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Selected literature Part 2

ASCO 2017: FLOT — a new perioperative chemotherapy regimen in patients with gastric cancer and gastroesophageal junction (GEJ) cancer

At the 2017 ASCO Annual Meeting the results of a German multicentre phase 3 clinical trial, FLOT4, were presented, which compared the efficacy of perioperative chemotherapy regimen 4×FLOT — OP — 4×FLOT (docetaxel 50 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and 5-FU 2600 mg/m^2 in 24-hour intravenous infusion on day 1 of a 14-day cycle) with 3×ECF/ECX — OP — 3×ECF/ECX regimen [epirubicin 50 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, and 5-FU 200 mg/m^2 (or capecitabine 1250 mg/m^2 in two divided doses) on days 1–21 of a 21-day cycle] in patients with resectable gastric or gastroesophageal junction cancer (NCT01216644). Between August 2010 and February 2015, 716 patients with locally advanced resectable gastric or GEJ cancer (IB–IIIC; cT2–4/any N or any cT/cN+) were included into the study (with ratio 1:1). The majority of the population were patients with T3 features (70% and 75% in the ECF/ECX and FLOT arms, respectively) and N+ patients (81% and 78%, respectively). The primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS), radical resection rate, perioperative morbidity and mortality, and safety. R0 resection was obtained in 77% of patients receiving ECF/ECX regimen and in 84% of patients receiving FLOT regimen. In the ECF/ECX group, 91% and 37% patients, respectively, completed scheduled preoperative and postoperative treatment, and 90% and 50%, respectively, in the FLOT group. In total, 94% of patients in the ECF/ECX arm and 97% of patients in the FLOT arm underwent surgery. After a median follow-up of 43 months, the median OS was 35 months in the ECF/ECX group and 50 months in the FLOT group (HR 0.77, p = 0.012). The three-year survival rate in the FLOT group was higher by 9% as compared to the standard treatment group (57% *vs.* 48%). There was also a significant increase in median PFS — from 18 months in the ECF/ECX group to 30 months in the FLOT group. Perioperative complications were observed in a similar proportion of patients (50% in the ECF/ECX group and 51% in the FLOT group). The most common grade 3 and 4 adverse reactions were nausea and vomiting in the ECF/ECX group and neutropaenia in the FLOT group.

Comment

Since the publication of the MAGIC study results in 2006, perioperative treatment with ECF regimen has become a standard practice in gastric cancer patients, and since 2008 capecitabine-based regimens, namely EOX and ECX, have been recognised as equivalent options. Chemotherapy regimens based on docetaxel instead of epirubicin have not been widely used outside the US, despite higher response rates during palliative treatment. The long-awaited results of the FLOT4 study represent a significant advance in potentially effective perioperative treatment of patients with early gastric or gastroesophageal junction cancer. At the time of final publication confirming the results presented at the 2017 ASCO Annual Meeting, the FLOT regimen should become the perioperative treatment of choice. Significant increase in R0 resection rate and significant down-staging of disease support the superiority of FLOT as compared to ECX/EOX regimen in patients with initially unresectable/borderline resectable tumours. Reducing the relative risk of death by 23% and increasing the proportion of patients surviving for three years (from 48% to 57%) including relapse-free rate (from 37% to 46%) with a comparable toxicity (and different adverse event profile) clearly indicate activity and safety of the FLOT regimen for perioperative treatment.

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Sources

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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. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008; 358: 36–46.

ESMO 2017: Nivolumab plus ipilimumab as a new option for the first-line treatment of patients with advanced renal cell carcinoma — results of the CheckMate-214 clinical trial

During the 2017 ESMO Annual Meeting the results of the phase 3 clinical trial CheckMate-214 were published, evaluating the efficacy of immunotherapy with immunomodulatory medication (IMM) nivolumab in combination with ipilimumab as compared to sunitinib (SU) in the first-line treatment of patients with advanced clear-cell renal cell carcinoma (ccRCC). The study involved 1096 patients, of whom 847 belonged to the high and intermediate risk group according to IMDC scale. Patients received sunitinib at standard dosing (50 mg/day, days 1–28 every 42 days) or checkpoint inhibitors (4 doses of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg mc. every 3 weeks, then nivolumab alone 3 mg/kg every 2 weeks). Treatment was continued until disease progression or unacceptable toxicity. Primary endpoints (assessed in the population of patients with intermediate/poor prognosis) were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The use of nivolumab in combination with ipilimumab in the intermediate/poor prognosis group was associated with a significant reduction in relative risk of death by 37% (HR = 0.63, $p < 0.0001$). Objective response rate in the intermediate/poor prognosis population was significantly higher for the immunotherapy arm (9% *vs.* 1% of complete responses, and 32% *vs.* 25% of partial responses in the IMM and SU arm, respectively). No significant differences were found in PFS in the intermediate/poor prognosis population. Comparative analysis of both treatment strategies in patients with favourable prognosis indicated the superiority of sunitinib as compared with immunotherapy in terms of both ORR (52% *vs.* 29%) and PFS (HR = 2.18) with $p < 0.0001$. Adverse events, including CTCAE G3/4, were more frequently observed in the sunitinib arm; however, in the immunotherapy arm twice as many patients discontinued treatment due to toxicity (22% *vs.* 12%). The quality of life in patients undergoing immunotherapy was markedly better in comparison to sunitinib.

Comment

The CheckMate-025 study confirmed the efficacy of immunotherapy in the treatment of patients with ccRCC after failure of treatment with VEGFR tyrosine kinase inhibitors. One of the intriguing hypotheses arising after subgroup analysis of patients participating in a study comparing nivolumab with everolimus was higher immunotherapy activity in the population of patients with unfavourable prognosis. A potential explanation for this phenomenon was the deep immunosuppression observed in patients in the unfavourable prognosis group, which is largely due to the activation of immunological checkpoints. In connection with this concept, the use of immunosuppressive therapy inhibiting checkpoints should probably be most active in a population of patients with a poor prognosis. In contrast to the classical MSKCC scale, the IMDC prognostic scale (the so-called Heng scale) used in the CheckMate-214 study takes into account the number of neutrophils and platelets instead of the LDH concentration. As regards primary endpoints in the CheckMate-214 study, a significant superiority of immunotherapy over the current standard of first-line treatment (sunitinib) in patients with intermediate/poor prognosis was confirmed. In turn, sunitinib was found to be more active in the population with favourable prognosis. Furthermore, despite the use of the most aggressive current immunotherapy (combination of PD-1 and CTLA4 inhibitors), the quality of life of patients undergoing experimental therapy was superior to that of conventional VEGFR tyrosine kinase therapy. There is no doubt that the CheckMate-214 study has identified a new standard for first-line treatment of patients with ccRCC and intermediate/poor prognosis.

Source

1. Escudier B, Tannir N , McDermott DF et al. CheckMate 214: Efficacy and safety of nivolumab + ipilimumab (N+I) *v* sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups. ESMO 2017, LBA5; Annals of Oncology (2017) 28 (suppl_5): v605-v649. 10.1093/annonc/mdx440.

Prognosis of colon cancer patients with *BRAF* mutation depends on the location of the mutation

In August 2017, the results of prognosis evaluation in patients with metastatic colorectal cancer (mCRC) with *BRAF* gene mutations located outside the codon 600 were published in "Journal of Clinical Oncology". The authors performed a multicentre retrospective cohort study on clinical, pathological, and prognostic implications in patients with colorectal cancer with *BRAF* mutation other than V600. They collected the data from patients whose mutations were identified by next-generation sequencing (NGS) in three large molecular genetics laboratories.

NGS was performed in 9643 mCRC patients. In total, 208 (2.2%) patients with *BRAF* mutations outside codon 600 were identified. These mutations accounted for 22% of all identified *BRAF* mutations. Survival analysis was performed in patients with *BRAF V600E* mutation (n = 99), without *BRAF* mutation (wild type, n = 249), and in patients with *BRAF* mutation other than V600E (n = 101). As compared to mutations in codon 600 of the *BRAF* gene, mutations in other sites were more common in younger patients (58 *vs.* 68 years), less frequent in female patients (46% *vs.* 65%), and more frequently in highly malignant tumours (13% *vs.* 64%) and initially located on the right side (36% *vs.* 81%). The median overall survival in patients with *BRAF* mutations outside codon 600 was significantly higher than in patients with *BRAF V600* mutations and in patients with wild type *BRAF* gene (60.7 *vs.* 11.4 *vs.* 43 months, respectively, $p < 0.001$). Based on the multivariate analysis, it was concluded that the presence of a *BRAF* mutation other than in codon 600 is an independent factor of favourable prognosis (HR = 0.18, $p < 0.001$).

Comments

BRAF gene mutations are found in approximately 10% of colorectal cancers, with the vast majority (80%) being V600 mutations (valine exchange in position 600). It has long been known that *BRAF V600* mutation is an activation mutation that induces permanent signalling activity of serine/threonine-protein BRAF kinase, resulting in continuous stimulation of cell proliferation through the MAPK pathway. The uncontrolled, continuous activity of MAPK pathway determines the aggressive biology of tumour cells and directly translates into poor prognosis in patients with colorectal cancer with the *BRAF V600* mutation. Unlike the mutation at position 600, mutations in other *BRAF* gene sites inactivate the BRAF kinase signalling activity and reduce MAPK cascade signal transduction. Analysis of the prognostic value of non-600 *BRAF* mutation confirmed that colon cancer with this type of genetic abnormality represents a different molecular subtype, and patients with such a genetic disorder have significantly better prognosis than patients with the V600 mutation and the wild-type *BRAF* gene. The usefulness of the entire gene sequencing, in order to look for non-V600 mutations in the *BRAF* gene in clinical practice, is currently unknown and should not be used for making therapeutic decisions.

Source

1. Jones JC, Renfro LA, Al-Shamsi HO, et al. Non-V600 BRAF Mutations Define a Clinically Distinct Molecular Subtype of Metastatic Colorectal Cancer. J Clin Oncol. 2017; 35(23): 2624–2630. doi: 10.1200/JCO.2016.71.4394. https://www.ncbi.nlm.nih.gov/pubmed/28486044.