Editorial

# Histopathological regression after taxane based neoadjuvant chemotherapy in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma

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*Provenance:* This is a Guest Editorial commissioned by Section Editor Rulin Miao, MD [Key laboratory of Carcinogenesis and Translational Research (Ministry of education/Beijing), Gastrointestinal Tumor Center, Peking University Cancer Hospital & Institute, Beijing, China].

*Comment on:* Al-Batran SE, Hofheinz RD, Pauligk C, *et al*. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17:1697-708.

Received: 18 April 2017; Accepted: 19 April 2017; Published: 16 May 2017.

doi: 10.21037/tgh.2017.05.01

**View this article at:** http://dx.doi.org/10.21037/tgh.2017.05.01

We read with great interest the phase 2 randomized trial FLOT4-AIO. Al-Batran *et al*. have published the results of the phase 2 part of this phase 2/3 randomized controlled trial (RCT). They have compared FLOT (Docetaxel, Oxaliplatin, 5FU and leucovorin) regimen to the standard neoadjuvant regimen [ECX/epirubicin, cisplatin and 5-flourouracil (ECF)] (1). The primary end point for this trial was tumour regression grade (TRG1a as per Becker's criteria) of primary tumor. All age group of patients with non-metastatic gastric and esophagogastric junction adenocarcinoma (GaCaGEJ), > cT2 and/or N+ve, were included and patients with adjacent organ invasion were excluded. The groups compared included 137 patients in ECX/ECF *vs.* 128 in FLOT group in a modified intention to treat analysis. The significant findings included an improved resectability rate, favorable pT stage and R0 resection rate with the use of FLOT. FLOT also resulted in an improved overall TRG1a and TRG1a + 1b and an improved TRG1a + 1b in the intestinal histology, without any increase in perioperative outcomes and non-surgical adverse events (1).

The level I evidence favoring the use of neoadjuvant chemotherapy (NAC) for GaCaGEJ was generated following the publication of landmark MAGIC trial in 2006 (2). This landmark phase III RCT compared six cycles of ECF administered peri-operatively to surgery alone for treatment of non-metastatic ≥ stage II GaCaGEJ cancers. The salient findings in favor of NAC were a significant T and N downstaging, improvement in R0 resection, disease free survival (DFS) and overall survival (OS), without any added morbidity and mortality (2). Subsequently, French FNLCC ACCORD 07 trial, which used the doublet of cisplatin and 5-flourouracil (CF) echoed the results of the MAGIC trial (3). In the real world-setting, a study has also shown that it is possible to replace cisplatin and 5-fluorouracil with oxaliplatin and capecitabine (EOX) without compromising delivery of care and efficacy (4).

Subsequently, EORTC 40954 was stopped due to poor accrual, but showed a significantly higher R0 resection rate with NAC without an associated improvement in survival (5). Another phase III trial, which was also closed early, compared NAC to NAC followed by chemoradiotherapy (CRT) (6). Addition of CRT resulted in a significantly higher percentage of pathological complete response rate (pCR) and node negativity but non-significant improvement in survival (6). These two phase III trials failed to show survival advantage, but showed that neoadjuvant therapy improves R0 resection and pCR rate for GaCaGEJ

(5,6). The CROSS trial, has shown that preoperative CRT is associated with significantly higher R0 resection, pCR rate and OS as compared to surgery alone (7). However, despite the use of neoadjuvant treatment options the 5-year OS as per these RCTs for GaCaGEJ has still not improved markedly.

Docetaxel, platinum (cisplatin/oxaliplatin) and 5-Flourouracil (5-FU) has been used as the regimen of choice for metastatic GaCaGEJ and the use of taxanes has been shown to be an independent prognostic factor if used in first-line setting (8) though DCF has been shown to be associated with substantial toxicity (9). FLOT (Docetaxel, Oxaliplatin, 5-Flourouracil and Leucovorin) has been evaluated in a phase II trial and has been found to be safe and efficacious for metastatic GaCaGEJ (9). FLO (Oxaliplatin, 5-Flourouracil and Leucovorin) was compared to FLP (Cisplatin, 5-Flourouracil and Leucovorin) in a phase III RCT and the former was associated with favorable toxicity profile in all age groups and significantly better response rate, PFS and OS in elderly (>65 years) patients (10). FLOT has been compared to FLO in a phase III RCT in elderly (>65 years) metastatic and locally advanced GaCaGEJ (11). FLOT was associated with significantly higher grade 3/4 adverse events and worse EORTC QOL score (11). However, FLOT significantly improved the response rate and PFS in subgroup of locally advanced and 65–70 years age group (11). The authors have included all age groups in FLOT4, despite a higher toxicity seen in the elderly population. The reason might be that this higher treatment toxicity did not translate into treatment discontinuations and deaths in this study (11).

Neoadjuvant docetaxel, cisplatin and 5-FU (DCF) regimen has been shown to be associated with 5-year OS of 54% in a retrospective study (12). Preoperative DCF has been compared to postoperative DCF for locally advanced gastric adenocarcinoma in a recently published phase III RCT. The trial was closed due to poor accrual, but showed a pCR of 12% with DCF (13). FLOT regimen has been studied in neoadjuvant setting in a multicenter phase II trial (14). Six cycles of this regimen resulted in a R0 resection of 86%, TRG1a rate of 20% and TRG1a + 1b rate of 40% (14). Majority (85%) of these excellent responders in this study were intestinal type (14). The pCR rate following FLOT regimen and better pCR rates for intestinal histology are similar to those observed in FLOT4 trial and are therefore not new findings. However, comparison of FLOT to epirubicin triplet regimen has never been attempted prior to this study in a randomized setting.

The pathological response of various neoadjuvant therapies has varied, based on the type of regimen and incorporation of radiation. The pCR rate with the use of epirubicin based chemotherapy have ranged from 6–8% (15,16). The use of docetaxel based chemotherapy has increased the pCR rate upto 20% as seen in Neo-FLOT (14). However, CRT has improved pCR rates even further, upto 29% in CROSS trial (7). The findings of FLOT-4 therefore confirm that docetaxel based regimen improved pCR rates.

Pathological tumor regression following chemotherapy has been found to be associated with pT, pN, R0 rate and is an independent predictor of survival in a clinic-pathological study of 480 resected GaCaGEJ (17). Major tumor regression was also less frequent in the non-intestinal variants and distal stomach primary (17). In FLOT 4 trial, the FLOT regimen resulted in a higher proportion of patients with TRG1a and 1b (1). Similarly this group has a more favorable pT stage and R0 resection rates, but not pN stage (1). TRG1a + 1b rates are better in the intestinal variant, however do not vary as per the tumor location (1). A large multi-institutional retrospective German study has also shown that pathological response rate is associated with a better survival and taxane based triplet regimen showed a trend towards OS (18). It would be interesting to see if the better TRG seen with in FLOT-4, mainly in the intestinal histology, will translate to an improvement in survival.

The authors have used Becker's grading in FLOT 4 (1). A recent study has compared various tumor regression grading criteria—Mandard, the Japanese Gastric Cancer Association, College of American Pathologists, China and Becker-TRG systems (19). TRG was not found to be an independent predictor of survival, however Mandard system was recommended due to its better prediction of prognosis (19). The RCTs should adopt a single TRG-system for uniform reporting of results.

The drawbacks of this trial are low compliance rates seen with both the chemotherapy regimens, exclusion of patients with adjacent organ invasion (cT4b) which in our opinion could have been included. Taxane—based regimens increase pCR rates and can form an important component for neoadjuvant treatment strategies in patients with resectable gastric or esophagogastric adenocarcinoma.

## Acknowledgements

None.

 

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

## References


1. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17:1697-708.
2. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
3. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29:1715-21.
4. Sirohi B, Barreto SG, Singh A, et al. Epirubicin, oxaliplatin, and capectabine is just as "MAGIC"al as epirubicin, cisplatin, and fluorouracil perioperative chemotherapy for resectable locally advanced gastro-oesophageal cancer. J Cancer Res Ther 2014;10:866-70.
5. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210-8.
6. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 2009;27:851-6.
7. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
8. Sirohi B, Rastogi S, Dawood S, et al. Treatment of patients with advanced gastric cancer: experience from an Indian tertiary cancer center. Med Oncol 2014;31:138.
9. Al-Batran SE, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2008;19:1882-7.
10. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 2008;26:1435-42.
11. Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). Eur J Cancer 2013;49:835-42.
12. Sudarshan M, Alcindor T, Ades S, et al. Survival and recurrence patterns after neoadjuvant docetaxel, cisplatin, and 5-fluorouracil (DCF) for locally advanced esophagogastric adenocarcinoma. Ann Surg Oncol 2015;22:324-30.
13. Fazio N, Biffi R, Maibach R, et al. Preoperative versus postoperative docetaxel-cisplatin-fluorouracil (TCF) chemotherapy in locally advanced resectable gastric carcinoma: 10-year follow-up of the SAKK 43/99 phase III trial. Ann Oncol 2016;27:668-73.
14. Schulz C, Kullmann F, Kunzmann V, et al. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma-Very good response predominantly in patients with intestinal type tumors. Int J Cancer 2015;137:678-85.
15. Starling N, Okines A, Cunningham D, et al. A phase II trial of preoperative chemotherapy with epirubicin, cisplatin and capecitabine for patients with localised gastro-oesophageal junctional adenocarcinoma. Br J Cancer 2009;100:1725-30.
16. Cunningham D, Stenning SP, Smyth EC, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. Lancet Oncol 2017;18:357-70.
17. Becker K, Langer R, Reim D, et al. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. Ann Surg 2011;253:934-9.
18. Springfeld C, Wiecha C, Kunzmann R, et al. Influence of Different Neoadjuvant Chemotherapy Regimens on


 

Response, Prognosis, and Complication Rate in Patients with Esophagogastric Adenocarcinoma. Ann Surg Oncol 2015;22 Suppl 3:S905-14.
19. Zhu Y, Sun Y, Hu S, et al. Comparison of five tumor regression grading systems for gastric adenocarcinoma after neoadjuvant chemotherapy: a retrospective study of 192 cases from National Cancer Center in China. BMC Gastroenterol 2017;17:41.

doi: 10.21037/tgh.2017.05.01
**Cite this article as:** Mitra A, Shrikhande SV, Sirohi B. Histopathological regression after taxane based neoadjuvant chemotherapy in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma. Transl Gastroenterol Hepatol 2017;2:46.

 