Colorectal Discovery

A two-centre experience of transanal total mesorectal excision

Buchs NC, Wynn G, Austin R, et al.
Colorectal Dis.
2016 Dec;18 (12):1154-61.

Transanal total mesorectal excision (TaTME) offers a promising alternative to the standard surgical abdominopelvic approach to rectal cancer. Our aim has been to report a two-centre experience of the technique, focusing on short-term and oncological outcome. A total of 40 selected patients with histologically proven rectal adenocarcinoma underwent TaTME in two institutions from May 2013 to 2015. Forty patients (80% men, mean body mass index 27.4 kg/m^2) requiring TME underwent TaTME. Procedures included low anterior resection (n=31), abdominoperineal excision (n=7) and proctocolectomy (n=2). A minimally invasive approach was attempted in all cases, with three conversions. The mean operation time was 368 min; 16 patients (40%) had a synchronous abdominal and transanal approach. No mortality and 16 postoperative complications occurred, with only 69% being minor. The median length of stay was 7.5 (3–92) days. A complete or near-complete TME specimen was delivered in 39 (97%) cases with a mean number of 20 lymph nodes harvested. R0 resection was successful in 38 (95%) patients. In the follow-up period (median 10.7 months), there were no local recurrences, but 6 (15%) patients had developed distant metastases.

Reviewer's comments: This paper is a short presentation of two-centre experience at doing TaTME operations for rectal cancer. TaTME can be used to treat malignant or benign disease of the rectum. From the above series, hese investigators found TaTME safe, feasible, safe and reproducible, without compromising the oncological principles of rectal cancer surgery. TaTME came into existent to facilitate proctectomy in patients in whom laparoscopic dissection can be difficult because of a narrow pelvis, a high body mass index, or where the position of the tumourws low in the rectum. However, patients selection for this series, even though predominantly male, had a mean BMI of <28kg/m^2, much less than in other reported series. The follow-up period in the series was short (median 10.7 months) and the median LOS in hospital of 7.5 days is comparable to laparoscopic low anterior resection in high volume centres. This paper highlights that, although the patients were selected carefully, the outcome is encouraging and provides further evidence of the feasibility and safety of the procedure. Current evidence on the safety and efficacy of TaTME to remove the rectum is limited in both quantity and quality. Therefore, it should only be used with special arrangements for clinical governance, consent and audit or research. TaTME aims to improve the clinical outcome of rectal excision, reduce the LOS in hospital and the post-operative morbidity. – TH

European Journal of Surgical Oncology

Intensified follow-up in colorectal cancer patients using frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging: Results of the randomised "CEA watch" trial

Verberne CJ, Zhan Z, van den Heuvel E, et al.
Eur J Surg Oncol.
2015 Sep;41(9):1188-96.

Purpose: The value of frequent Carcino-Embryonic Antigen (CEA) measurements and CEA-triggered imaging for detecting recurrent disease in colorectal cancer (CRC) patients was investigated to find evidence-based follow-up protoco in a randomised-controlled multicentre prospective study, using a stepped-wedge cluster design. From October 2010 to October 2012, surgically treated non-metastasised CRC patients in follow-up were checked in 11 hospitals. An intensified follow-up schedule consisting of CEA measurements every two months, with imaging in case of two CEA increases, was adopted. The primary outcome measures were the proportion of recurrences that could be treated with curative intent, recurrences with definitive curative treatment outcome, and the time to detection of recurrent disease. A total of 3,223 patients were included, of which 1,725 patients participated in both the control protocol and in intervention protocol; 1,182 patients participated only in the control protocol, and 316 patients participated only in the intervention protocol. In total, the control period comprised 2,907 patients and the intervention period 2,041 patients. A total of 243 (7.5%) recurrences were detected during the study; 104 (43%) were found while the patient participated in the control protocol and 139 (57%) were detected while the patient participated in the intervention protocol. Ninety (37%) of all recurrences could be treated with curative intent. Recurrences eligible for curative treatment during the intervention protocol was higher than in the control protocol (42% versus 30%). The proportion of curative treatment outcome was also higher in the intervention than the control (35% versus 22%). The proportion of recurrences that could be treated with curative intent was also significantly higher in the intervention protocol (OR=2.84, 95%-CI: 1.38–5.86, p-0.0048).

Reviewer's comments: This paper highlights the feasibility and effectiveness of an intensified protocol with CEA and assessment on CEA rise rather than absolute value in detecting recurrences earlier than the standard protocol, which is related to an increase in curable recurrence rate. In the trial, CEA slope analyses instead of absolute values and imaging in case of two subsequent CEA rises detects recurrences with a higher rate of curable options (42% versus 30%), higher rate of definitive treatment outcome (35% versus 22%) and less time-to-detection compared to a care as usual follow-up protocol. To date there has been no randomised trial for colorectal cancer follow-up with as many participants as in this case. Knowledge about intensive monitoring of CEA advances the diagnosis of recurrent disease, as is well known from the finding of previous CEA second look Trial (CEASL), in which detection was nine months sooner than clinical detection, as also from the FACS trial where it was 24 months sooner than control. However, this trial fails to answer, unlike contemporaries (CEASL, FACS), is whether early detection and treatment of recurrent disease translate into disease-free and/or overall survival benefits. Survival in metastatic disease is highly case-dependant, since in patients with fewer metastases, a longer

interval since primary resection, lesser or non-elevated CEA and a favourable metastasis biology, do better as far as observational studies are concerned. It will be interesting from this trial will be how Verberne et al. report on the disease-free and overall survival for each of the strategies. – TH

New England Journal of Medicine

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

Hortobagyi GN, Stemmer SM, Burris HA, et al.
N Engl J Med
2016, doi: 10.1056/NEJMoa1609709

Background: The inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6) could potentially overcome or delay resistance to endocrine therapy in advanced breast cancer positive for hormone receptor (HR) and negative for human epidermal growth factor receptor 2 (HER2).

Methods: We conducted a double-blind, placebo-controlled trial to assess the effect of the extended use of letrozole for an additional five years. Our primary end point was disease-free survival.

Results: In this randomised, placebo-controlled, phase 3 trial, we evaluated the efficacy and safety of the selective CDK4/6 inhibitor, ribociclib, combined with letrozole for first-line treatment in 668 postmenopausal women with HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received systemic therapy for advanced disease. We randomly assigned the patients to receive either ribociclib (600mg per day on a three-weeks-on, one-week-off schedule) plus letrozole (2.5mg per day), or placebo plus letrozole. The primary end-point was investigator-assessed progression-free survival. Secondary end-points included overall survival, overall response rate, and safety. A preplanned interim analysis was run on January 29, 2016, after 243 patients had disease progression or died. Prespecified criteria for superiority required a hazard ratio of 0.56 or less, with $p<1.29\times10^{-5}$.

Conclusion: Among patients receiving initial systemic treatment for HR-positive, HER2-negative advanced breast cancer, the duration of progression-free survival was significantly longer among those receiving ribociclib plus letrozole than among those receiving placebo plus letrozole, with a higher rate of myelo-suppression in the ribociclib group. (Funded by Novartis Pharmaceuticals; ClinicalTrials.gov)

Reviewer's Comments: The results of the preplanned interim analysis of the Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA-2) trial, which evaluated the efficacy and safety of the combination of ribociclib and letrozole as first line therapy in patients with HR-positive, HER2-negative advanced breast cancer, are encouraging.

In this multi-centre, double blind, phase 3 trial conducted in 29 countries, post-menopausal hormonal receptor positive, HER2 negative primarily stage IV breast cancer patients were randomly assigned to receive either oral CDK4/6 inhibitor ribociclib (600mg per day on a three-weeks-on, one-week-off schedule in 28-day treatment cycles) plus letrozole (2.5mg per day on a continuous schedule) or placebo plus letrozole. The ribociclib dose of 600mg per day was selected on the basis of results from a phase 1 study involving patients with advanced cancer. Ribociclib can be administered with or without food. Randomisation was stratified according to the presence or absence of liver or lung metastases. Patients received treatment until disease progression, unacceptable toxicity, death, or discontinuation of ribociclib or letrozole for any other reason. Dose reductions for only ribociclib (from 600 to 400 to 200mg) were permitted to manage treatment-related adverse events. Patients who discontinued either ribociclib or placebo were permitted to continue receiving letrozole. No treatment crossover was allowed.

The characteristics of MONALEESA-2 patients at baseline were well balanced on all accounts, with the median age of 62 years and PS 0, 1. It is noteworthy that patients with PS >2 were excluded. In real life, clinical practice assessment of performance status can, at times may not be as accurate as in a trial. This trial ensured that the patient's that were randomised included a high proportion who had disease that was expected to be sensitive to endocrine therapy (i.e., those with newly diagnosed advanced breast cancer or with a disease-free interval of >24 months).

There was unprecedented 44% improvement in PFS in the ribociclib group (as assessed by investigators), which was observed across all predefined subgroups (HR 0.56; 95% CI, 0.43 to 0.72; $P<3.29\times10^{-6}$ for superiority). The median duration of PFS was not reached in the ribociclib group and was 14.7 months in the placebo group. Preplanned subgroup analysis showed that the duration of PFS was longer in all subgroups receiving ribociclib, including those with newly diagnosed or pretreated metastatic disease, and those with or without liver or lung metastasis. Patients with measurable disease at baseline showed a significantly higher objective response rate to ribociclib plus letrozole compared to letrozole alone (53 vs. 37%; $p=0.00028$) as well as improved clinical benefit rate (80 vs. 72% $p=0.02$).

Most patients had an acceptable adverse-event profile with long-term administration of ribociclib plus letrozole. CDK4/6 inhibitors can cause bone marrow stem cell inhibition. Neutropenia (59 vs 1%) in the ribociclib arm occurred mainly within the first four weeks of treatment with five cases (1.5%) of febrile neutropenia. Like other CDK4/6 inhibitors when combined with aromatase inhibitors, grade 3 or 4 elevations of liver functions were low with ribociclib (9 vs 1%). Moreover, the majority of liver-enzyme increases were isolated, asymptomatic and reversible with dose adjustment. There were 7.5% of patients requiring permanent discontinuation of both ribociclib and letrozole because of adverse events and similar percentages due to decisions made by either patients or physicians in the two groups. Non-hematological adverse events in the ribociclib group were of grade 1 or 2, and grade 3 or 4 events were reversible by dose interruptions and reductions, which allowed most patients to remain on treatment. Prolongation of the QTcF interval, a dose-dependent side effect, occurred in 3.3% of patients treated at the 600mg dose of ribociclib, with changes mostly occurring within the first four weeks of treatment. Careful cardiac monitoring was essential, particularly for those on higher dose, and patients with cardiac dysfunction or at a higher

risk of cardiac impairment needed to be excluded.

Nearly one-third of early stage hormone receptor positive, HER2 negative patients relapse despite appropriate adjuvant therapy. Many relapses are due to distant visceral and/or bone metastasis, with a poor prognosis. Based on these results, the FDA has granted Breakthrough Therapy designation to ribociclib, a selective cyclin-dependent kinase inhibitor, in combination with letrozole for the management of locally advanced or metastatic breast cancer. These pivotal phase 3 results showing impressive early separation of the PFS curves are very encouraging and validate the use of CDK4/6 inhibitors on relapse. Monaleesa programme is evaluating ribociclib with fulvestrant and in the pre-menopausal age group. The main challenge will be selection between palbociclib (PALOMA), ribociclib (MONALEESA) and Abemaciclib (MONARCH) based on their efficacy, side effects and cost. The other problem is the lack of biomarkers to select patients who are going to get the most benefit. – SU

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

Mirza MR, Monk BJ, Herrstedt J, et al. Matulonis, for the ENGOT-OV16/NOVA Investigators.
N Engl J Med
2016; 375:2154-64.December 1, 2016. doi: 10.1056/NEJMoa1611310

Background: Niraparib is an oral poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) 1/2 inhibitor that has shown clinical activity in patients with ovarian cancer. We evaluated the efficacy of niraparib versus placebo as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer.

Methods: In this randomised, double-blind, phase 3 trial, patients were categorised according to the presence or absence of a germline *BRCA* mutation (g*BRCA* cohort and non-g*BRCA* cohort) and the type of non-g*BRCA* mutation and were randomly assigned in a 2:1 ratio to receive niraparib (300mg) or placebo once daily. The primary end-point was progression-free survival.

Results: Of 553 enrolled patients, 203 were in the g*BRCA* cohort (with 138 assigned to niraparib and 65 to placebo), and 350 patients were in the non-g*BRCA* cohort (with 234 assigned to niraparib and 116 to placebo). Patients in the niraparib group had a significantly longer median duration of progression-free survival than those in the placebo group, including 21.0 vs. 5.5 months in the g*BRCA* cohort (hazard ratio, 0.27; 95% confidence interval [CI], 0.17 to 0.41), as compared with 12.9 vs. 3.8 months in the non-g*BRCA* cohort for patients who had tumours with homologous recombination deficiency (HRD) (hazard ratio, 0.38; 95% CI, 0.24 to 0.59) and 9.3 vs. 3.9 months in the overall non-g*BRCA* cohort (hazard ratio, 0.45; 95% CI, 0.34 to 0.61; $P<0.001$ for all three comparisons). The most common grade 3 or 4 adverse events that were reported in the niraparib group were thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%), which were managed by dose modification.

Conclusion: Among patients with platinum-sensitive, recurrent ovarian cancer, the median duration of progression-free survival was significantly longer among those receiving niraparib than those receiving placebo, regardless of the presence or absence of g*BRCA* mutations or HRD status, with moderate bone marrow toxicity. (Funded by Tesaro; ClinicalTrials.gov number, NCT01847274.)

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Clinical Lymphoma, Myeloma and Leukaemia

Discontinuing Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukaemia: Current Understanding and Future directions

Bhalla S, Tremblay D, Mascarenhas J. Clinical Lymphoma, Myeloma and Leukaemia 2016; 16: 9: 488-94.

Background: Tyrosine kinase inhibitor (TKI) treatment revolutionised the treatment pathway for patients with chronic myeloid leukaemia (CML). First generation TKI imatinib, a competitive inhibitor of the ATP binding site on the BCR-ABL1 protein, showed a significant improvement in major molecular response (MMR) and overall survival compared to the previous standard of care interferon + cytarabine. Despite this, after 8 years of follow-up, 45% of patients had discontinued treatment due to intolerance/disease progression. This outcome drove the development of second generation TKIs dasatinib and nilotinib. Clinical trials have shown that these compounds induce a faster MMR and improved sustained response when compared to imatinib.

Responses are monitored according to hematological, cytogenetic and molecular responses. Molecular response is assessed according to international standards (IS) as the ratio of BCR-ABL/ABL. The first target is the 3 log reduction, major molecular response (MMR). More recently newer targets are recorded including MR4.5 (4.5 log reduction) and UMRD (undetectable minimal residual disease).

In patients achieving a sustained MMR, there may be a cohort who can successfully stop TKI treatment. This is an important consideration for the following reasons; patients on TKIs often have side effects that affect their quality of life; patients on TKIs often have problems with drug/drug interaction; treatment with TKIs can often impact on conception and pregnancy; the cost of TKIs are substantial as patients are expected to have nearly normal life expectancy and historically were expected to stay on treatment for life.

Methods: A review of all major clinical trials of TKI discontinuation was undertaken. In patients treated with imatinib, in all five discontinuation trials reviewed (STIM, TWISTER, A-STIM, STIM2, KID) patients were treated with imatinib for at least 36 months and had been in a MR4.5 or MR5 for >2 years. In patients treated with nilotinib, in the five discontinuation trials (ENESTfreedom, ENESTop, ENESTgoal, ENESTPath and Tiger) patients were treated with nilotinib for at least 12 to 24 months and had achieved either an MR4 or MR4.5 for at least 12 to 24 months. In patients treated with dasatinib, four trials were reviewed (DASFREE, EURO-SKI, STOP 2G-TKI, LAST). All but one had been on dasatinib for 36 months and had been in MR4 or MR4.5 for at least 12 to 24 months. Discontinuation was classified as a failure when there was a loss of MMR. Patients in on-going treatment free remission (TFR) were assessed. Patients who responded to re-introduction of TKI were recorded.

Results: OIn the imatinib discontinuation trials, the duration of follow-up ranged from 12 to 60 months. Treatment free remission ranged from 39 to 64%. Patients with an initial deeper response (UMRD or digital PCR negative group) had a higher probability of a sustained MMR off treatment. In the earlier studies (STIM and TWISTER), a proportion of patients had been previously treated with interferon as well as imatinib, which may have increased the chances of TFR through a cytotoxic T-lymphocyte driven mechanism. In all studies apart from STIM, 100% of patients who relapsed regained an MMR when imatinib was reintroduced.

In the European Stop Kinase Inhibitor (EURO-SKI) trial, prognostic markers that could potentially influence the rate of TFR were analysed. Duration of MR4 influenced TFR. In patients with MR4 for <5 years, 33/71 patients (46%) loss MMR within the first six months compared to 28/87 (32%) of patients who had an MR4 for >5 years (p= 0.07). In groups with different depths of molecular response at the time of discontinuation (MR4, MR4.5, MR5), there was no significant difference in relapse risk at six months.

In the KID study, patients in the digital PCR negative group had a higher chance of a sustained MMR than those in the digital PCR positive group (63.8 vs 37.5%, p=0.021).

In the STOP 2G-TKI study, second generation dasatinib and nilotinib were either used as first line treatment or after prior imatinib. The majority of relapses occurred in the first six months. Patients in a sustained MMR at six months had a high probability of TFR at 12 and 24 months (91.2 and 84.7%, respectively). In multivariate analysis, prior sub-optimal response or resistance to imatinib was associated with a significantly lower chance of a successful discontinuation of treatment.

Nilotinib and dasatinib induce a deeper molecular response when used in the front line setting. The findings of these studies in terms of TFR and response following re-introduction of TKI are currently outstanding.

Conclusion: The development and treatment of CML patients with BCR-ABL1 TKIs transformed the prognosis and outcomes in this patient group. Longterm, however, these treatments can have a significant impact on patientspatientshe prognosis and outcomes in this patient gff treatment and avoid adverse effects as well as reduce financial costs. These studies have shown that upto 40% of patients could qualify for a trial of TKI discontinuation with some patients achieving a stable remission off treatment. Further research is required to identify biomarkers or parameters that predict a stable TFR.

Reviewer's Comments: Tyrosine kinase inhibitors (TKI) have dramatically changed the landscape of treatment of patients with chronic myeloid leukaemia. This paper showed that certain patients can come off TKIs and achieve durable TFR, which is an important development. Treatment with both first and second generation TKIs, although associated with great success, have also been associated with considerable morbidity in a cohort of patients, with a reduced quality of life. These intolerances lead to non-compliance or even withdrawal from treatment with the devastating risks of disease progression in some patients.

The second generation TKIs, dasatinib and nilotinib, are associated with more rapid responses and deeper molecular responses. In younger patients, in whom fertility may be important, opting for a second generation TKI first line and planning discontinuation of treatment, once a stable MR4.5 or MR5 has been achieved, allows for a safe conception and pregnancy whilst the TFR is actively monitored.

There is an on-going debate over the optimal first line treatment for newly diagnosed CML patients. With imatinib coming off patent, drug costs will be dramatically reduced. Caution, however, is required in high risk patients in whom there is a reduced MMR rate when treated with imatinib compared to second generation TKIs. Patients who achieve an MMR with a second generation TKI after treatment failure with imatinib are less likely to have a sustainable TFR if they discontinue treatment. This could mean that the overall health costs will be greater as patients may need to continue with the second generation TKI long term.

As health care services become increasingly stretched, schemes in which high cost drugs can be discontinued and patients enter a period of active surveillance will be encouraged. Further trials that clearly identify those subgroups of CML patients that most benefit will be critically important. – FMW