Europa Donna – The European Breast Cancer Coalition held a webinar on metastatic breast cancer (MBC) advocacy to provide women with the latest knowledge on the topic as well as an opportunity to connect and share strategies to advocate with and for other women with this disease. Twenty-nine participants from 14 of the Coalition’s 47 member countries connected on this virtual course on 17 and 18 June, which covered topics ranging from MBC treatments to patient-doctor communication and the financial impact of MBC. Among the participants with MBC, many had been diagnosed in the last 2 years – a first breast cancer diagnosis for some – and many were under 45 years old. A few had been advocates since they were diagnosed 5 or 6 years ago, and one had just returned to work. Europa Donna began holding yearly MBC conferences and training in 2017 in keeping with its priorities of education and addressing the unmet needs of women with MBC. This was the third virtual conference – virtual by choice this time – given that the remote format may make participation more feasible for women with MBC.

In the conference opening, Europa Donna CEO Marzia Zambon reminded advocates of the Coalition’s continued collaboration with the European Parliament and its commitment to implementing the 2015 Written Declaration on Breast Cancer that calls for women with MBC to be treated in specialist breast centres by a multidisciplinary team. She provided the top-line results of an ED survey in 2021 showing that the main issues of concern for women with MBC in 30 countries included having national cancer registries that incorporate MBC as a secondary diagnosis, access to treatment, support for women with MBC and their families, and a better understanding of MBC by the lay public. “Based on all of our findings and our priorities, we need to train advocates to intercede on behalf of other women with this disease. That is what we are doing here today,” she said.
Focus on Treatment & Research on MBC*

Dr Fatima Cardoso, Director of the Breast Unit in Champalimaud Clinical Centre in Lisbon, Portugal and President of the ABC Global Alliance, outlined the complex topic of treatment and ongoing research for MBC. Regarding definitions, advanced breast cancer (ABC) comprises both breast cancer that is locally advanced and inoperable (stage 3) and MBC, where cancer has spread to distant sites, such as bone, lung or liver (stage 4). Although cancer at the advanced stage is not curable, she said that the aim is to balance treatment efficacy and toxicity and delay distant disease, such that ideally, one day soon, MBC will become a chronic disease.

Treatment choice should consider patient preferences, and characteristics of the patient, the disease, and the tumour, to create a fine balance between quantity and quality of life. She added that patient preferences are always important, especially when treating a disease that is not curable. In the case of a relapse, it is valuable to know what previous treatments were used and the interval time, to determine the tumour burden, the patient characteristics and the biological age.

Tumour biomarkers can help to match the right treatment to the right patient. In routine clinical practice, ABC6 guidelines recommend evaluating tumours for: oestrogen receptor (ER) and HER2 status; presence of BRCA gene mutations; PIK3CA mutation status in ER+/HER2– disease; and PD-L1 status in triple negative breast cancer (TNBC). Dr Cardoso stressed that the quality of care and treatment starts with the quality of the pathology report. She added that, at this point, multi-gene panels are not recommended due to a lack of treatment to address the information they provide. The other main challenge in MBC is “outsmarting” the cancer, as eventually treatments become resistant to therapy. It is important to have access to multiple treatment options so that therapy can be changed when it becomes necessary. Approaches to treatment depend on the tumour characteristics identified in the pathology report: HER2+, triple negative, or ER+/HER2– MBC.

**HER2+ MBC**

In the case of HER2+ MBC, ABC6 guidelines recommend that patients be offered anti-HER2 therapy from diagnosis and that it should be continued during subsequent therapy, unless there are contraindications. The issue of resistance that occurs with other therapies is not a concern. This type of targeted therapy blocks the HER2 receptor on the tumour and stops the tumour from spreading. Dr Cardoso said these therapies, the first being trastuzumab, transformed this subtype of breast cancer from one of the worst outcomes to one of the better outcomes. Pertuzumab, another anti-HER2 therapy, blocks different areas of the HER2 receptors. Based on studies such as CLEOPATRA showing a median overall survival (OS) of almost 5 years with a combination of trastuzumab, pertuzumab and chemotherapy (CT), the ABC6 guidelines recommend this as standard first-line therapy for patients who have not had previous anti-HER2 therapy, and as an important option in those who have it in a neoadjuvant setting. The next advance came with trastuzumab emtansine (T-DM1), an antibody drug conjugate that uses trastuzumab to transport CT inside the tumour cell, making it more targeted and less toxic. Then came trastuzumab deruxtecan (T-DXd), which delivers even more CT into the cell. The DESTINY trial compared T-DXd and T-DM1 in patients who had mostly been on previous lines of therapy. An interim analysis showed 1-year progression-free survival (PFS) rates of almost 76% for T-DXd vs 34% for T-DM1, as well as a greater improvement in overall survival (OS). However, this was not without risk, as rare cases of fatal lung disease can occur. With this as a caveat, ABC6 recommends T-DXd, where approved and available, as a second-line option in patients previously treated with trastuzumab + pertuzumab. It could also be used in later lines of therapy. For those without access or with contraindications to T-DXd, T-DM1 is the preferred second-line therapy. Lastly, the tyrosine kinase inhibitor tucatinib combined with trastuzumab and capecitabine is an option for later lines of therapy, as this combination led to a small difference (median 4 months) in OS vs trastuzumab plus capecitabine in heavily pre-treated patients. An advantage of this therapy is that it can cross the blood-brain barrier into the brain for patients with active brain metastases.

In conclusion, Dr Cardoso said that for this ABC subtype, trastuzumab is a must-have, pertuzumab is very important to have, and T-DM1, T-DXd and tucatinib are good to have, and emphasised that it is crucial to keep blocking the HER2 pathway even after the disease has progressed several times. She said that in patients with complete remission (ie, no visible signs of disease), it may be possible to stop anti-HER2 treatment after 5 years, although evidence for the optimal duration is lacking. It is important for women to be able to restart this therapy if the disease progresses, and health systems must support this approach.

**Triple-Negative MBC**

In TNMBC, which has no currently identified targets for treatment and has the worst outcome, research is underway to identify hidden subtypes. Currently, chemotherapy is the mainstay of therapy for TNMBC. Sequential monotherapy (ie, one therapy given at a time) is preferred over combinations, and the latter should be reserved for rapid progression. Giving lower doses can make the drugs tolerable for longer and also make it possible to give them for a longer period of time (ie, metronomic CT, where minimum effective doses are administered continuously, although randomized trial results are needed). Dr Cardoso added that, when possible, the side effects of each drug and the characteristics and wishes of each patient can guide treatment choice. Oral CT is an effective, cost-effective and more convenient approach for women than intravenous CT. In the case of PD-L1+ tumours, immunotherapy with checkpoint inhibitors plus CT has shown better PFS (4 months) over CT alone and is the ABC6 preferred first-line option in this MBC subtype. PARP
Inhibitors are a targeted approach for patients with BRCA mutations and are a preferred option over CT due to their benefit for PFS, better quality of life (QoL) and toxicity profile. An antibody drug conjugate sacituzumab govitecan (SG) has shown a 5.5-month OS benefit, and is recommended in patients with 2 or more earlier treatments, alongside early management of side effects. Dr Cardoso added that maintaining QoL by preventing or addressing adverse events early is important so that patients can remain on each therapy option for as long as possible. She added that while benefit in survival has been seen for the first time with some treatments in TNMBC, their cost remains a barrier to treatment in some settings.

ER+/HER2– MBC

In cases of ER+/HER2– tumours, endocrine therapy (ET) is the preferred approach and should be continued in multiple lines without chemotherapy, unless it is needed (eg, in severe organ dysfunction). To delay ET resistance, the standard of care is combining ET with a CDK4/6 inhibitor, which increases OS and QoL. ET with a CDK4/6 inhibitor can be given in newly occurring or recurrent MBC, as first- or second-line therapy to post-menopausal women, and, in combination with an LHRH agonist, to pre-menopausal women, and men. Dr Cardoso noted that no CT provides such a benefit for OS as this combination of ET and a CDK4/6 inhibitor. It has been shown to delay the time to first CT by about 1 year. She said that it is important to advocate for this approach over CT. When ET resistance occurs, the next option is mTOR inhibitors (eg, everolimus), which prolong PFS. Adverse events such as stomatitis (mouth sores and inflammation) can be prevented with a steroid mouthwash; the DESIREE study showed that starting with a lower dose led to better QoL with the same efficacy as the standard dose. Following aromatase inhibitor (AI) therapy, PI3KCA inhibitors (eg, alpelisib) in combination with fulvestrant are the next approach in PIK3CA-mutant tumours for an approximate 5.5-month PFS benefit. Some adverse events can also be prevented with treatment such as antihistamines. In conclusion, Dr Cardoso said that several ETs (tamoxifen, AIs and fulvestrant) are a must-have; CDK4/6 inhibitors are important to have; mTOR inhibitors and PI3KCA inhibitors are good to have; and several CT agents are must haves, for when the prior list is no longer effective.

Research

In terms of research, many trials are ongoing. Some research has shown that in tumours with an ESR1 mutation, AI therapy is not the optimal approach. The ABC6 recommendation is that treatment should not be changed based solely on the presence of this mutation and the confirmation of disease status is mandatory. Nonetheless, ESR1 mutation status is not mandatory for management. Newer therapies are also being investigated that target HER2-low MBC (ie, where HER2 is present but not sufficient enough to be considered HER2+). T-DXd has shown encouraging results with an increase in median PFS of 4.8 months, although some high-grade toxicity was recorded. As a general rule, Dr Cardoso noted that in clinical trials, in addition to the severe adverse events, it is always important to check for the number of patients discontinuing treatment due to adverse events. She also advised patients to always inform their doctors about all of the treatments they are taking, including complementary approaches, as these can affect the efficacy and safety of their other therapies.

Patient-Doctor Communication is a Two-Way Street

Dr Gabriella Pravettoni, Director of the Psycho-oncology Division at the European Institute of Oncology in Milan, Italy, outlined the main communication challenges surrounding MBC. She said that as most information in the lay press and elsewhere focuses on early breast cancer, there can be misperceptions that all breast cancer can be prevented or cured. At the same time, contrary to the common perception that MBC always has a poor outcome, many women with MBC can now live long-term with the disease, although the duration of survival varies. An important challenge for patients is learning to live with uncertainty because the illusion of being eternal is lost: birth and death are the beginning and end, life is the period in between, but birth is the only known factor for everyone. She said that most women with MBC report that the disease has a negative impact on their lifestyle, finances and work life, among other areas. As a result, communicating with patients involves a global view that takes into consideration their overall environment and encourages them to share their experiences and to seek emotional support. For the clinician’s side of the communication, she said that it is important for them to focus on cognition rather than emotion and help patients make decisions. Patients can fill in mood questionnaires (eg, depression and anxiety screeners) in the waiting room and this can help oncologists adjust their approach according to the results. Dr Pravettoni quoted a Cancer Australia statement on influencing best practice in MBC from 2019, including 3 entries on communication: 1) involve a multidisciplinary team with a key contact person in charge of supporting communication and coordinating patient-centred care; 2) communicate effectively and sensitively with patients and families, providing timely and comprehensive information; and 3) take into account unmet needs (eg, pain management, psychosocial symptoms). She emphasised that patients with MBC have different personalities and needs and make decisions differently, and communication must be adjusted accordingly.
Benefits of Exercise & Physical Activity in Managing Side Effects

Dr Jana Müller, an exercise oncology researcher from the National Center for Tumor Diseases in Heidelberg, Germany, is collaborating on the EFFECT study, which is currently underway to define the role of structured exercise on QoL, fatigue, and other disease- and treatment-related effects in MBC. The study is part of PREFERABLE, an international collaborative project funded by the European Union, in which Europa Donna is a partner. Dr Müller said that most research is based on early breast cancer, and generally indicates that exercise has benefits for QoL. More specifically, she outlined the evidence for three of the main side effects of therapies: fatigue, chemotherapy-induced peripheral neuropathy (CIPN), and joint pain. Fatigue is the most common and most-studied side effect. She cited two meta-analyses indicating that exercise (whether strength training, endurance or yoga), psychological interventions, or a combination of both, were more beneficial for cancer-related fatigue after primary treatment than pharmacological interventions. In CIPN, multimodal training (ideally a combination of balance, strength, and endurance training) can be beneficial for both symptom prevention and usual care. For joint pain, which affects about 50% of women on aromatase inhibitors, a combination of strength and endurance training can reduce this symptom by almost 30% compared with usual care. Regarding the general amount of exercise recommended, she cited the American College of Sport Medicine guidelines FITT criteria (frequency, intensity, time, type). For example, endurance training at moderate intensity at least three times per week for at least 30 minutes can reduce fatigue but also anxiety and depression, whereas resistance training twice weekly can help control lymphoedema. Dr Müller concluded that, overall, a combination of strength and endurance training provides the greatest benefits, and that any physical activity is better than none at all.

The Financial Impact of MBC & Inequalities Among Countries

Dr Richard Sullivan, Professor of Cancer and Global Health at King's College London and Director of the Institute of Cancer Policy and co-Director of the Conflict and Health Research Group in London, United Kingdom, told the participants that there are vast disparities in health care access and provision among countries and within them. The reality of affordable cancer care is difficult to estimate as it requires putting a monetary value on a human life. Cost assessments need to balance many factors, including cost of treatment and loss of productivity due to illness or death. Increased delays in diagnosis and treatment have human and economic consequences, including higher prescription costs and loss of productivity. A 4-week delay in breast cancer surgery is estimated to lead to 10 extra deaths per 1000 women. One of the main issues to be addressed is the lack of trained medical personnel – even before the pandemic – and technology will not be able to replace these highly skilled individuals. Dr Sullivan added that for cancer medicines, only 40% of the cost is from manufacturing, while the rest goes to the supply chain. While the goal of universal health care is for no woman to have to pay for her breast cancer care, the costs of treatments surpass the average annual income in some countries. Across Europe, 60 to 70% of the breast cancer costs (drugs, etc) are paid privately, mostly out of pocket. For advocacy, he said this type of research provides the kind of data needed to change political minds and can be harnessed in advocacy campaigns.

Workshops & Networking

As a fundamental portion of the webinar agenda, the MBC advocates participated in two separate workshops to discuss their experience and advocacy strategies related to overcoming the stigma and taboos of an MBC diagnosis and managing side effects. The second day of the course consisted of an advocacy skills training workshop, designed specifically for this event.