Curing more colorectal cancer

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SUMMARY

Colorectal cancers (CRC) are among the top five causes of death due to cancer in India and in most parts of the world.[1,2] Although *The Cancer Genome Atlas* (TCGA) project did not reveal major differences in colon cancer and the rectal cancer genome,[3] cancer of these two sites are managed differently to avoid recurrences based on anatomical differences between the colon and rectum. Colon cancer is best treated by radical surgery including total mesocolic excision with adequate lymph nodal harvesting and is followed by adjuvant chemotherapy for those at high risk of recurrence.[4] Rectal cancer with threatened circumferential margins on pelvic MRI are best treated with preoperative chemoradiotherapy (CRT) followed by radical surgery that includes total mesorectal excision.[4] Gaps persist in our knowledge, including which patients with node-negative colon cancer can benefit from adjuvant chemotherapy; can capecitabine monotherapy replace 5-fluorouracil (5FU) infusion during neoadjuvant CRT of rectal cancer or will the addition of oxaliplatin to neoadjuvant CRT improve disease-free survival (DFS) and overall survival (OS)? The results of these two studies are likely to introduce some change in practice.

The first study by Dalerba *et al*. is a classical biomarker discovery and validation study that identifies a subgroup of patients with stage II colon cancer who could benefit from adjuvant chemotherapy. The investigators tested this in three steps. First, they identified clinically actionable biomarkers (i.e. markers for which a standardized diagnostic test is available) using Boolean logic analysis. After mining a large amount of data of 2329 human colon gene-expression array experiments, they identified 16 candidate genes, with only one gene encoding a protein that could be studied by means of immunohistochemical (IHC) analysis using clinical-grade diagnostic test: the *CDX2* gene is a master regulator of intestinal development and oncogenesis, and highly specific for the intestinal epithelium. Colon cancers without *CDX2* expression are often reported to have aggressive features. The lack of *CDX2* expression was restricted to a small subgroup of 87 of 2115 colorectal cancers (4.1%).

The authors then tested the prognostic association of *CDX2* with 5-year DFS in two independent patient datasets. Their analysis using the National Center for Biotechnology Information–Gene Expression Omnibus (NCBI-GEO; Discovery) dataset showed that the rate of 5-year DFS was lower among the 32 patients (6.9%) with *CDX2*-negative tumours than among the 434 (93.1%) with *CDX2*-positive tumours (41% *v.* 74%, p<0.001). The hazard ratio (HR) for disease recurrence among patients with *CDX2*-negative versus *CDX2*-positive tumours was 2.73 (95% CI 1.58–4.72, p<0.001) in their multivariate analysis, which included common confounding variables. To validate these results they determined CDX2 protein expression by IHC analysis using a validated anti-CDX2 monoclonal antibody in the human colon-cancer tissue microarray obtained from the National Cancer Institute–Cancer Diagnosis Program (NCI-CDP) dataset. They confirmed *CDX2*-negative tumours to have worse prognosis than *CDX2*-positive tumours, with lower 5-year DFS (48% *v.* 71%, p<0.001), lower OS (33% *v.* 59%, p<0.001) and lower DFS (45% *v.* 72%, p<0.001). The association remained significant in multivariate analyses. Exploratory evaluation in both the discovery and validation datasets suggested a positive association between the use of adjuvant chemotherapy and better DFS in the *CDX2*-negative subgroups.

Finally, the authors evaluated the predictive role of *CDX2* non-expression during adjuvant chemotherapy in a pooled database of historical cohorts of treated and untreated patients with the use of Kaplan–Meier curves and interaction tests. This experiment was done on an expanded database of 669 patients with stage II colon cancer and 1228 patients with stage III colon cancer by pooling data from four independent patient cohorts (NCBI-GEO, NCI-CDP, NSABP C-07 and Stanford Tissue Microarray Database [TMAD]). The results confirmed that adjuvant chemotherapy was associated with a higher DFS in both stage II (91% with chemotherapy *v.* 56% with no chemotherapy, p=0.006) and stage III (74% with chemotherapy *v.* 37% with no chemotherapy, p<0.001) of the *CDX2*-negative patient population. The benefit of DFS observed in the *CDX2*-negative cohorts was superior to that observed in *CDX2*-positive cohorts in both the stage II subgroup (p=0.02 for the interaction) and the stage III subgroup (p=0.005 for the interaction). Multivariate

analysis revealed that the superior DFS in the *CDX2*-negative patients receiving adjuvant chemotherapy was not confounded by conventional risk factors such as depth of invasion of the tumour (T3 *v.* T4), the number of lymph nodes resected at surgery (≥12 *v.* <12), and the number of metastatic lymph nodes (N1 *v.* N2). The authors concluded that patients with stage II colon cancer lacking *CDX2* expression can benefit from adjuvant chemotherapy.

The second study by Allegra *et al*. was a large phase 3 randomized clinical trial (RCT). This study started in July 2004 as a two-arm RCT and another intervention was added in October 2005 to create a 2×2 factorial design. In this trial, patients with rectal cancer with threatened margins (stages II or III with at least 1 cm lymph node on imaging) with ECOG performance scores of 0–1 were randomized. Initially, patients were randomized into two groups: group 1 received radiation therapy (RT)+5FU (225 mg/m^2 continuous intravenous (i.v.) infusion 7 days a week) and group 2: received RT+capecitabine (825 mg/m^2 orally twice a day throughout radiation 7 days a week). This study protocol was amended in October 2005 (15 months later), to add oxaliplatin (50 mg/m^2 i.v. weekly×5 during RT), creating a 2×2 factorial design with four treatment groups: RT+5FU (Group 3), RT+5FU+oxaliplatin (Group 4), RT+capecitabine (Group 5), and RT+capecitabine+oxaliplatin (Group 6). The daily dose of chemotherapy remained the same, but the number of days of capecitabine and 5FU treatment was reduced in all four arms from 7 days a week to 5 days a week, with administration of chemotherapy only on days of RT to reduce the incidence of severe diarrhoea. The primary end-point of this study was locoregional tumour control (LRTC) at 3 years. The secondary end-points were OS, DFS and time to locoregional recurrence (TLRR). All analyses were intention to treat. For final analysis, groups 1 and 3 and groups 2 and 4 were combined as 5FU and capecitabine arms, respectively (Table I).

The investigators enrolled 1608 patients from July 2004 to August 2010. There were no statistically significant differences between the arms using 5FU or capecitabine in the 3-year LRTC rates (11.2% *v.* 11.8%), 5-year DFS (66.4% *v.* 67.7%) or 5-year OS (79.9% *v.* 80.8%). There were no statistically significant differences between the arms using oxaliplatin or no oxaliplatin for the same three end-points of LRTC (11.2% *v.* 12.1%), DFS (69.2% *v.* 64.2%), and OS (81.3% *v.* 79.0%). The addition of oxaliplatin was associated with statistically significantly more overall and grade 3–4 diarrhoea. In an unplanned analysis, patients with high risk for recurrence (lymph node-positive and clinical stage T-III/IV disease) did not show any difference in locoregional control with or without oxaliplatin (HR 1.27, p=0.38).

As for adverse events, diarrhoea, fatigue and anal pain were the most common toxicities observed in all the groups. Overall grade 3 to 5 toxicities (primarily diarrhoea) were substantially greater in the oxaliplatin-containing arms. Peripheral neuropathy was observed in the oxaliplatin groups. There were more deaths in the capecitabine arms but were not statistically significant.

The authors state that the lack of complete information on the type and use of postoperative adjuvant therapy among the study participants is a drawback of their study. They conclude that this study establishes capecitabine with RT as the standard of care for managing rectal cancer in the preoperative setting. They also state that the addition of oxaliplatin to the preoperative CRT regimen did not improve the LRTC, DFS or OS for any patient risk group and resulted in increased toxicity.

COMMENT

Colorectal cancer is the third most common cause of cancer mortality in the world and the fifth common cause of cancer mortality in India.[1] Population-based survival data reveal that the ratio of mortality to incidence for CRC in India is very high.[2] Epidemiological data from several countries show that five practical considerations in the community can improve the cure rates for CRC.[4] These are: (i) use of preoperative MRI of the pelvis in all patients with rectal cancer to identify those with threatened margins; (ii) use of preoperative neoadjuvant CRT in those with threatened margins to reduce local recurrence; (iii) en-bloc total mesorectal excision along with the rectal cancer resection; (iv) total mesocolic excision to provide adequate yield of at least 12 lymph nodes for pathological evaluation; and (v) use of adjuvant chemotherapy in all lymph node positive and high-risk lymph node-negative colon cancers irrespective of age without any delay. These five practical measures must be implemented immediately in India.

The two studies provide high-quality evidence for changing practice while managing patients with CRC. Distant metastasis is the most common cause of treatment failure in colon cancer after curative resection. Postoperative adjuvant chemotherapy combinations (FOLFOX or CAPEOX) have consistently increased cure rates and have become the standard of care for more than a decade. Stage II (lymph node-negative) colon cancer is made up of a heterogeneous group of patients many of whom benefit from adjuvant chemotherapy. Much effort has gone into identifying the high-risk subgroup of stage II colon cancer, including molecular markers beyond the traditional risk factors including stage of

TABLE I. Summary of major findings from the study by Allegra *et al.*

Item	Final treatment arms			
	5FU+RT	5FU+oxaliplatin+RT	Capecitabine+RT	Capecitabine +oxaliplatin+RT
Patients enrolled	477	329	472	330
Patients analysed	474	327	466	328
Protocol compliance (%)	90	84	97	96
Primary and secondary end-points	Based on the 2×2 factorial design groups			
	5FU	Capecitabine	Oxaliplatin No	Oxaliplatin Yes
3 year-locoregional recurrence: All (R0-R2) resections (%)	11.2	11.8	12.1	11.2
3 year-locoregional recurrence: R0 resections (%)	4.0	3.9	5.1	3.1
5 year disease-free survival (%)	66.4	67.7	64.2	69.2
5 year overall survival (%)	79.9	80.8	79.0	81.3
Grade 3–5 toxicity (%)	31.9	39.0	28.3	40.9
Grade 3–5 diarrhoea (%)	15.6	17.1	6.9	16.5

5FU 5-fluorouracil RT radiotherapy

tumour, adequacy of lymph node harvest, presence or absence of obstruction and perforation. Among the molecular markers, the microsatellite instability (MSI) mutation testing and multigene panel have been gaining importance. Testing for MSI or expression of mismatch repair (MMR) protein in tumour samples by IHC is a simple, low-cost technique that helps in taking a decision on adjuvant chemotherapy.[5] Few smaller studies have reported an association between the absence of *CDX2* expression in colon cancer with poor prognosis.[6] The study by Dalerba *et al*. provides robust evidence by applying a stringent study design and using discovery and validation cohorts and then revalidating the predictive ability of *CDX2* in a larger cohort. *CDX2* expression by IHC is widely available at low cost and can be used in India. A major drawback is that *CDX2* mutation is found in <5% of colon tumours. Hence, a large number of patients need to be screened before identifying the few *CDX2*-negative patients suitable for adjuvant therapy.

The standard of care for rectal cancer with threatened margins is the use of neoadjuvant CRT followed by surgery. Although the OS with this approach has not improved significantly, the local recurrence (a major problem in patients with advanced rectal cancer) has been minimized and sphincter preservation has increased.[7] Further, the treatment-related toxicity of preoperative neoadjuvant CRT is less than that of postoperative adjuvant CRT. One practical difficulty is the need for continuous infusion of 5FU during CRT. This creates logistic issues and increases the costs from vascular access and hospitalization. The results of clinical trials trying to replace 5FU infusion with oral capecitabine, including a smaller phase 3 randomized trial, have been encouraging.[8] Many oncologists are already using oral capecitabine during CRT as an alternative. Allegra *et al*. convincingly establish oral capecitabine-based CRT as a new standard for patients with rectal cancer. Moreover, the better compliance with capecitabine-based CRT will lead to widespread use of neoadjuvant CRT in patients with locally advanced rectal cancer. The availability of high-quality generic capecitabine in India will reduce the cost of treatment. Less toxic and more convenient ambulatory CRT therapy will be welcomed by Indian patients as well as oncologists.

Allegra *et al*. have reported that the addition of oxaliplatin to the CRT regimen did not improve any of the primary or secondary outcomes and increased the toxicity. Results of six other randomized trials have also shown increased toxicity in the oxaliplatin-containing CRT regimen.[9–14] All in all, the efficacy data from these seven trials have been mixed. Most experts recommend not adding oxaliplatin to CRT outside the settings of a clinical trial, because the toxicity is worse with oxaliplatin-based CRT and the efficacy is not yet proven beyond doubt.

Evidence-based medicine is a science of uncertainty and an art of probability.[15] The final results of a German (CAO/ARO/AIO-04) trial recently reported the addition of oxaliplatin to 5FU-based neoadjuvant CRT, followed by total mesorectal excision and postoperative oxaliplatin-based adjuvant chemotherapy to have acceptable toxicity, low surgical morbidity and significantly higher DFS.[16] This study did have a small non-significant increase in deaths in the oxaliplatin arm from treatment-related causes, secondary malignancies, and associated illnesses. With a median follow-up of over 50 months, no significant improvement of OS was observed. Response rates are important when rectal surgery is not attempted in complete responders. The best standard combined modality treatment for improving OS of locally advanced rectal cancer remains elusive and the standard of care varies substantially across Europe and the Americas. The concept of total neoadjuvant treatment is currently being addressed in the CAO/ARO/AIO-12 randomized phase 2 study (*ClinicalTrials.gov*, number NCT02363374)

In conclusion, these two studies provide high-quality evidence for managing patients with colon and rectal cancers. This includes using oral capecitabine-based preoperative CRT for patients with locally advanced rectal cancer and the use of adjuvant therapy for patients with *CDX2*-negative stage II colon cancer. These easy interventions can improve the recurrence-free survival of thousands of patients with colon and rectal cancer in India.

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