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Changes in perioperative chemotherapy for resectable gastric and gastroesophageal junction cancer — rather FLOT than ECF/ECX

Over a decade ago, as a result of the MAGIC trial [1], the combination of epirubicin, cisplatin, and fluorouracil (ECF) became the standard perioperative chemotherapy regimen for resectable gastroesophageal cancer. Perioperative triplet chemotherapy, when compared to surgery alone, resulted in significantly reduced hazard ratio (HR) for death [0.75; 95% confidence interval (CI) 0.60–0.93; $p = 0.009$] and for progression (0.66; 95% CI 0.53–0.81; $p < 0.001$), as well as increase in five-year survival rate from 23% in the surgery-only arm to 36% in the perioperative chemotherapy arm. However, despite the development of a multimodality approach for the treatment of gastric and gastroesophageal cancer, long-term results remained disappointing.

Novel data regarding optimisation of perioperative chemotherapy were shown at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting, when Al-Batran et al. [2] presented results from the FLOT4-AIO trial, which compared standard of care epirubicin, cisplatin and fluorouracil, or capecitabine (ECF/ECX) with a regimen consisting of docetaxel, oxaliplatin, and fluorouracil with leucovorin (FLOT). FLOT4-AIO was a randomised, phase 3 trial that included patients with potentially resectable gastric cancer or adenocarcinoma of the gastroesophageal junction. Patients were randomised in a 1:1 ratio to perioperative chemotherapy with ECF/ECX (three cycles every three weeks both pre-operatively and post-operatively) or to perioperative chemotherapy with FLOT (four cycles every two weeks before and after surgery), with a primary endpoint of overall survival (OS) and secondary endpoints of progression-free survival (PFS). The study recruited 360 patients to the ECF/ECX arm and 356 patients to the FLOT arm. Patients were stratified according to performance status, location of primary tumour, age, and nodal status. After the median follow-up

of 43 months, the study met its primary endpoint as median OS reached 50 months in the FLOT arm and 35 months in the ECF/ECX arm, which resulted in HR of 0.77 (95% CI 0.63–0.94; $p = 0.012$) and improvement in rates of 3-year OS from 48% to 57%. The FLOT regimen was also superior regarding median PFS: 18 months with ECF/ECX vs. 30 months with FLOT (HR 0.75; 95% CI 0.62–0.91; $p = 0.004$). The results of both OS and PFS were consistent along all analysed subgroups. No differences were seen in perioperative complications (50% with ECF/ECX vs. 51% with FLOT) as well as in 90-day mortality (8% vs. 5%, respectively). Regarding grade 3/4 adverse events, the FLOT arm resulted in more diarrhoea (10% vs. 4%), infections (18% vs. 9%), neutropaenia (51% vs. 39%), and sensory complications (7% vs. 2%), and the ECF/ECX arm resulted in more vomiting (2% vs. 8%), nausea (7% vs. 16%), thromboembolic events (3% vs. 6%), and anaemia (3% vs. 6%). However, rates of serious adverse events (62% with ECF/ECX and 61% with FLOT), as well as serious adverse events related to treatment (34% vs. 35%, respectively), were similar between compared arms.

As a result of the presented study, FLOT can be considered as a new standard regimen of perioperative chemotherapy for gastric and gastroesophageal junction cancer. Improvements in both OS and PFS were obtained without meaningful increase in adverse events, most of which can be easily managed. Significantly, modifying perioperative chemotherapy regimens from ECF/ECX to FLOT, when compared to costly novel therapies, is widely applicable and can instantly change current practice. However, considering that only 37% of patients in the ECF/ECX arm and 46% of patients in the FLOT arm completed allocated pre- and post-operative chemotherapy without major adjustment, further studies regarding a more convenient perioperative approach are needed.

Impact of proton pump inhibitors on effectiveness of capecitabine in gastroesophageal cancer — secondary analysis of the TRIO-013/LOGIC trial

Among factors determining the effectiveness of an anticancer drug is adequate plasma concentration is very important. Several modifiable factors can alter

chemotherapy pharmacokinetics, such as interaction with other concomitantly used drugs. Addressing those interactions can maximise chemotherapy effectiveness

and enhance patient prognosis. As proton pump inhibitors (PPI) are one of the most commonly used drugs in the management of gastric and gastroesophageal cancer symptoms, new data regarding association between PPIs and capecitabine efficacy provide clinically beneficial insights.

In June 2017 Chu et al. [3] published in an edition of the JAMA Oncology the results from a secondary analysis of the TRIO-013/LOGIC trial concerning the relation between usage of PPIs and the efficacy of capecitabine in advanced gastroesophageal cancer. The TRIO-013/LOGIC trial was a phase 3, placebo-controlled, randomised trial, comparing the combination of capecitabine and oxaliplatin (CapOX) with or without small molecule tyrosine kinase inhibitor lapatinib. The study randomised 545 patients with gastroesophageal cancer in a 1:1 ratio and failed to meet a primary endpoint of improving OS. The secondary analysis evaluated effects of PPI use (identified by medication records) on disease control rate (DCR), PFS, and OS in both the placebo and lapatinib arms. In the placebo arm, PPI-usage was associated with lower DCR (72% vs. 83%; $p = 0.02$), shorter median PFS (4.2 vs. 5.7 months, with HR of 1.55 [95% CI 1.29–1.81; $p < 0.001$]), and median OS (9.2 vs. 11.3 months, with

HR of 1.34 [95% CI 1.06–1.62]). Results regarding PFS and OS remained statistically significant also in multivariate analysis. In the lapatinib arm, no effect of PPI usage on DCR and PFS was seen, and the effect on OS was statistically significant only in multivariate analysis (HR of 1.38; 95% CI 1.06–1.66; $p = 0.03$). PPI usage had no effect on the incidence of capecitabine or lapatinib reductions, grade 3 and 4 diarrhoea, and only a statistically non-significant effect on reduction in rates of hand-foot syndrome incidence was seen (14.2% vs. 10.2% in the control arm and 20.8% vs. 18.0% in the lapatinib arm).

The presented results, despite being only a secondary analysis and not assessing exact pharmacokinetic data, have the potential to influence routine practice. Capecitabine is widely used not only in gastric and gastroesophageal cancer, but also in breast cancer, colon cancer, and other gastrointestinal tumours. Despite the inability to extrapolate results obtained from gastroesophageal trial to other areas of oncology, clinicians should consider that PPI — capecitabine interaction may occur on a daily basis in clinical practice. Every case of PPI and capecitabine co-administration should be carefully reviewed to exclude PPI overuse, at least until further research dispel the doubts.

All that glitters is not gold — results from the CheckMate 026 trial evaluating nivolumab in first-line treatment of non-small-cell lung cancer

The introduction of modern immunotherapy with checkpoint inhibitors, mostly antibodies targeting programmed cell death protein 1 (PD-1) or its ligand (PD-L1), transformed the therapeutic management in many types of cancer, including non-small-cell lung cancer (NSCLC). Nivolumab, pembrolizumab, and atezolizumab changed the standard-of-care in second-line treatment of NSCLC. Recently, pembrolizumab showed superiority over chemotherapy in first-line treatment of NSCLC patients who had PD-L1 expression on at least 50% of tumour cells [4]. However, despite the fact that negative cancer trials rarely draw much attention, recent reports from the CheckMate 026 trial triggered discussion over the strength and limitations of checkpoint inhibitors in NSCLC treatment.

Results from CheckMate 026, an open-label, phase 3, randomised trial, were published on 22nd June 2017 in The New England Journal of Oncology by Carbone et al. [5]. CheckMate 026 compared nivolumab, PD-1 antibody, with standard platinum-based doublet in first-line treatment of patients with NSCLC and over 1% PD-L1 tumour-expression, with primary endpoint of PFS in patients with over 5% PD-L1 tumour-expression. The trial enrolled 1325 patients, 541 (41%) of whom

underwent randomisation in a 1:1 ratio to receive nivolumab or chemotherapy. PD-L1 tumour-expression of over 5% was identified in 423 patients (78% of randomised patients). After the median duration of follow up of 13.5 months, the study failed to meet its primary endpoint. Median PFS in the population with over 5% PD-L1 tumour-expression was 4.2 months in the nivolumab arm (95% CI 3.0–5.6) and 5.9 months (95% CI 5.4–6.9) in the chemotherapy arm, with HR for disease progression or death 1.15 (95% CI 5.4–6.9; $p = 0.25$). Median OS in this population was 14.4 months (95% CI 11.7–17.5) in patients receiving nivolumab and 13.2 months (95% CI 10.7–17.1) in patients receiving chemotherapy, with HR for death 1.02 (95% CI 0.80–1.30). Both nivolumab and chemotherapy achieved similar response rates (26% vs. 33%, respectively), although progressive disease as a best response was more common in nivolumab (27% vs. 10%, respectively). Analyses including all randomised patients showed similar results in terms of PFS and OS. The achieved results were consistent in all investigated subgroups. In the safety analyses, rates of treatment-related adverse events (TRAE) were similar to those described in other studies: any grade TRAE occurred in 71% of

patients in the nivolumab arm and in 92% of patients in the chemotherapy arm. Rates of grade 3–4 TRAE were lower with nivolumab compared to chemotherapy (18% vs. 51%), but rates of TREA leading to the study drug discontinuation were similar (10% and 13%, respectively). An exploratory analysis assessed effects of tumour-mutation burden on patients' outcomes, and results achieved in patients with high tumour-mutation burden with nivolumab were better in terms of response rate (47% for nivolumab vs. 28% for chemotherapy) and median PFS [9.7 vs. 5.8 months, with HR of 0.62 (95% CI 0.38–1.00)]. However, overall survival for nivolumab and chemotherapy in those patients was similar, which might be due to the high crossover rate to nivolumab after progression on chemotherapy (68%).

Despite compelling evidence of checkpoint inhibitor activity in NSCLC, CheckMate 026 is definitely a negative study. In contrast to KEYNOTE-024 [4], results

from the presented study show no evidence of checkpoint inhibitor superiority over classic platinum-doublet in the first-line treatment of NSCLC. Several hypotheses possibly explaining the difference can be made: the use of different PD-L1 expression thresholds, different PD-L1 tests, and some imbalances in baseline patient characteristics favouring better prognosis in the chemotherapy arm (including more patients with high tumour-mutation burden). With results of early phase trials, it was expected that immunotherapy showed activity in nearly all types of cancer in nearly all clinical stages. Despite that, as we see more and more results from late phase trials, it seems that the approach “for everyone, at any stage” might offer limited benefit. Further studies, including combinations of checkpoint inhibitors and usage of novel biomarkers such as tumour-mutation burden, are needed in order to fully utilise the potential of immunotherapy modulation.

The evolving role of prophylactic cranial irradiation in patients with extensive-disease small-cell lung cancer

Patients with extensive-disease small-cell lung cancer (ED-SCLC) are at a high risk of developing brain metastases, even in the case of a good response to initial systemic treatment. As a result, several studies have addressed role of prophylactic cranial irradiation (PCI) as a method of reducing rates of central nervous system progression. Since the publication the results by Slotman et al. [6] in 2007, PCI was considered the standard-of-care for ED-SCLC patients who achieve response during first-line chemotherapy. However, considering the burden of radiation therapy and some imprecisions in Slotman et al.'s study, further studies were aimed at clarifying the role and benefits of routine PCI in ED-SCLC. Recently, new and somewhat provocative data has come from a phase 3 trial from Japan.

In the May 2017 in *Lancet Oncology*, Takahashi et al. [7] published results from a randomised, open-label, phase 3 trial comparing PCI with observation in patients with ED-SCLC, who responded to initial platinum-doublet chemotherapy. Among key inclusion criteria, patients had to have no evidence of brain metastases in magnetic resonance imaging (MRI) within the four weeks before enrolment. During the study, patients underwent MRI control every three months for up to 12 months and every 6 months thereafter. The primary endpoint of the study was OS. After the median follow-up time of 11.3 months in the PCI group and 12.0 months in the observation group, during the first planned interim analysis that included 163 enrolled patients, no evidence of PCI superiority was seen. Median OS was 10.1 months (95% CI 8.5–13.2) in patients

receiving PCI and 15.1 months in patients under observation, with HR of 1.38 (95% CI 0.95–2.02; two-sided $p = 0.091$). In the Bayesian predictive, the probability of PCI superiority over observation was 0.011% and the safety monitoring committee advised the study to be terminated. In the final analysis of all 224 patients, similar results regarding OS were seen (11.6 vs. 13.7 months for PCI and observation, respectively; HR 1.27 [95% CI 0.96–1.68; two-sided log rank $p = 0.094$]). During the study, brain metastases developed in 48% of patients in the PCI group and in 69% of patients in the observation group, with the cumulative incidence of brain metastases at 18 months 40.1% (95% CI 31.0–49.1) and 63.8% (95% CI 54.0–72.1) in PCI and observation arm, respectively. In the safety analysis, PCI treatment was associated with numerically higher rates of anorexia and malaise. No treatment-related deaths occurred in either group.

In the presented study, patients with ED-SCLC derived no clear benefit from PCI, which is in contrast to the earlier results published by Slotman et al. [6]. Nevertheless, several differences between studies should be emphasised: clear exclusion of patients with asymptomatic brain metastases by MRI and intermittent MRI screening in the trial by Takahashi et al. [7], as well as disparities in MRI availability and ethnic differences in Japan. Therefore, it is currently impossible to extrapolate results from the presented study to countries other than Japan. However, the provocative nature of the obtained results sow the seed of doubt concerning role of PCI in all ED-SCLC patients, and further studies are warranted.

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