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Direct oral anticoagulants as a new option in the treatment of venous thromboembolic disease in cancer patients

Venous thromboembolic events (VTE), especially pulmonary embolism (PE), are one of the leading causes, other than progression, of death in cancer patients. Cancer itself increases the risk of developing VTE, with a relative risk up to 13 times higher than in the general population. Additionally, cancer patients have a high risk of VTE reoccurrence, regardless of whether they receive proper anticoagulation or not. The CLOT trial established six-month treatment with low-molecular-weight heparin (LMWH) as the standard of care after VTE in cancer patients, showing clear superiority of LMWH over vitamin K antagonist. Despite the lack of direct evidence, most of the national and international guidelines support prolonged usage of LMWH after VTE in patients with active cancer, due to the persistent risk of VTE recurrence. However, because LMWH is administered subcutaneously, many patients interrupt the treatment. The introduction of direct oral anticoagulants (DOAs), such as factor Xa inhibitor rivaroxaban or direct thrombin inhibitor dabigatran, provided a new option for patients requiring long-term anticoagulation. Unfortunately, initial studies regarding DOAs in VTE treatment included a minor percentage of cancer patients, which prevented drawing conclusion regarding the safety of DOAs in this population. Chronic cancer symptoms (such as nausea, vomiting, or diarrhoea), as well as active anti-cancer treatment (either with chemotherapy or molecularly targeted agents), were speculated to affect the pharmacokinetics or pharmacodynamics of DOAs, which could reduce effectiveness of DOA anticoagulation. Role of DOAs in the treatment of VTE in cancer patients recently changed, as two important studies provided evidence for DOAs effectiveness and safety in cancer patients.

The results of the first of the aforementioned studies, the SELECT-D trial, was published by Young et al. [1] on 10 July 2018 in the "Journal of Clinical Oncology". The trial compared rivaroxaban, one of the DOAs, with a standard of care LMWH dalteparin in cancer patients with symptomatic or incidental PE or symptomatic deep vein thrombosis (DVT). Dalteparin was used at a dose of 200 IU/kg for the first 30 days and thereafter at a dose of 150 IU/kg for six months. Rivaroxaban was administered at a dose 15 mg daily for the first three weeks and then continued at a dose of 20 mg for six months. The primary end-point was VTE recurrence, with rates of major bleeding and clinically relevant non-major bleeding (CRNMB) as the secondary end points. The trial recruited 406 out of 2060 patients screened. During the study, after recognition of a trend toward increased rates of bleeding events, patients with oesophageal and gastroesophageal junction cancers were excluded from further enrolment as a precaution. The rate of cumulative VTE incidence at six months was significantly lower in patients receiving rivaroxaban (4%; 95% confidence interval [CI] 2–9%) compared to patients receiving dalteparin (11%; 95% CI 7–16%), with the hazard ratio (HR) of 0.43 (95% CI 0.19–0.99), meeting the primary end point of the study. The rate of major bleeding event at six months was 6% (95% CI 3–11%) in the rivaroxaban arm and 4% (95% CI 2–8%) in the dalteparin arm, which resulted in HR of 1.83 (95% CI 0.68–4.96). Major bleeding events related to rivaroxaban were more common in patients with cancer arising from oesophageal and gastroesophageal junction. Moreover, rivaroxaban was associated with significantly higher rates of CRNMB compared to dalteparin (13% *vs.* 4% [HR 3.76; 95% CI 1.63–8.69]). The difference in VTE recurrence rate, major bleeding rate, and CRNMB rate did not translate into a difference in overall survival, which was comparable between both arms (overall survival at six months was 70% [95% CI 63–76%] in the dalteparin group and 75% [CI 69–81%] in the rivaroxaban group).

The second trial, the Hokusai VTE Cancer trial, compared another DOA, factor Xa inhibitor edoxaban, with a standard of care LMWH, dalteparin. The results were published by Raskob et al. [2] in the issue of "New England Journal of Medicine" from 15 February 2018 and also provided positive evidence for the usage of DOA for the treatment of VTE in cancer patients. Edoxaban was used at a dose of 60 mg, administered once daily for six to 12 months after initial five-day course of subcutaneous LMWH, while dalteparin was used at a dose of 200 IU per kg for a month and then at a dose of 150 IU per kg until reaching a 6- or 12-month landmark. VTE required for a qualification to the trial included both

symptomatic and asymptomatic DVT (confined to vena cava inferior or popliteal, femoral, and iliac veins), as well as symptomatic and asymptomatic PE. Patients known to have risk factors for bleeding (such metastatic disease including brain metastases, receiving bevacizumab, receiving anti-platelet agents, or cancer arising from gastrointestinal or urinal systems) could receive a reduced dose of edoxaban — 30 mg daily — at the investigator's discretion. The primary end point comprised recurrent VTE or major bleeding in a non-inferiority analysis. The trial enrolled 1050 patients, randomised in a 1:1 ratio to both of the arms. The trial met its primary end point with a rate of VTE recurrence or major bleed reaching 12.8% in the edoxaban arm and 13.5% in the dalteparin arm, with HR of 0.97 (95% CI 0.70–1.36; p = 0.006 for non-inferiority). However, when analysed independently, rates of VTE and major bleeding showed differences between the arms. There was a trend towards reduction of VTE recurrence rate (7.9% *vs.* 11.3%; HR 0.71; 95% CI 0.48–1.06; p = 0.09) and a significantly higher rate of major bleeding events (6.9% *vs*. 4.0%; HR 1.77; 95% CI 1.03–3.04; p = 0.04) in the edoxaban arm. The obtained results were similar in all subgroups except patients with cancer originating from the gastrointestinal system, who had a significantly higher risk of developing major bleeding (p = 0.02).

Both presented trials support the usage of DOAs in the population of cancer patients requiring anticoagulation after VTE. As both rivaroxaban and edoxaban proved non-inferior compared to LMWH, they can be considered the standard of care in patients not accepting prolonged subcutaneous injections. Oral administration is usually better tolerated because the burden associated with subcutaneous form of the drug accrues with time. This might explain the longer median duration of treatment reached with both rivaroxaban and edoxaban when compared to LMWH, observed in both of the described trials. Additionally, it seems that DOAs provide better anticoagulation because they lower the rates of VTE recurrences. Nonetheless, the leading disadvantage related to DOAs is clearly higher rates of both major and non-major bleedings. This might be at least partially mitigated, because some patients with higher risk of bleeding can be identified, e.g. those with cancer originating from the gastrointestinal system. Another issue might be the long-term safety of DOAs: both SELECT-D and Hokusai VTE Cancer assessed patients receiving anticoagulation for 12 months only. Several international guidelines suggest prolongation of anticoagulation in cancer patients as long as cancer remains active. With the current advances in the treatment of metastatic cancer, many patients survive more than 12 month and may need coagulation for years. Whether DOAs can be safely used in such patients remains unclear. Other groups of cancer patients that should be considered ineligible to receive DOAs include those with chronic diarrhoea, vomiting, malabsorption, and any other conditions that might impair absorption of the drug from the digestive tract. Nonetheless, both rivaroxaban and edoxaban can be considered valuable tools in the management of cancer-related VTE. Evidence regarding the safety of DOAs might also impact the treatment of cancer patients requiring anticoagulation due to diseases other than VTE, such as atrial fibrillation. This, however, should be addressed in other, eagerly awaited trials.

Time to change paradigm — no need for initial nephrectomy in patients with metastatic renal cell carcinoma?

Classically, metastatic renal cell carcinoma (mRCC), both its clear cell and non-clear cell variants, was considered refractory to systemic treatment and associated with extremely poor prognosis. Introduction of early forms of immunotherapy, cytokines IL-2 and interferon α, provided only limited benefit. The limited activity of systemic therapy brought a lot of attraction to the idea of combining different modalities, including cytoreductive nephrectomy combined with systemic therapy. Question, whether combination of nephrectomy and systemic therapy would yield better results than systemic therapy alone, was addressed by several trials that led to the establishment of nephrectomy as a necessity before cytokine therapy [3, 4]. Introduction of targeted therapies, such as vascular endothelial growth factor (VEGF) kinase inhibitors or mTOR inhibitors, revolutionised systemic treatment of mRCC and replaced cytokine-based therapies. Nevertheless, because most of the patients participating in randomised clinical trials that lead to registration of VEGF/mTOR inhibitors had their primary tumours removed, the role of primary nephrectomy was widely accepted, despite the lack of evidence for clinical benefit from this procedure. Most of the attention was paid to the novel compounds that gradually reached clinical practice, with the most novel introduction of immunotherapy based on check-point inhibitors and the next-generation VEGF inhibitor cabozantinib. However, novel data from the CARMENA trial shattered our previous paradigm of surgery as an initial treatment in all patients with mRCC. These results hold the potential to significantly change routine clinical practice.

Méjean et al. [5] published the results of the CARMENA trial on 3 June 2018 in the "New England Journal

of Medicine". The trial compared two approaches to newly diagnosed mRCC patients deemed to be suitable for nephrectomy: initial nephrectomy with subsequent sunitinib therapy versus treatment only with sunitinib (without nephrectomy). The design of the study was based on the assumption of both-arm non-inferiority. The patients were required to be clinically eligible for both nephrectomy and sunitinib treatment, have a diagnosis of clear cell mRCC without prior systemic treatment, and were stratified to intermediate or poor prognosis according to Memorial Sloan-Kettering Cancer Centre criteria. In patients not undergoing nephrectomy sunitinib was initiated within 21 days after randomisation, at a standard dose of 50 mg daily for 28 days with a 14-day break. In the surgical arm of the trial, nephrectomy was performed within 28 days from the point of randomisation, and sunitinib was initiated 3–6 weeks after nephrectomy (delay from the randomisation to the first sunitinib administration was up to 10 weeks). The trial enrolled 450 patients, randomised in a 1:1 ratio to both arms of the trial. After a median follow-up time of 50.9 months (95% CI 44.0–56.9), the trial met its primary end point of non-inferiority regarding overall survival: the intention to treat analysis sunitinib-only arm showed a trend towards improvement of median overall survival (mOS) (18.4 months [95% CI 14.7–23.0] *vs.* 13.9 months [95% CI 11.8–18.3]), with a stratified hazard ratio of 0.89 (95% CI 0.71–1.10), which implied non-inferiority between both arms. Similar results were obtained in both intermediate-risk group and poor-risk group. As for median progression-free survival (mPFS), the sunitinib-only arm showed numerical improvement compared to the nephrectomy-sunitinib arm: 8.3 months (95% CI 6.2–9.9) *vs*. 7.2 months (95% CI 6.7–8.5), with a stratified HR of 0.82 (95% CI 9.67–1.00). Response rates observed were similar in both arms (29.1% in the sunitinib-only group and 27.4% in the nephrectomy-sunitinib group), while median duration of sunitinib treatment was significantly longer in the sunitinib-only arm (8.5 months *vs.* 6.7 months; p = 0.04). Rates of sunitinib dose reductions were comparable between both arms, despite the fact that rates of grade 3 and 4 adverse event were higher in the sunitinib-only group (42.7% *vs*. 32.8%; p = 0.04). This includes a clinically relevant increase in renal or urinary tract disorders in patients receiving only sunitinib (4.2% *vs*. 0.5%; p = 0.051).

The CARMENA trial is the first randomised, controlled clinical trial that provided data regarding efficacy of nephrectomy in the era of targeted therapies. In the contrast to available retrospective studies, CARMENA clearly shows no benefit of primary nephrectomy before systemic therapy in patients with mRCC and intermediate or poor prognosis defined by MSKCC criteria. Because most of mRCC patients have intermediate or poor prognosis, the impact of the CARMENA trial on clinical practice should not be underestimated. Still, a few limitations of skipping nephrectomy should be considered. First, we currently do not have good quality evidence regarding the role of nephrectomy in a favourable risk MSKCC prognostic group, and we currently cannot recommend forgoing nephrectomy in this group. Secondly, MSKCC criteria were developed in the cytokine-therapy era and we currently dispose of better prognostic scales, such as IMDC score. Thirdly, with novel data regarding ipilimumab and nivolumab combination or cabozantinib in the first-line treatment of mRCC patients with an intermediate and poor risk prognosis, sunitinib cannot be considered the standard of care in this setting, and this limits relevant conclusions from the CARMENA trial. Nevertheless, it should be emphasised that the CARMENA trial answered important clinical questions and its authors should be congratulated on accomplishing such a difficult trial. From a Polish perspective, due to the limitations of National Health Fund Drug Programmes, the results of the CARMENA study provide little to no benefit. Unfortunately, despite good quality evidence supporting forgoing nephrectomy in the specific subpopulation of patients with mRCC, we can expect changes in the National Health Fund Drug Programmes later rather than sooner.

A new chapter in adjuvant treatment of pancreatic ductal adenocarcinoma — modified FOLFIRINOX as the new standard of care

Plenary sessions during American Society of Clinical Oncology (ASCO) meetings sometimes provide results of studies with a huge impact on clinical practice, despite the lack of a full manuscript publication. This includes data regarding perioperative FLOT chemotherapy in gastric cancer during ASCO 2017, and it seems that in 2018 we have a similar situation with a new standard of care in adjuvant treatment of pancreatic ductal adenocarcinoma (PDCA) — the modified FOLFIRINOX regimen (mFOLFIRINOX). It is debatable whether an abstract or a plenary oral session provides enough data to impact clinical practice, but sometimes the results are too impressive to ignore. This is particularly important, when it comes to a disease with an exceptionally poor prognosis, just as with PDCA. Despite radical, curative resection, patients with confirmed PDCA have about 90% rate of relapse without any adjuvant treatment. Even with the most potent adjuvant chemotherapy available, a combination of gemcitabine and capecitabine, the rate of five-year survival barely reaches 30%. Those

might be the arguments for praising mFOLFIRINOX as a new standard of care for adjuvant treatment of PDCA, despite the lack of full data availability.

Adjuvant mFOLFIRINOX after R0 or R1 resection of PDCA was evaluated within the UNICANCER GI PRODIGE 24/CCTG PA.6 trial, presented by Conroy et al. [6] during the ASCO 2018 annual meeting. The trial compared a modified FOLFIRINOX regimen, consisting of irinotecan at a dose of 150 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and 5-fluorouracil 2400 mg/m^2 (given as a 46-hour infusion) biweekly for a total of 12 cycles with a former standard of care gemcitabine given at a dose of 1000 mg/m^2 on days 1, 8, and 15 of a 28-day cycle for a total of six cycles. Key inclusion criteria included R0 or R1 resection, PDCA diagnosis, good performance status (ECOG 0 or 1), and no prior exposure to chemotherapy or radiotherapy. Of important exclusion criteria, patients had to have postoperative CA 19-9 concentration lower than 180 U/ml. The primary end point was disease-free survival (DFS), with overall survival and metastasis-free survival as the secondary endpoints. The trial included 493 patients, randomised in a 1:1 ratio to both assessed arms. Patients in the mFOLFIRINOX arm more often stopped adjuvant chemotherapy prematurely ($p = 0.002$), underwent more administration delays ($p < 0.001$), less often received more than 70% of relative dose-intensity ($p < 0.001$), and were less likely to complete all planned chemotherapy cycles ($p = 0.002$). Despite the problems described above, treatment with mFOLFIRINOX resulted in a significant improvement of median DFS: 21.6 months (95% CI 17.7–27.6) in the mFOLFIRINOX arm *vs.* 12.8 months (95% CI 11.7–15.2) in the gemcitabine arm, with a stratified HR of 0.58 (95% CI 0.46–0.73; $p < 0.0001$). Additionally, three-year DFS was nearly doubled with mFOLFIRINOX (39.7%), compared to gemcitabine (21.4%). Similar results were obtained regarding metastasis-free survival, with a median of 30.4 months (95% CI 21.7–not reached) in patients receiving mFOLFIRINOX and 17.7 months (95% CI 14.2–21.5) in patients receiving gemcitabine (stratified HR 0.59; 95% CI 0.46–0.75; $p < 0.0001$). What seems to be a major advantage of this trial, survival was also improved and median OS reached an impressive 54.4 months (95% CI 41.8–not reached) in the mFOLFIRINOX arm *vs*. 35.0 months (95% CI 28.7–43.9) in the gemcitabine arm, with stratified HR 0.64 (95% CI 0.48–0.86; $p = 0.003$). The achieved results were consistent in all sub-groups analysed. Patients receiving mFOLFIRINOX had similar rates of haematological grade 3 and 4 events compared to patients receiving gemcitabine, despite more frequent administration of G-CSF in the mFOLFIRINOX arm (59.9% of patients in the experimental arm required G-CSF support). Unfortunately, rates of grade 3 and 4 non-haematological adverse events were more common in patients receiving mFOLFIRINOX, and this includes diarrhoea, peripheral neuropathy, fatigue, vomiting, hand-foot syndrome, and mucositis. This, however, did not result in an increase in mortality, with no toxic deaths in the mFOLFIRINOX group and one toxic death in the gemcitabine group.

The available results of the UNICANCER GI PRODIGE 24/CCTG PA.6 trial, despite being only published as an abstract and oral plenary presentation, provide significant stimulus to incorporate mFOLFIRINOX in routine clinical practice. Median OS, which reached more than four years, is truly remarkable and should be considered a breakthrough. Nevertheless, it should be emphasised that considering the high rates of adverse events, mFOLFIRINOX is a demanding regimen and should be used with caution. Because it may be valuable option for a young patients with a good performance status and unremarkable postoperative period, a significant proportion of patients after PDCA resection might not be suitable for such an intensive regimen and should receive gemcitabine — alone or with capecitabine.

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