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Safety and effectiveness of direct oral anticoagulants in the primary prophylaxis of venous thromboembolic disease among cancer patients initiating chemotherapy

Modern oncology relies not only on the advances in cancer treatment, but also on the optimization of supportive care. Proper pain management, intensive nutritional care and appropriate identification and treatment of adverse events results improve outcomes in the both palliative and radical setting. Venous thromboembolic disease, including its' most dangerous form — pulmonary embolism, has direct effect on patient's survival and quality of life. Thromboembolic disease affect not only cancer patients in the in-patient setting, who nearly always require primary prophylaxis for thromboembolic disease, but also patients treated in the out-patient setting, who present various risk of thromboembolic complications depending on a cancer type and the specific risk factors (Khorana scale [1]) Depending on the number of risk factors, Khorana scale stratify patients into low, intermediate or high risk group. Achieved result may provide physician with guidance on whether specific patient may benefit from primary venous thromboembolic prophylaxis with low-molecular weight heparin (LMWH) administered subcutaneously. Currently, no guidelines recommend routine venous thromboembolic prophylaxis during chemotherapy, leaving this decision to the leading physician. Unfortunately, mostly due to the way of administration, primary prophylaxis with LMWH presents a major burden for cancer patients and can be unacceptable, especially if used long-term. Considering this burden, application of direct oral anticoagulants (DOAs) instead of LMWH offers attractive alternative. However, due to the increased risk of bleeding events and potential drug interactions, introduction of DOAs into clinical practice had had to be preceded by clinical trials dedicated specifically to the cancer patients. Currently, we can refer to the results of two trials assessing effectiveness of DOAs in primary prophylaxis of venous thromboembolic diseases. The results, as often in medicine, are not fully convergent.

The results of first trial were published by Carrier et al. in "The New England Journal of Medicine" on the 21 of February 2019 [2]. The AVERT trial was randomized, double-blinded, phase III clinical trial that compared apixaban, administered orally at a dose of 2.5 mg twice daily, with placebo in cancer patients who initiated chemotherapy and had intermediate or high risk of thromboembolic events (2 or more point in the Khorana scale). No screening for asymptomatic venous thrombotic disease was performed before treatment initiation. The intervention was planned for 180 days in both trial arms. The trial's primary endpoint was objective occurrence of venous thromboembolic event in 180-day observation. The primary safety endpoint was occurrence of major bleeding episode. Additionally, safety analysis included also outcomes regarding rate of clinically relevant non-major bleeding (CRNMB) episodes and overall survival. The trial included 574 patients, randomized in 1:1 ratio to both arms, from all 1809 patients screened for eligibility. The primary analysis included 563 patients who received at least one dose of allocated treatment. Median treatment time and rate of treatment discontinuation before planned 180 days was similar between arms. Primary endpoint occurred in 12 patients (4.2%) in the apixaban arm and 28 patients (10.2%) in the placebo arm (hazard ratio [HR] 0.41; 95% confidence interval [CI] 0.26–0.65; $p < 0.001$). During active treatment period the primary endpoint occurred in 3 (1%) patients receiving apixaban and in 20 (7.3%) patients receiving placebo. In the safety analysis, major bleeding episode was detected in 10 patients (3.5%) patients in the apixaban arm and in 5 patients (1.8%) in the placebo arm, which resulted in HR of 2.0 (95% CI 1.01–3.95; $p = 0.046$). Most bleeding episodes were mild, without critical organ bleedings or bleeding-related deaths. During the active treatment period, major bleeding episodes were seen in 6 patients (2.1%) receiving apixaban and in 3 patients (1.1%) receiving placebo. Rate of adverse events were similar between both arms. During observation, 35 patients (12.2%) in the apixaban arm and 27 patients (9.8%) in the placebo arm died, with 87% of deaths related to cancer. As the primary endpoint was met, AVERT study is clearly a positive one. It confirmed value of apixaban in the primary prophylaxis of venous thromboembolic diseases in cancer patients receiving chemotherapy.

The results of second trial were published by Khorana et al. in the same issue of "The New England Journal of Medicine" from the 21 of February 2019 [3]. CASSINI

was randomized, double-blinded, phase III trial that compared rivaroxaban 10 mg orally per day with placebo in cancer patients who were initiating chemotherapy, had intermediate or high risk of venous thromboembolic disease according to Khorana scale and who had no asymptomatic venous thrombosis. The intervention period was 180 days. Every 8 weeks participants underwent ultrasonographic screening to exclude presence of thrombotic changes in lower extremities. Primary endpoint was composite and consisted from objective occurrence of proximal deep-vein thrombosis in lower extremities, symptomatic deep-vein thrombosis in upper extremities or distal deep-vein thrombosis in lower extremities, symptomatic or asymptomatic pulmonary embolism and death due to venous thromboembolism as assessed up to 180 days from the treatment initiation. Additional analysis assessing primary endpoint during active treatment was pre-planned. The primary safety endpoint was the occurrence of a major bleeding episode, with the rate of CRNMB as a secondary safety endpoint. The trial included 1080 patients, among whom 49 (4.5%) were excluded due to the presence of asymptomatic thrombosis, and 190 (17.5%) were not randomised due to other reasons. In the end, 841 patients who underwent randomisation (in a 1:1 ratio) represented the intention-to-treat population assessed in efficacy analysis, and 809 patients who received treatment represented the safety-analysis population. About 43.7% of patients receiving rivaroxaban and 50.2% of patients receiving placebo discontinued the intervention before reaching the planned 180 days (with similar rates of reasons for discontinuation and mean intervention time of 4.3 months). The primary composite endpoint occurred within the 180-day observation period in 25 patients (6.0%) receiving rivaroxaban and in 37 patients (8.8%) receiving placebo (HR 0.66; 95% CI 0.40–1.09; p = 0.1), with nearly 39% of all events occurring after the treatment discontinuation. In a pre-planned analysis limited to the active treatment period, primary endpoint was noted in 11 patients (2.6%) in the rivaroxaban arm and 27 patients (6.4%) in the placebo arm (HR 0.40; 95% CI 0.20–0.80). Lower rate of thromboembolic complications within the arterial system and visceral organs was also noted in the patients receiving rivaroxaban. Additionally, a lower number of deaths was observed in the rivaroxaban arm compared to the placebo arm (20% *vs.* 23.8%). This was confirmed by a pre-planned composite analysis that included primary endpoint combined with death from all-causes, which occurred in 23.1% of patients receiving rivaroxaban compared to 29.5% of patients receiving placebo (HR 0.75; 95% CI 0.57–0.97). Major bleeding episodes were noted in eight patients (2.0%) receiving rivaroxaban and in four patients (1.0%) receiving placebo, with a HR of 1.96 (95% CI 0.59–6.49). Rates of CRNMB were similar (2.7% in the rivaroxaban group and 2.0% in the placebo group; the difference did not reach statistical significance). Rates of all adverse events also did not differ between both arms. One case of bleeding-associated death was observed in the rivaroxaban arm. Generally, the CASSINI trial is a negative study, because the primary endpoint was not met. Nevertheless, in contrast to the AVERT trial, no statistically significant increase of rivaroxaban-associated bleeding was observed, and the numerical outcomes achieved during active treatment were clearly superior in the rivaroxaban arm, which argues in favour of rivaroxaban activity in the primary prophylaxis of venous thromboembolic disease.

The presented trials bring important data allowing for better understanding of cancer-related venous thromboembolic disease. However, it is difficult to predict their impact on routine clinical practice. Despite the fact that according to the AVERT trial every cancer patient initiating chemotherapy with intermediate or high risk according to Khorana scale should receive primary prophylaxis for venous thromboembolic disease with apixaban, we must be aware of the details that hinder extrapolation of AVERT data to the general population. Firstly, the AVERT trial included only 574 patients from all 1809 screened for eligibility, which indicates significant patient selection. Secondly, despite the reduction of risk of venous thromboembolic events, not even a numerical reduction of deaths was seen in the apixaban arm. In contrast, a marginal trend for improved survival was seen in the placebo arm (HR 0.98–1.71). The decision regarding initiation of apixaban prophylaxis should include the fact that no impact on mortality should be expected. Nevertheless, we may currently recognise apixaban as an oral alternative to LWMH in the primary prophylaxis of venous thromboembolic disease. Concurrently, independently of the negative results of the CASSINI trial, data regarding rivaroxaban activity can be considered interesting. Rivaroxaban prophylaxis numerically reduced the risk of thromboembolic events, with low rates of bleeding complications. Moreover, even though the CASSINI trial was too underpowered to detect differences in survival, a lower rate of deaths was seen among patients receiving rivaroxaban (with number-needed-to-treat [NNT] of only 26). Both trials bring valuable data regarding the safety of DOAs in cancer patients, confirming their acceptable and manageable toxicity profile. We currently dispose evidence regarding DOA safety not only in the primary prophylaxis of venous thromboembolic disease (AVERT and CASSINI trials) but also in treatment and secondary prophylaxis (SELECT-D and Hokusai VTE Cancer trials). If further research provides better tools for patient selection in terms of safety, we may soon expect DOAs to fill in for LMWH as the basic anticoagulants in oncology.

It is not a change; it is a revolution — novel options in the first-line treatment of clear cell renal cell carcinoma

Recent years have brought tremendous changes in the treatment of patients with renal cell carcinoma, comparable only with the introduction of tyrosine kinase inhibitors (TKIs) over a decade ago. Renal cell carcinoma, like melanoma or lung cancer, are an example of cancers in which modern immunotherapy shows greatest potential. Currently, nivolumab is an option in second-line treatment after TKI failure and a combination of nivolumab and ipilimumab can be considered as the standard of care in the first-line treatment of patients with intermediate and poor prognosis according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. Promising data coming from other trials assessing combinations of immunotherapy with other molecularly driven agents suggest further changes in the field of renal cell carcinoma. With the recent results of two phase III trials it is becoming increasingly clear that we should forget about monotherapy in the first-line treatment of patients with advanced clear cell renal cell carcinoma.

The results of the first aforementioned trial, KEYNOTE-426, were published by Rini et al. in "The New England Journal of Medicine" of 21 March 2019 [4]. KEYNOTE-426 was a randomised, non-blinded, phase III trial that compared standard first-line treatment with sunitinib (50 mg orally per day for four weeks with a two-week break) with an experimental combination of pembrolizumab (200 mg intravenously every three weeks) and axitinib (5 mg orally two times per day continuously, with dose titration if applicable). The trial included patients with previously untreated advanced clear cell renal cell carcinoma and performance of at least 70 according to the Karnofsky scale. The primary endpoint was overall survival (OS) and progression-free survival (PFS). The presented data came from the first interim analysis. From 1062 screened patients, 861 were randomised in a 1:1 ratio to both trial arms. After a median observation time of 12.8 months, the trial met its primary endpoint at statistical significance predicted for first interim analysis. The rate of 12-month survival was 89.9% (95% CI 86.4–92.4) in the combined treatment arm compared to 78.3% (95% CI 73.8–82.1) in the sunitinib arm. Median OS was not reached in either of the arms, but the risk of death was 47% lower in patients receiving pembrolizumab with axitinib (hazard ratio for death 0.53; 95% CI 0.38–0.74; $p < 0.0001$). Median PFS reached 15.1 months (95% CI 12.6–17.7) in the combination group *vs.* 11.1 months (95% CI 8.7–12.5) in the sunitinib group, with HR reaching 0.69 (95% CI 0.57–0.84; $p < 0.001$). Benefit in OS and PFS was confirmed in all analysed subgroups, including all IMDC prognostic groups, and PD-L1 expression status. The objective response rate was also higher in the pembrolizumab and axitinib arm — 59.3% (95% CI 54.5–63.9) as compared to 35.7% (95% CI 31.1–40.4) in the sunitinib arm ($p < 0.001$). The rates of all adverse events were similar in both arms — 98.4% in patients receiving combination *vs.* 99.5% in patients receiving sunitinib. Rates of adverse events grade 3 and were, respectively, 75.8% and 70.6%. Rates of patients who required treatment discontinuation reached 10.7% in the combination arm and 13.9% in the sunitinib arm. Rates of treatment-related adverse events that led to death were 0.9% (four patients) in the pembrolizumab-axitinib group and 1.6% (seven patients) in the sunitinib group. The toxicity profile of the pembrolizumab and axitinib combination was similar to previous studies except for the increased incidence elevated liver enzymes of grade 3 and higher. About 50% of patients who progressed on pembrolizumab and axitinib received subsequent treatment, as compared to 60.7% of patients who progressed on sunitinib (including 37.6% who received PD-1/PD-L1 inhibitors). Based on the results of KEYNOTE-426 we can currently recognise the combination of pembrolizumab with axitinib as a novel option in the first-line setting for patients with advanced clear cell renal cell carcinoma, irrespective of IMDC prognostic group or PD-L1 expression.

The results of a second trial were published in the same issue of "The New England Journal of Medicine" from 21 March 2019 by Motzer et al. [5]. JAVELIN Renal 101 was randomised, unblinded phase III trial that compared standard first-line treatment with sunitinib (50 mg orally per day for four weeks with a two-week break) with an experimental combination of avelumab (10 mg/kg of bodyweight every two weeks) and axitinib (5 mg orally two times per day continuously, with dose titration if applicable) in patients with advanced renal cell carcinoma with a clear cell component, who did not receive prior systemic treatment. The trial included patients with very good (ECOG 0) or good (ECOG 1) performance status irrespective of IMDC prognostic group. The primary endpoint was PFS, but an amendment implemented before data unblinding introduced two new, independent primary endpoints: PFS and OS in patients with present expression of PD-L1. Secondary endpoints included, among others, PFS and OS in the overall population and response rate. Altogether, 886 patients were recruited and randomised in a 1:1 ratio to both trial arms. A group of 560 patients with PD-L1-positive tumours constituted the primary endpoint population. After a median follow-up in PD-L1-positive population of 9.9 months in combination arm and 8.4 months in sunitinib arm, statistically significant improvement in PFS

was seen in the combination arm: 13.8 months (95% CI 11.1 to not reached) *vs*. 7.2 months (95% CI 5.7–9.7) in the sunitinib arm (stratified HR for progression or death 0.61; 95% CI 0.47–0.79; $p < 0.001$). The difference in PFS was significant in all analysed subgroups. Due to the low number of deaths in the PD-L1-positive population (13.7% in the combination arm *vs*. 15.2% in the sunitinib arm), evaluation of overall survival difference did not show statistically significant differences, but the wide range of confidence intervals should be noticed. Benefit in term of PFS was also seen in the general population: 13.8 months (95% CI 11.1 to not reached) in the patients receiving avelumab and axitinib *vs.* 8.4 months (95% CI 6.9–11.1) in the patients receiving sunitinib (stratified HR for progression or death 0.69; 95% CI 0.56–0.84; $p < 0.001$). Similarly to the PD-L1-positive population, low death rates in the general population (14.3% in the combination arm *vs.* 16.9% in the sunitinib arm) hindered evaluation of overall survival and only showed a trend towards benefit from avelumab and axitinib (stratified HR for death 0.78; 95% CI 0.55–1.08; $p = 0.14$). The response rate in the PD-L1-positive population was 55.2% (95% CI 49.0–61.2) in the combination arm *vs.* 25.5% (95% 20.6–30.9) in the sunitinib arm. Similar response rates were achieved in the general population (51.4% *vs*. 25.7%, respectively). Rates of all adverse events were 99.5% in patients receiving combination *vs*. 99.3% in patients receiving sunitinib. Rates of adverse events grade 3 and higher were, respectively, 71.2% and 71.5%. Adverse events that led to treatment discontinuation occurred in 7.6% of patients in the combination arm and 13.4% of patients in the sunitinib arm. Deaths related to adverse events occurred in three patients receiving avelumab with axitinib and in one patient receiving sunitinib. After disease progression, 20.8% of patients in the combination arm and 39.2% of patients in the sunitinib arm received subsequent treatment. Most of the patients (66.7%) in the sunitinib arm received therapies aimed at PD-1 or PD-L1 after study discontinuation. Results of the JAVELIN Renal 101 trial suggest that a combination of avelumab and axitinib provides benefit over standard treatment for patients with advanced clear cell renal cell carcinoma in the first line of treatment. Considering the increase in overall survival seen in the KEYNOTE-426 trial, it currently seems that pembrolizumab-based combinations are more promising, at least until publication of further results of the JAVELIN Renal 101 trial.

Both described trials are examples of revolutionary changes in the first-line treatment of renal cell carcinoma. Although standard treatment for a long time, monotherapy with TKIs is now outdated. Currently important clinical questions include the choice, which patients should receive immunotherapy doublet (nivolumab + ipilimumab) and which combination of immunotherapy with TKIs or another antiangiogenic agent. Moreover, including only advanced trials, the nearest future may provide us with at least four immunotherapy combinations with proven benefit on overall survival. In perfect conditions, the decision regarding treatment in each individual is becoming more difficult. In Poland, we are left with technology that should be called obsolete. From a bitter, ironic perspective, one must admit that the decisions are a lot simpler if there is no choice.

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