CARDIO-ONCOLOGY AT THE 2018 ESC CONGRESS: FROM OBSERVATION TO TREATMENT

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Cardio-oncology has gained growing consideration among clinicians in the last years. In parallel, anticancer strategies are constantly improving and many new antineoplastic drugs are being developed. However, these therapies do not exclusively target malignant cancer cells, but also nontumor cells. Depending on cancer diagnosis and treatment strategies, cardiotoxicity is observed in up to 48% of patients with tumors.[1] A lot of research worldwide is focusing on understanding the underlying mechanisms and related negative effects on the myocardium better.

To promote research and understanding of this field, a joint session on cardio-oncology was implemented between the ESC and the American Heart Association during the 2018 ESC congress in Munich, Germany. This session looked at clinical and instrumental possibilities to recognize cardiovascular toxicity in patients with cancer and different treatment options. The congress itself was attended by more than 30 000 participants from >150 countries.

CARDIOVASCULAR TOXICITY

Dr Nicola Maurea (Naples, IT) illustrated possible cardiovascular side effects, such as heart failure, arterial hypertension, acute coronary syndromes, and venous thromboembolism, with respect to the most frequently used target agents. He presented a classification of cardiotoxic events based on the currently existent 9 classes of anticancer drugs[2] (anthracyclines, HER2 inhibitors, vascular endothelial growth factor inhibitors, Bcr-Abl inhibitors, 5-fluoruracil, checkpoints inhibitors, proteasome inhibitors, histone deacetylase inhibitors, tyrosine kinase inhibitors).

In accordance with this model, heart failure associated with targeted cancer therapies is most commonly reported in patients treated with trastuzumab (2% to 28%).[2] In particular, trastuzumab alone and together with anthracyclines were demonstrated to be strongly associated with the development of left ventricular dysfunction in 45 537 elderly female patients with breast cancer.[3] After 3 years of

follow-up, the occurrence of heart failure or cardiomyopathy differed depending on the treatment received: 32% in patients treated with trastuzumab, 42% with trastuzumab and anthracyclines, and 18% in patients without adjuvant therapy (P<0.001).

Other anticancer drugs that are frequently associated with the development of heart failure are proteasome inhibitors. In particular, after carfilzomib treatment, patients develop heart failure in up to 25% of cases.[1] Furthermore, we have recently learned that immune checkpoint inhibitors (eg, nivolumab, ipilimumab) can be associated with the sudden onset of fulminant myocarditis, but we still do not know how to identify patients at high risk before the commencement of treatment. A recent report looked at 101 case reports of severe myocarditis following immune checkpoint inhibitor treatment.[4] The authors found that this adverse event occurred in all ages, was mostly seen in patients with lung cancer or melanoma, and two-thirds developed myocarditis after only one or two doses of the medication. Death occurred in 46% of patients and each year more cases are described in the literature, which might be due to a more frequent use of this new therapy in recent years and greater awareness for such severe complications.

VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER

Professor Farouk Mookadam (US) focused on venous thromboembolism in patients with cancer, which is considered a frequent cause of morbidity and mortality and may affect as many as 20% of hospitalized patients.[1] Venous thromboembolism is observed with different anticancer therapies, such as histone deacetylase and tyrosine kinase inhibitors.[2] With respect to the treatment of venous thromboembolism in patients with cancer, the CLOT trial,[5] in 672 patients, showed significantly reduced venous thromboembolism recurrence with dalteparin (9%) compared with warfarin (17%) in the 6-month follow-up (HR, 0.48; 95% CI, 0.30-0.77; P=0.002). At the same time, the CATCH trial,[6] in 900 patients, did not show reduced mortality or recurrence of venous thromboembolism with tinzaparin vs warfarin, but tinzaparin was associated with less frequent clinically relevant nonmajor bleeding (HR, 0.58; 95% CI, 0.40-0.84; P=0.004).

Until recently, few data was available about the management of venous thromboembolism with novel anticoagulants, since patients with cancer are often excluded from trials testing novel anticoagulants. The Hokusai VTE Cancer study[7] recently reported noninferiority of edoxaban vs dalteparin in 1050 patients with cancer in reducing the composite of major bleeding or recurrent venous thromboembolism. Further analysis revealed that edoxaban treatment, compared with dalteparin, was associated with a higher rate of major bleeding, but a lower risk of recurrent venous thromboembolism.

DIAGNOSIS OF CARDIOVASCULAR SIDE EFFECTS

Dr Ana Barac (US) discussed the current challenges in the early detection of antineoplastic treatment-related cardiovascular complications. Macroscopic alterations can be detected through different diagnostic tools, such as cardiac biomarkers, echocardiography, cardiac magnetic resonance, or nuclear cardiac imaging.[1] Dr Barac stated that patients with cancer treated with anthracyclines and HER2-target agents frequently receive routine cardiac imaging before, during, and after anticancer therapy,[1] whereas patients treated with other agents, such as tyrosine kinase inhibitors, vascular endothelial growth factor antagonists, and immune checkpoint inhibitors, are infrequently referred to a cardiologist in the clinical routine. She recommended, particularly in high-risk patients, to perform echocardiography before treatment and then reassess left ventricular ejection fraction at least every 3 months. If abnormalities are detected, an interdisciplinary team, including oncologists and cardiologists, should discuss a joint treatment plan.

A rather new tool, which is considered more sensitive than the assessment of left ventricular ejection fraction, is the determination of global longitudinal strain.[8] It has been discussed as a good predictor of subsequent deterioration of left ventricular function; therefore, it may help identify patients who need additional attention. Cardiac magnetic resonance is another option, which is particularly useful in suspected cardiac injuries, not detectable by standard echocardiograms. Its accuracy and characterization of myocardial fibrosis helps in the definition of different phenotypes of myocardial injuries.[1] However, this diagnostic procedure is supplementary to the echocardiogram and only accessible in specialized centers.

ESC REGISTRY ON CARDIO-ONCOLOGY

Professor Maurizio Galderisi (IT) showed the first results obtained from the ESC Cardio-Oncology Toxicity Registry,[9] which involves 132 participating centers in 26 different countries and is aiming to include 3 000 patients. At the congress, the baseline characteristics of the first 1972 female patients with breast cancer were shown and discussed: 2% of patients presented with atrial fibrillation, 9% had a diagnosis of diabetes mellitus before or during enrollment, 29% had arterial hypertension (15% not pharmacologically controlled), 21% suffered from dyslipidemia, 23% presented with obesity, and 12% had thyroid disturbances. Concerning the prevalence of metabolic syndrome, 19% of the patients had at least two cardiovascular risk factors and 10% of the patients were in NYHA classes II-IV. Regarding prior anticancer drug treatment, 30% of patients had completed therapy at the time of the recruitment and 32% were currently undergoing chemotherapy treatment (39% anthracycline-based therapy), with 15% of patients having already received radiotherapy before. At the time of enrollment, an echocardio-

gram was performed in 96% of participants, whereas a resting electrocardiogram was conducted in 73%. Moreover, the percentage of patients who presented with any signs of anticancer drug cardiotoxicity was 15%. After 3 months of follow-up, uncontrolled hypertension had decreased from 15% to 10%, while no significant differences were reported concerning change in NYHA class.

CONCLUSION

This session dealt with new possibilities in terms of clinical interventions and diagnostic instruments to contrast cardiovascular complications that frequently occur during and after antineoplastic treatment in patients with cancer. Improvements in the early detection of cardiovascular dysfunctions are promising and research interest in this field is steadily growing. To continue advancing treatments in cardio-oncology, cardiologists and oncologists have to work together in a multidisciplinary team. ■

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