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LETTERS TO THE EDITOR

Chimeric antigen receptor macrophages for breast cancer: An emerging treatment modality

Dear Editor,

Since the introduction of the chimeric antigen receptor (CAR) concept in 1989 [1], T cell therapy has shown promise in hematologic malignancies; however, applications to solid tumors have been challenging [2]. Breast cancer is no exception. Ongoing and concluded clinical trials on leveraging CAR-T cell therapy for breast cancer have not materialized in new treatments [3]. This and other solid tumor failures have resulted in the exploration of other immune cells for this approach.

Recently, Klichinsky et al in humanized mouse models with five different xenografts (esophageal, gastric, osteosarcoma, NSCLC, and ovarian) and metastatic tumor nests, have demonstrated the potential of CAR macrophages (CAR-M) towards employing their phagocytic and adaptive immune response stimulation capabilities. Their experiments showed induction of pro-inflammatory pathways, activation and maturation of dendritic cells, recruitment and activation of T-cells after phagocytosis. Overall, they have demonstrated that programmed macrophages can help diminish the tumor burden, influence tumor microenvironment and generate a vaccinal effect [4].

From a breast cancer perspective, we found two points in this research to be notable. First, these effects were maintained in the presence of tumor-associated macrophages (TAMs), which are associated with poor outcomes [5]. Second, the CAR-Ms had a significant impact on HER2+ ovarian cancer cell lines. Given the unmet need in refractory and advanced-stage breast cancer populations, we believe research into the utilization of CAR macrophages in breast cancer is warranted and look forward to advances in this field.

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Machine learning, AI, and breast cancer: A rallying call to drive adoption

Dear Editor,

The application of machine learning in healthcare is exponentially growing. Breast cancer is no exception. In a recently published paper in the Lancet Digital Health, Kim et al demonstrated that a machine learning model was more sensitive in detecting cancers with mass, distortion or asymmetry, T1 and node-negative cancers than radiologists [1]. Such findings warrant a closer look at the growing convergence of artificial intelligence (AI) technologies and breast cancer.To this end, we performed a brief literature review and discovered that the number of publications in this emerging field has tripled over the last five years. We further found that the scope of research cuts across the breast cancer patient journey, including screening [1] and breast cancer risk prediction [2], grading [3], staging [4], and characterization of intratumoral heterogeneity [5].

We believe there is an opportunity for the breast cancer community to mobilize a concerted effort to validate emerging techniques and algorithms towards developing reusable best-in-class tools for both research and clinical applications.We also think that clinicians must upskill to be able to leverage machine learning solutions made available. We are confident that partnering with and incorporating the insights of AI will drive a paradigm shift in breast cancer care.

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Should estrogen receptor positive and progesterone receptor negative and HER-2 negative breast cancer patients be considered as a luminal B subtype?

Dear Editor,

The St. Gallen International Expert Consensus 2013 defined luminal A breast cancer as estrogen receptor (ER)-positive, human epidermal growth factor receptor negative (HER2 -), Ki-67 low, and progesterone receptor (PgR) high, and luminal B breast cancer as ER-positive, HER2 -, and either Ki-67 high or PgR low [1]. Haque et al [2] analyzed response rates and pCR by breast cancer molecular subtype following neoadjuvant chemotherapy (NAC). Among ER-positive breast cancer patients, 322 (2%) cases and 5941 (43%) cases were luminal A and luminal B. Compared with luminal A, luminal B was nearly 30 times more likely to achieve pCR. Interestingly, the overall pCR rate was only 0.3% in luminal A disease. Furthermore, Boland and colleagues assessed the impact of PgR status on the response to NAC in ER +, HER- breast cancer patients [3]. They found that over 30% of ER+, PgR-, and HER- patients will have a breast pCR after NAC and PgR- is the only significant predictor of breast pCR/cRR in this tumor subtype. Taken all together, one would expect that ER+, PgR-, and HER- patients should be categorized in the subgroup of luminal B subtype. This issue needs further investigation.

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T1b with ER negative, HER2-positive, and node-negative breast cancer patients might get benefit from adjuvant chemotherapy

Dear Editor,

The effect of adjuvant treatment in small node-negative HER2-positive breast cancer is a debatable issue. Lin and colleagues [1] in their retrospective study evaluated whether patients with T1a/b, node negative (N-), HER2-positive (HER2+) breast cancers benefited from adjuvant therapy, and explored better treatment strategies for these patients. They concluded that chemotherapy, which is mainly decided by tumor size, failed to show survival benefits for patients with T1a/b, N-, HER2+ breast cancers. ER status, rather than tumor size, is important for clinicians to make adjuvant treatment decisions. In clinical practice, we have a difficulty to decide about the use of adjuvant chemotherapy, especially in T1b with ER negative patients. Data about benefit of chemotherapy in this specific group is scarce. However, chemotherapy is generally recommended in NCCN guideline [2]. Different chemo-options are avail-

able such as APT regimen, TC +trastuzumab, TCH, and AC followed by paclitaxel and trastuzumab. Although authors stated that chemotherapy rendered no survival benefit for T1a/b, N-, HER2+, T1b with ER negative patients should be exceptional and should receive chemotherapy. This issue merits further investigation.

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COVID-19 pandemic and some observations about management of breast cancer at private practice

Dear Editor,

COVID-19 pandemic changed common practice in breast cancer [1]. I want to summarize my observations at my private breast cancer clinic in Ankara, Turkey. First of all, some patients feel a lump in the breast. However, they do not visit hospitals for diagnostic procedures due to fear of COVID-19 pandemic. Commonly, they visit the clinic when the lump increases in size. Therefore, patients would come with higher stages of breast cancer. Second troublesome events happen in the follow-up of patients. Some breast cancer patients feel pain in the bone but do not visit the clinic and postpone this visit till the end of the pandemic period. When the pain becomes worse, the patient admits to hospital with possible final diagnosis of multiple metastases. For patients receiving adjuvant treatment (usually 3-weekly chemotherapy regimens) and for metastatic breast cancer patients who need intravenous chemotherapy, this chemo regimen switches to oral chemo-like oral capecitabine or oral vinorelbine. Last but not the least, patients refuse to get radiological procedures to observe progression of their metastatic diseases. Alltogether, it seems that COVID-19 pandemic changed common practice in the management of breast cancer. Further studies will confirm negative effects of COVID-19 pandemic in the management of breast cancer.

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Association between common risk factors and molecular subtypes of breast cancer: Still debatable issue?

Dear Editor,

Breast cancer (BC) is the most commonly diagnosed malignancy in women worldwide and is charsacterized by molecular and clinical heterogeneity. Gene expression profiling studies have classified BCs into four main subtypes: luminal A, luminal B, HER-2 overexpressing, and triple negative breast cancer (basal-like). Although clinical differences between subtypes have been well described in the literature, etiologic heterogeneity has not been fully studied [1,2]. Pizzato and his colleagues [3] compared selected risk factors with BC subtypes, using a case-case approach in 1321 invasive BCs. This case-only study showed that triple negative, compared to luminal A, was negatively associated with higher breast density (BD), while it was positively associated with positive family history of BC, higher education and late age at menarche. Furthermore, this study suggested that luminal BH+(ER+and/or PR+, HER2+), compared to luminal A, was positively associated with higher BD, whereas it was negatively associated with parity. Likewise, we evaluated the associations between several hormonal and nonhormonal risk factors and molecular subtypes of BC [1]. This cross-sectional study consisted of 1884 invasive female BC cases. We found that reproductive and hormonal characteristics (breastfeeding, parity, age at first full-term birth, hormone replacement therapy) were associated with luminal subtype, compared to non-luminal BC, consistent with previous studies. Obesity and overweight increased the risk of triple negative subtype, particularly in premenopausal women. Older age and use of hormone replacement therapy were related to the risk of HER-2 overexpressing BC. Two clinical studies suggest a significant heterogeneity in the association of BC risk factors and tumor subtypes. These studies [1,3] support further evaluation of common risk factors with robust data in large BC population.

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Physiotherapists should be included in multidisciplinary team treating breast cancer patients with axillary lymph nodes dissection

Dear Editor,

Treatment of early breast cancer is managed with multidisciplinary team including breast surgeon, medical oncologist, radiation oncologist, psyho-oncologist. However, the role of physiotherapist is not properly defined. The effectiveness of early physiotherapy in reducing the risk of secondary lymphoedema after surgery (axillary dissection) for breast cancer is hot issue and and was studied. The early physiotherapy group was treated by a physiotherapist with a physiotherapy programme including manual lymph drainage, massage of scar tissue, and progressive active and action assisted shoulder exercises. Researchers found that early physiotherapy could be an effective intervention in the prevention of secondary lymphoedema in women for at least one year after surgery for breast cancer involving dissection of axillary lymph nodes [1]. Physiotherapist could do more to inform patients before and during breast cancer treatment about their risk for lymphedema and the need for prompt diagnosis and treatment of the condition. In conclusion, physiotherapists should be included in multidisciplinary team treating breast cancer involving dissection of axillary lymph nodes.

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Is there any association between conversion rates of HER2 status and metastatic sites in breast cancer patients?

Dear Editor,

In common practice, the receptor status of the primary breast cancer is mainly used to decide the therapeutic management of patients with metastatic breast cancer. However, hormonal receptor and HER-2 receptor status of the primary tumor may change during tumor progression from primary breast cancer to metastatic lesions [1]. The American Society of Clinical Oncology/ College of American Pathologist (ASCO/CAP) guidelines of 2015 recommended that in patients with accessible metastases,biopsy for confirmation and retesting of ER, PgR and HER2 should be offered [2]. Van Raemdonck and his colleagues [3] evaluated progression-free and overall survival by HER2 concordance when treating women with taxane–trastuzumab (± pertuzumab) in first or second line and trastuzumab-emtansine (T-DM1) or capecitabine–lapatinib in later lines. They reported that conversion of HER2 status was seen in 28 out of 74 cases and was mostly observed in hormone receptor-positive tumors. They concluded that patients with a positive conversion of HER2 status derived substantial benefit from first line treatment with taxane–trastuzumab–(pertuzumab) in contrast to patients with HER2 loss. The authors did not report conversion rates of HER2 status according to metastatic sites like bone, liver, lung or brain. Although there were no studies in the literature reporting any association between conversion rates of HER2 status and metastatic sites, one would expect that if positive conversion of HER2 occurs in patients with bone meastases, they would get more benefit in contrast to patients with visceral metastases. This issue merits further investigation.

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