ESMO Open
Cancer Horizons

Shortening adjuvant chemotherapy in stage III colon cancer: are we ready for a change?

Desamparados Roda,[1] Fortunato Ciardiello,[2] Andrés Cervantes[1]

To cite: Roda D, Ciardiello F, Cervantes A. Shortening adjuvant chemotherapy in stage III colon cancer: are we ready for a change? *ESMO Open* 2018;**3**:e000392. doi:10.1136/esmoopen-2018-000392

Received 30 April 2018
Accepted 1 May 2018

[1]CIBERONC, Department of Medical Oncology, Biomedical Research Institute INCLIVA, University of Valencia, Valencia, Spain
[2]Oncologia Medica, Dipartimento di Internistica Clinica e Sperimentale 'F. Magrassi', Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy

Correspondence to
Professor Andrés Cervantes; andres.cervantes@uv.es

Oxaliplatin-based adjuvant chemotherapy for 6 months is considered the standard of care after a curative resection in patients with stage III colon cancer. The addition of oxaliplatin provides a benefit on overall survival confirmed in three randomised phase 3 trials[1–3] with an long-term absolute increase ranging from 2.7% to 6%. Since oxaliplatin was incorporated into the adjuvant setting more than a decade ago, the standard in adjuvant therapy has remained unchanged because of the lack of novel agents with relevant activity in this scenario. Unfortunately, this combination can have also acute and long-term side effects that can interfere with daily life activities in potentially cured patients. According to the MOSAIC trial, the incidence of grade 3 acute peripheral sensory neurotoxicity among oxaliplatin-treated patients was 12%, and a similar proportion developed chronic peripheral neurotoxicity that unpredictably could last for years.[1]

In addition, the risk and severity of oxaliplatin-induced sensory neurotoxicity is associated with the cumulative dose administered. This toxicity may sometimes increase several months after the last dose of the drug. It is always changing for a physician to predict the exact risk of a patient to develop oxaliplatin-induce neurotoxicity while they are on active therapy. Besides, there are no established methods for preventing chemotherapy-induced neuropathy other than limiting exposure. Therefore, the rationale to explore the impact of a shorter duration of oxaliplatin-based chemotherapy in the adjuvant setting is well justified.

If the role of oxaliplatin was assessed according to the last version of the ESMO-Magnitude of Clinical Benefit Scale,[4] the global benefit would have not obtain grade A, but B, because a 5% benefit on overall survival was only achieved by the XELOXA study[2] (6%) but not in the other two trials.[1 3] Moreover, HR for disease-free survival was 0.80 in the three referred trials, far from the 0.65 recommended to get score A. Another issue of interest, when the MOSAIC data were analysed at long-term follow-up, is that the benefit of the addition of oxaliplatin is almost lost in the subset of patients with N1 disease, but it largely maintains a significant improvement at 10-year survival of more than 12% in those with N2 disease.[5] As subset analysis, these findings are mainly hypothesis generating, but they certainly justify an stratified analysis for those patients with stage III with N1 versus N2 in current and future studies.

To investigate 3 months versus 6 months duration of adjuvant chemotherapy with FOLFOX or CAPOX, six randomised phase 3 trials were conducted concurrently across 12 countries.[6] This international proposal culminated in a prospective and independent academic collaboration, the The International Duration Evaluation of Adjuvant Therapy (IDEA) study, a pooled analysis of 12 834 patients enrolled across the six trials. In the publication of the final results of the IDEA collaboration, the non-inferiority of 3 months versus 6 months standard duration of treatment was not confirmed. In an exploratory analysis, 3 months of adjuvant chemotherapy met the predefined criterion for non-inferiority in patients who were at low risk for recurrence (T1–3 and N1), a subgroup that included nearly 60% of the patients in the trials. However, in high-risk patients (T4 or N2), 6 months of adjuvant chemotherapy was clearly superior. Side effects were significantly reduced with 3 months of therapy versus 6 months. Grades 2–3 neurotoxicity was substantially lower (16%) in the 3-month therapy, compared with the 6-month duration arm (47%).

These results on toxicity were reproduced in the Adjuvant Chemotherapy for colon cancer with HIgh EVidencE trial (ACHIEVE) trial by Kotaka *et al*[7] in this issue of *ESMO Open*. These authors confirmed that delivering adjuvant therapy for only 3 months reduced the incidence of key adverse events. More

importantly, a significant reduction by 23% in grades 2–3 acute peripheral sensory neurotoxicity was detected. In addition, the authors outlined the potential association between baseline creatinine clearance and some other adverse events in those patients receiving capecitabine therapy.

According to the last version of the ESMO-Magnitude of Clinical Benefit Scale, the global benefit of stopping adjuvant therapy at 3 months versus 6 months would achieve a grade B recommendation, as non-inferior in disease-free survival with significantly reduced toxicity was shown in the subset of low-grade stage III colon cancer. However, shortening therapy for high-risk patients could be inappropriate. During a recent ESMO expert-panel discussion, patients were classified as either 'fighters' or 'fatalists'.[8] Three months of treatment was considered standard for patients classified as fatalists, even if they had high-risk disease. However, those considered as 'fighters', would only receive 3 months of therapy if they had low-risk disease but would always receive 6 months of adjuvant treatment if they had T4 or N2 disease. However, how are we supposed to identify and select between fighters and fatalists? Are patient's attitude and personality enough arguments to finally decide regarding individual benefit from adjuvant chemotherapy? Certainly, although of importance, this is not the only point, but we should share with patients in an open conversation what we know and the data we have and how we interpret them. We are in a setting where shared decisions are always to be part our clinical routine.

Improvements in several areas are expected to impact in the selection of patients for adjuvant chemotherapy. The consensus molecular classification of colon cancer has to be further studied to confirm if it could give some level of prediction for patients belonging to the different groups.[9] Moreover, the definition of minimal residual disease is advancing and has to be better developed in a research setting to find a right position as a valuable tool in the clinical practice.[10] Novel biomarkers are really needed in this area, where decisions are mainly taken on the TNM staging system and some histological factors. We need precision medicine to come to this important area hoping to improve the balance among efficiency of the adjuvant treatment and the toxicity related to it.

Contributors All authors contributed equally.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES

1. André T, Boni C, Mounedji-Boudiaf L, *et al*. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343–51.
2. Haller DG, Tabernero J, Maroun J, *et al*. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol* 2011;29:1465–71.
3. Kuebler JP, Wieand HS, O'Connell MJ, *et al*. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 2007;25:2198–204.
4. Cherny NI, Dafni U, Bogaerts J, *et al*. ESMO-Magnitude of clinical benefit scale version 1.1. *Ann Oncol* 2017;28:2340–66.
5. André T, de Gramont A, Vernerey D, *et al*. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage ii to iii colon cancer: updated 10-year survival and outcomes according to braf mutation and mismatch repair status of the MOSAIC study. *J Clin Oncol* 2015;33:4176–87.
6. Grothey A, Sobrero AF, Shields AF, *et al*. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med* 2018;378:1177–88.
7. Kotaka M, Yamanaka T, Yoshino T, *et al*. Safety data from the phase III Japanese ACHIEVE trial: part of an international, prospective, planned pooled analysis of six phase III trials comparing 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer. *ESMO Open* 2018;3:e000354.
8. Sobrero A, Grothey A, Iveson T, *et al*. The hard road to data interpretation: 3 or 6 months of adjuvant chemotherapy for patients with stage III colon cancer? *Ann Oncol* 2018;29:1099–107.
9. Guinney J, Dienstmann R, Wang X, *et al*. The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015;21:1350–6.
10. Tie J, Wang Y, Tomasetti C, *et al*. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med* 2016;8:346ra92.