Adjuvant chemotherapy in carcinoma colon: Is there a rationale to change practice for Asian patients?

Dear Editor,

The randomized trial evaluating the usefulness of Oxaliplatin in adjuvant chemotherapy for Stage II and III colon cancer published in the May 2013 edition of the journal by Shaiq *et al*[1] and the accompanying editorial[2] are interesting and once again bring into focus the controversies that exist in this area. There is definite consensus on the use of 5-Flourouracil (5FU) and Leucovorin (LV) -high/low dose based chemotherapy in the adjuvant setting in Stage III colon cancer. However the use of any adjuvant chemotherapy in Stage II colon cancer and the use of a third agent – Oxaliplatin in Stage III colon cancer have been the subject of debate for the last decade.

Two major trials evaluating addition of Oxaliplatin to the 5FU-LV backbone – the MOSAIC and NSABP Protocol C-07 in stage II and Stage III colon cancer in the adjuvant setting showed significant improvement in disease free survival confined to Stage III patients.[3,4] The MOSAIC trial maintained the DFS benefit at 6 years with a small but significant improvement in overall survival (OS) at 6 years. The C-07 protocol also showed significant improvement in DFS at 7 years, but did not demonstrate significant OS advantage. The results of these two trials have been discussed at length with consensus emerging regarding the use of an oxaliplatin based regimen in the adjuvant setting at least in stage III colon cancer. The use of oxaliplatin in Stage III (Duke's C) colon cancer was allowed by the National Institute for Health and Clinical Excellence (NICE) in 2006 as a part of 100th technology appraisal guidance and oxaliplatin based chemotherapy in the adjuvant setting in Stage III is currently recommended by most bodies. The use of any chemotherapy in Stage II colon cancer has been a similar area of intense debate with one trial – QUASAR – which enrolled Stage II colon cancer, showing an improvement in survival with the relative risk of death from any cause with chemotherapy versus observation alone being 0.82 (95% CI 0.70-0.95; (P=0.008) favoring adjuvant chemotherapy with 5FU and LV.[5] The other trials which included Stage II and Stage III patients did not show any improvement in DFS / OS for patients with Stage II disease with 5FU and LV chemotherapy or with addition of Oxaliplatin. The use of adjuvant chemotherapy in high risk patients with stage II disease defined by perforation/obstruction at baseline, <12 lymph nodes dissected, lymphatic/vascular emboli, mismatch repair (MMR) evaluation with Microsatellite Instability-Low (MSI-L) status etc are still areas that require more prospective data.

We recognize that the generation of evidence for adjuvant chemotherapy specific for Indian patients with colon cancer and the lack thereof is our responsibility and will require both trials initiated in India/Asia and more participation in global clinical trials designed to address these questions. In the light of deficient Asia specific data we will need to base our practice on the available evidence- even if the evidence is from the west. The use of oxaliplatin based chemotherapy either with 5FU LV backbone or with Capecitabine in Stage III colon is very common in the sub-continent. The cost considerations in Indian scenario are very different and the cost-benefit analysis and Cost per life year gained from the published studies may not be relevant. The cost of chemotherapeutic agents is much less in India with the availability of multiple generics as compared to the US/ western Europe as are costs of hospitalization and administration. The cost of chemotherapy and other medical care is largely borne by the patient/family in India. Furthermore the burgeoning economy has created a very large middle income group in India with increasingly large number of patients with adequate insurance cover. Many state governments (Eg: Andhra Pradesh, Tamil Nadu, Karnataka) have introduced insurance cover for cancer care as a private –public partnership and these schemes also allow the use of FOLFOX chemotherapy in the adjuvant setting in Stage III colon cancer. The State Government backed FOLFOX chemotherapy allows approximately Rs. 1,10000 ($2000) which includes costs of chemotherapeutic drugs and 12 infusions of FOLFOX (24 weeks of therapy). This is very largely utilized by the population below poverty line and these schemes have successfully delivered FOLFOX chemotherapy across the country to large numbers of stage III patients over the last 4 years. The costs of 12 infusions (24 weeks of therapy) of FOLFOX inclusive mediport placements/ infusion pumps in the privately run medical institutions and cancer centers ranges between Rs.1,70000 and Rs. 3,00,000 ($2900 -$6000) approximately. In patients who do not consent for mediport placements, the alternative regime of CapeOX is commonly employed and costs approximately Rs.1,30,000 and Rs. 3,00,000 ($2500 -$ 6000) for a total of 24 weeks of therapy. We strongly feel that that cost considerations, while essential in planning chemotherapy in Asia, should not be the only or even most important factor in deciding adjuvant chemotherapy in Stage II and III colon cancer. (The differences in above costs are due to the cost differences between Innovator drugs and generics and the differences in institutional billing practices)

While the strength of evidence for any adjuvant chemotherapy in stage II and the benefits of Oxaliplatin addition in Stage III colon cancer can be debated, these issues are as relevant globally as for Asian patients and the validity of the end points used in trials has been addressed with the meta-analysis by the adjuvant colon cancer end points (ACCENT) collaborative group.[6] The study published by Shaiq *et al.* uses FOLFOX 7 x 6 cycles

which is not the current practice in our patients especially in Stage II patients. It would also be interesting to know the delays due to myelosupression and G-CSF use in the FOLFOX 7 arm especially as the dose of Oxaliplatin used was 130mg/m^2 as opposed to the 85mg/m^2 that is used in FOLFOX 4 and mFOLFOX 6 which most of us are employing in adjuvant setting in India. Furthermore 92% patients in this study were in Stage II where we commonly use 5FU-LV/Capecitabine and not Oxaliplatin based regimes - FOLFOX x 12 / CapeOx x 8. We strongly agree regarding the need to select patients appropriately for adjuvant chemotherapy with the need to individualize decision in patients above the age of 70 yrs, patients with predilection for neuropathy, financial constraints etc. The MMR testing is not yet widely available and used in Indian patients yet and we will need to develop strategies to address this issue.

In this scenario we feel that the adjuvant chemotherapy in stage III patients should continue to be Oxaliplatin based regimens like FOLFOX 4/mFOLFOX 6/CapeOx for 24 weeks and the benefits/lack thereof in Stage II have to be discussed with patients and caregivers in India too, as in any other part of the world. Efforts to generate more evidence from India should continue and Shaiq et al have initiated the steps in the right direction and more collaborative work in this area is the need of the hour.

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