8.6% of the capecitabine group compared to 7% of control; N2 disease (four or more involved nodes) was present in 30.8% versus 29.4% respectively.

The primary endpoint of the X-ACT trial was 3 year disease free survival (DFS) and the statistical plan required 632 events to exclude a non-inferiority margin of 1.25 with a type 1 error of 2.5%. At the time of original publication, 728 DFS events had occurred and 427 patients had died and the data confirmed the primary hypothesis of non-inferiority of capecitabine compared to 5FU/LV [3]. The selection of such a wide non-inferiority margin is worth consideration. If the upper limit of the 95% confidence interval of the hazard ratio had been 1.24, the primary endpoint of the trial would have been met. However there would have been a chance that the outcome with capecitabine was inferior to 5FU/LV by 24%, sacrificing nearly a quarter of the benefit of adjuvant therapy. Had the results turned out that way there is a question as to whether clinical practice would have changed so significantly on the basis of this trial. In fact, the upper limit of the confidence interval of the hazard ratio was 1.00 (HR 0.87 (0.75–1.00) p < 0.001) and the question is rather whether capecitabine may be superior to 5FU/LV rather than simply non-inferior.

In the long term follow up reported now, the database was closed in June 2007 with 6.9 years median follow up at which time 670 patients had died, 319 patients (32%) in the capecitabine arm and 351 patients (36%) in the 5-FU/FA arm. It is remarkable that it has taken nearly 5 years from database closure to see the results published. For this overall survival analysis, a non-inferiority margin of 1.14 was predefined. The results confirm the findings of the 3 year DFS analysis, in that the hazard ratio for overall survival for capecitabine versus 5FU/LV was 0.86 (95% CI, 0.74–1.01); the upper limit of the 95% CI was significantly less than the predefined non-inferiority margin of 1.14 (p < 0.001). This trial therefore adds to the growing confidence in 3 year disease free survival as a good surrogate for 5 year overall survival for adjuvant chemotherapy trials in colorectal cancer [9].

So is capecitabine superior to 5FU/LV? From a pure statistical perspective, the answer has to be No on the basis of this analysis. The test for superiority showed only a trend (p = 0.06). However the point estimate of the hazard ratio was 0.86, indicative of a useful effect of a 14% reduction in risk of dying with capecitabine rather than 5FU/LV. The validity of switching the objective of a comparison from a non-inferiority trial to a superiority trial has been discussed by the Committee for Proprietary Medical Products of the European Agency for the Evaluation of Medicinal products (EMEA)[10]. They conclude it is feasible provided the trial has been properly designed and carried out in accordance with the strict requirements of a non-inferiority trial. Further actual p-values...
for superiority must be presented to allow independent assessment of the strength of the evidence. Finally the analysis according to the intention to treat principle must be given greatest emphasis (rather than the per-protocol analysis which is equally important for a non-inferiority trial). The X-ACT trial conforms to these criteria and with further follow up it is very likely that the current point estimate of the hazard ratio (currently 0.86) will remain the same but the confidence intervals will narrow resulting in a significant p-value for superiority. This view is supported by the multivariate analysis in which the allocation to capecitabine is statistically significant (overall survival HR 0.826 [0.705-0.971]; p 0.0203).

Examination of the survival curves shows that the capecitabine curve is visibly separable from the 5FU/LV curve right out to 7 years. So with these provisos and with further follow up, it is quite likely that superiority will be shown.

What about toxicity? The toxicity data was published in 2002 [11] and showed less adverse events than the Mayo clinic schedule, which is no great recommendation.

The toxicities experienced by patients taking capecitabine are particularly hand foot syndrome (HFS or palmar plantar dysaesthesia), diarrhoea and cardiotoxicity. It is now established that there is very significant variation in toxicity experienced by patients around the world [12]. Whether this is due to variation in folate supplementation in the diet or to pharmacogenomics variance is unclear. However it is certain that patients vary very markedly in their tolerance of this agent.

Hand Foot syndrome (HFS) is highlighted in this report and is suggested to be a pharmacodynamics biomarker for increased efficacy. What is the data? In patients with no HFS on capecitabine (40% of the population) a DFS of 55.5% was observed and this is comparable to the DFS of 54.5% in the 90% of patients with no HFS on 5FULV (HR 1.01 (0.85–1.21)). In contrast, the 60% of patients with capecitabine induced grade 1-3 HFS had a DFS of 61.3%, compared with 56.2% in the 10% of patients with 5FU/LV (HR 0.83 (0.6–1.15)). Thus for patients with grade 1-3 HFS treated with capecitabine there is about a 5% increment in outcomes of DFS and OS compared to those treated with capecitabine without any HFS and those treated with 5FULV whatever the cutaneous toxicity.

What do we learn from this? HFS is a dose related toxicity of chronic infusions of 5FU as originally described by Lokich [13]. The dose intensity of that regimen usually given at 300mg.m-2 and those treated with 5FULV whatever the cutaneous toxicity is a hallmark of the particular chronicity of thymidylate synthase inhibition that is a consequence of the continuous intravenous administration or the 2 weeks duration of capecitabine dosing.

Is this a useful biomarker and does it inform clinical practice in any way? Firstly the authors and the data reassure us that even those receiving capecitabine with no HFS are obtaining the same benefit from adjuvant chemotherapy as if they were having the 5FU/LV regimen. Could such patients obtain improved outcome if the capecitabine dose is escalated to achieve grade 1 HFS? This is an intriguing possibility for which there is no data. Secondly, what of those patients who experience HFS? The authors show that those patients who require a dose delay, modification or interruption have marginally improved outcomes compared to those requiring no dose modifications [8]. This finding is not seen with any clarity in the similar comparison with the 5FU treated patients. Therefore it appears that the development of HFS may be a type of pharmacodynamic marker. The data suggests that it is appropriate to reduce the capecitabine dose in patients who develop HFS and be confident that by so doing we are not harming the patient’s outcome. However, caution is required as the statistical validity of this finding cannot be considered to be proven. There is improvement in outcome in those patients with HFS due to capecitabine is not statistically significant and no test for interaction has been performed to confirm this finding as a predictive biomarker.

The second toxicity which can cause major problems with capecitabine as with 5FU is diarrhoea. This is well known, can be catastrophic and occasionally fatal. A particular concern with capecitabine is in those patients with ileostomies in whom a vicious circle of increased ileostomy output, dehydration of which the patients may not be aware, gradual worsening renal function, impaired renal excretion of capecitabine and its metabolites, with accumulation of those metabolites, worsening GI toxicity and collapse. The only remedy to avoid this situation which can creep up unobserved is continual vigilance and repeated instructions to patients to maintain full hydration and control their gastrointestinal output by loperamide or other anti-diarrhoeals.

Finally cardiac toxicity is a well-known toxicity of all fluoropyrimidine therapy, and it is a chastening experience for any oncologist if a patient dies due to a myocardial infarct during adjuvant therapy. There is no clear data to indicate this is more common with capecitabine than with other fluoropyrimidine based adjuvant therapies. However, the oral dosing at home means that the patient is more likely to be away from hospital care if they do develop chest pain secondary to coronary artery spasm. Again, good patient information and clinician awareness is vital to ensure that such symptoms are properly investigated and further fluoropyrimidines avoided or used with extreme caution if chest pain that cannot be confidently diagnosed of a non-cardiac cause occurs.

Perhaps the most controversial issue that has been raised in this paper is the issue of age and the degree of benefit which occurs in patients over the age of 70, which of course is more than half the patients who develop colorectal cancer in the population. In 2009 an analysis form the ACCENT database examined data from over 10,000 patients under 70 and 2170 patients over 70 of whom three quarters had stage 3 disease from 6 phase 3 adjuvant trials comparing regimens including newer agents to 5FU/LV [14]. For oral chemotherapy agents including capecitabine and UFT (in whom we are considering non-inferiority comparisons rather than superiority), in patients over 70, point estimates for the hazard ratio were 1.19 with the upper bound of the confidence intervals of 1.57 for overall survival, and similar data was obtained for RFS and DFS. The risk of death was increased from 1.68% to 2.5% in the over 70s (p 0.4) and though the difference lacks statistical significance, this consideration should be factored into our patient consultations. For oxaliplatin and irinotecan containing
regimens, no evidence of the expected superiority of the novel adjuvant therapy was demonstrated [14].

The age related 5 year survival data from the X-ACT trial presented in the updated report is interesting [8]. For those aged under 40 (only 79 patients in the trial) the 5 year survival for capcitabine was 79.1% compared with 65.6% for 5FU/LV (HR 0.65 [0.30–1.44]). For those between 40 and 69, who comprise the majority of the population in the trial, the 5 year survival on capcitabine was 70.9%; compared to 68.6% with 5FU/LV (HR 0.87 [0.73–1.04]). All these patients would now be routinely treated with oxaliplatin plus fluoropyrimidine regimens so these data are of less ongoing clinical relevance. This trial includes 396 patients aged between 70 and 75 in whom the 5 year survival was 68.8% with capcitabine and 65.0% with 5FU/LV (HR 0.91 [0.65–1.26]). So, although the hazard ratios in this older group are nearer to 1 than in the younger patients, there is still ample confidence that capcitabine is non-inferior to 5FU/LV in this group.

In the clinic there are several issues to be borne in mind. Firstly, renal function deteriorates as a function of age, and toxicity from capcitabine will increase so dose modification in the light of accurately assessed renal function should be used. Secondly, competing causes of death become increasingly common in the elderly. Thus it has been reported that patients 50 years old or younger had a 2% chance of death unrelated to cancer while those >70 years had a 13% chance [15]. To this should be added the slightly increased risk of toxicity related death in the elderly. Given the uncertainty about the superiority of oxaliplatin based adjuvant therapy in the elderly, for many stage III patients over the age of 70 capcitabine offers an acceptable and highly effective adjuvant therapy which is increasingly widely used.

The X-ACT trial has been of immense importance in the evolution of adjuvant therapy in colorectal cancer. It has shown that an oral therapy provides at least equivalent survival benefit compared to the previous bolus 5FU/LV regimens. This finding has led to widespread uptake in geographical areas where the toxicity profile is good to intermediate, though concerns remain because of the high toxicity experienced in patients in the USA. To this should be added the economic [16] and patient acceptability [17] perspectives which for many patients has reduced the burden of adjuvant treatment This follow up study confirms that 5 year survival data confirm the earlier report of DFS that capcitabine is non-inferior to the previous international standard regimen.

However, we must not be complacent because we are now at a standstill on further improvement in the adjuvant therapy of colorectal cancer following the failure of recent trials of the addition of biological to chemotherapy. There are several potential directions for research going forward. The current international focus is on testing the reduction in duration of oxaliplatin based adjuvant chemotherapy from 6 to 3 months such as the SCOT trial [18]. The use of aspirin in colorectal cancer as an adjuvant is the subject of a major international trial application currently and the recent publication showing that regular use of aspirin was associated with a reduced proportion of cancers with distant metastasis (OR 0.69, 95% CI 0.57—0.83, psig < 0.0001, phet = 0 · 89, five studies) supports this concept [19]. Stratification of colorectal cancer by molecular biomarkers has altered practice in metastatic disease. The observation that patients with mismatch repair deficient stage II cancer may not need adjuvant treatment because of the markedly improved survival [20] has introduced this into the adjuvant setting. The hope that demonstration of efficacy in advanced disease may translate in benefit in the adjuvant in biomarker defined populations failed with cetuximab in the NO147 trial [21] but still holds promise for differing combinations and other therapies. The adjuvant treatment of stage III colorectal cancer represents both one of the major opportunities but also one of the main challenges for our field to further reduce relapse after initial successful resection in node positive patients. The X-ACT trial was one important landmark on this journey.

Disclosure

The author has no disclosures to declare

T. Maughan*
Clinical Oncology, Gray Institute for Radiation Oncology and Biology, University of Oxford, Oxford OX3 7DQ, UK
*e-mail: tim.maughan@oncology.ox.ac.uk

References


13. Lokich JJ, JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. JCO April 1989 vol. 7 4425–43


18. SCOT – Short Course Oncology Therapy: a study of adjuvant chemotherapy in colorectal cancer by the CACTUS and QUASAR3 groups. http://www.controlled-trials.com/ISRCTN59757862


21. Alberts SR, Sargent DJ, Smyrk TC. Adjuvant mFOLFOX6 with or without cetuximab (Cmab) in KRAS wild-type (WT) patients (pts) with resected stage III colon cancer (CC): Results from NCCCTG Intergroup Phase III Trial N0147. J Clin Oncol 28:18s, 2010 (supp; abstr CRA3507).