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LETTERS TO THE EDITOR

Patient perspective on sequence order of anthracyclines and taxanes in neoadjuvant chemotherapy in HER2-negative breast cancer patients

Dear Editor,

Neoadjuvant chemotherapy (NACT) is the standard of care for the treatment of patients with locally advanced breast cancer. In addition, NACT is commonly used for primary operable early-stage breast cancer patients with higher proliferative subtypes, such as triple-negative breast cancer and human epidermal growth factor receptor 2-positive disease. Pathologic complete response (pCR) after NACT has been validated as a surrogate marker for improved long-term outcomes. Anthracyclines and taxanes are the most widely used drugs in the neoadjuvant treatment of breast cancer. Traditional practice has been to administer the anthracycline component first, followed by paclitaxel or docetaxel. More recently, data have suggested improved outcomes in the neoadjuvant setting with the reverse sequence of taxane followed by anthracycline. Data exploring optimal sequencing of anthracyclines and taxanes as NACT for breast cancer are limited and inconsistent [1,2]. Tesch and their colleagues [3] investigated the impact of sequence order of anthracyclines and taxanes in NACT on pCR rate in HER2-negative breast cancer patients. They reported that there was no differential impact on pCR rate or clinical outcomes from NACT with sequence order of anthracyclines and taxanes in this real-world analysis of HER2-negative breast cancer patients. However, there have been no studies in the literature that decribe preference of sequence order of anthracyclines and taxanes from patient perspective. Starting with weekly paclitaxel is really easy in most patients and it helps them get over the anxiety and fear of chemotherapy compared to starting anthracyline first. It is a bit longer than other regimens, but it is still better deal for patients than dose dense paclitaxel or full dose every 3 weeks docetaxel. This issue merits further investigation.

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Microsatellite instability (MSI) markers in thyroid carcinoma

Dear Editor,

Among the genetic mechanisms that provide a stable micro-environment inside the molecule, DNA mismatch repair system (DNA MMR) plays a leading role. Specific genomic alterations –germline mutations, accompanied by usually allelic loss (loss of heterozygosity -LOH), or epigenetic changes such as promoter hypermethylation- in the MMR genes lead to loss of their expression affecting their function in repairing the corresponding base to base errors. Microsatellites are referred to repetitive nucleotide sequences including usually 1 to 5 base pairs repeated for 15-30 times which are normally relatively stable. Thousands of microsatellites are detectable throughout the human genome. In fact, during DNA replication accumulation of them forms a small loop in any of two strands. Insertion or deletion of these repeated nucleotide chains are identified also inside the introns of the genes. For all these molecular reasons, microsatellite instability (MSI) is a biomarker for detecting DNA MMR deficiency in colorectal cancers and also in a variety of malignancies of different histogenetic origin [1]. Among the genetic mechanisms that provide a stable micro-environment inside the molecule, DNA mismatch repair system (DNA MMR) plays a leading role. Humanized homologues of DNA MMR main genes are located on chromosomes 2, 3, 5 and 7 including MLH1,

MSH2, MSH3, GTBP/MSH6, PMS1 and PMS2 [2]. Specific genomic alterations-germline mutations, accompanied by usually allelic loss (LOH), or epigenetic changes such as promoter hypermethylation- in the MMR genes lead to loss of their expression, affecting their function in repairing the corresponding base to base errors. In contrast to colon adenocarcinoma, there are limited data regarding DNA MMR deregulation and MSI in thyroid carcinomas. Interestingly, there are differences in MSI levels comparing normal, neoplastic (adenomatous) and malignant thyroid epithelia. A molecular analysis based on a polymerase chain reaction amplification of specific MSI markers (PCR-MSI), detected low-frequency MSI regarding benign follicular adenomas, whereas thyroid carcinoma tissues were characterized by higher levels [3]. Concerning papillary thyroid carcinoma (PTC), a combined comparative genomic hybridization (CGH) and MSI analysis showed lack of MSI for hmlh1 and hmsh2 molecules. In contrast, gross chromosome aberrations were detected associated to vascular or thyroid capsule invasion, evidence of an aggressive phenotype (advanced stage) [4]. Furthermore, genetic (mutations) and also epigenetic modifications (ie promoter aberrant methylation) lead to gene silencing in MSI molecules involved in thyroid cancer rise and progression. Based on quantitative polymerase chain reaction (qPCR) and methylation-specific PCR a study group analyzed MLH1 MSI marker combined with other critical genes including BRAF, RET, IDH1 and NRAS [5]. They observed that MLH1 low expression was correlated with BRAF V600E mutations, RET/PTC rearrangements and transitions (IDH1 and NRAS) in thyroid carcinoma patients.

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Adjuvant pertuzumab plus trastuzumab or adjuvant T-DM1; Which is better?

Dear Editor,

Patients with HER2-positive non-metastatic breast cancer (BC) generally receive adjuvant or neoadjuvant treatment with chemotherapy and trastuzumab, though other HER2-directed agents (pertuzumab, T-DM1) may also play a role in the management. Piccart et al [1] investigated the report the preplanned second interim overall survival (OS) and descriptive updated invasive disease-free survival (IDFS) analysis with median follow-up 74 months in in the APHINITY Trial in which 4.805 patients with node-positive or high-risk node-negative and HER2-positive BC were randomly assigned (1:1) to either 1-year pertuzumab or placebo added to standard adjuvant chemotherapy and 1-year trastuzumab after surgery. They reported that the IDFS benefit from adding pertuzumab to standard adjuvant therapy for patients with node-positive HER2-positive early BC. They also added that longer follow-up is needed to fully assess OS benefit. One of the weaknesses of this study was that node positive patients did not receive neoadjuvant chemotherapy and targeted treatment. Accordingly, KATHERINE study showed a 50% reduction in the risk of recurrence or death with adjuvant T-DM1 versus trastuzumab in patients with residual invasive early breast cancer after neoadjuvant chemotherapy plus HER2-targeted therapy [2]. Therefore, there is a debate for patients having received neoadjuvant treatment, especially with residual disease. Do we go with adjuvant pertuzumab plus trastuzumab or give only adjuvant T-DM1? Persistence of HER2-positivity in residual tumor might signify real trastuzumab resistance in which T-DM1 works better com¬pared to the patients who had HER2-loss in residual disease. However, those patients who had HER2-loss in residual disease might get benefit from adjuvant pertuzumab plus trastuzumab. This issue merits further investigation.

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Considerations for the treatment of esophageal cancer during the COVID-19 pandemic

Dear Editor,

The rapidly expanding coronavirus disease 2019 (COVID-19) has evolved to a pandemic in public health, caused by widespread infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. This pandemic can affect healthy population, oncologic patients and health care professionals without discrimination. The dramatically increasing number of healthy population and health care professionals infected in Western Countries is profoundly changing in daily clinical practice. Resources of health care systems have been redistributed to cope with the pandemic. For patients with cancer, COVID-19 can be challenging, as many of them are immunosuppressed following systemic anticancer therapies [2]. As a result, they are more prone to infection with higher risk of severe effects. All non-urgent procedures such as elective surgery for cancer patients have been severely reduced. During this crisis, the lack of availability of operating theatres, endoscopic suites or planned hospital admissions have forced the entire oncologic community to carefully consider how to treat esophageal cancer (EC).

EC is a highly lethal disease as indicated by the reported overall survival rate of 10-20%. Surgery of EC is particularly associated with higher mortality rates comparing to other malignancies, between 6.7 and 11.5% in tertiary cancer centers [3]. The rate of postoperative respiratory complications is as high as 25% in published literature; hence, a severe acute respiratory syndrome from COVID-19 would present a major risk to life, particularly if respiratory and intensive care resources were unavailable or suboptimal [2]. Furthermore, a question undoubtedly arises: which is the best time for an EC patient to be treated with curative intent.

Given the implications of serious respiratory distress in response to COVID-19 postoperatively, every EC patient planned for elective esophagectomy should be triaged and investigated properly. Recent data suggest that in T1N0 esophageal adenocarcinoma (EAC) or squamous cell carcinoma (ESCC) endoscopic therapy should be considered. In T2N0 disease, both for EAC and ESCC, esophagectomy should be considered possible. In EAC and ESCC patients with advanced disease, initiation or continuing of neoadjuvant chemo/radiotherapy is strongly recommended [2].

Currently, there is no evidence regarding the adoption of esophageal systemic treatments during the COVID-19 pandemic. Alternative schemes for every digestive cancer have been proposed, including esophageal and esophagogastric tumors, based on the consensus of experts [4]. Physicians will also need to consider the level of immunosuppression associated with individual therapy. Neoadjuvant therapy that requires clinic visits and clinician–patient contact must also be considered, and potentially be modified or protracted [5].

The COVID-19 pandemic represents an unprecedented challenge for healthcare systems. Every esophageal surgeon should take into consideration the previous daily battle, trying to help patients deal with a particularly difficult cancer, and this battle within a pandemic on a potentially devastating virus must be maintained as best as we can; these suggestions, not formal recommendations, are a proposed algorithm that hopefully will be of value at a time where traditional paradigms are ended. Every crisis can create numerous opportunities to improve our knowledge and techniques and perhaps the most important aspect of our calling as physicians, to treat our patients effectively.

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Sequential anthracycline and weekly paclitaxel might be more effective compared to docetaxel and cyclophosphamide in the adjuvant treatment of HER2-negative breast cancer patients

Dear Editor,

Standard adjuvant chemotherapy for HER2-negative breast cancer consists generally in an anthracycline and taxane-based regimen (A+T) [1]. The TC (docetaxel and cyclophosphamide) regimen became as a potential alternative treatment. Randomized controlled trials (RCTs) could not demonstrate the non-inferiority of TC over A+T. Caparica and his colleagues [2] performed a systematic literature review and a meta-analysis of RCTs that compared 6 cycles of TC versus sequential A+T in HER2-negative early breast cancer patients and reported that sequential A+T regimen was associated with increased risk of toxicities and no clear survival benefit as compared to 6 cycles of TC. However, schedule information (weekly versus three-weekly paclitaxel or docetaxel) in sequential A+T arm was not defined in that analysis. Interestingly, large The ECOG 1199/Intergroup trial compared the efficacy of 2 different taxanes, docetaxel and paclitaxel, given either q3w or weekly, in the adjuvant treatment of breast cancer patients. They reported that weekly paclitaxel (dose-dense) had improved DFS (p=0.009) and OS (p=0.03), irrespective of their hormone receptor status,especially in patients with HER2-negative disease [3]. As a consequence weekly paclitaxel became a preferred standard regimen, especially given sequentially after 4 cycles of anthracycline. Taken all together, weekly paclitaxel use in sequential A+T arm might be superior to 6 cycles of TC in terms of efficacy. This issue merits further investigation.

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VEGF- mediated mechanisms in nasopharyngeal carcinoma

Dear Editor,

Vascular endothelial growth factor (VEGF) acts as a key mediator of angiogenesis in cancers of different origins. VEGF gene is a member of the PDGF/VEGF growth factor family and is located on chromosome 6 (6p12). Its protein product (VEGF A) is a glycosylated mitogen acting as an endothelial cell growth factor, promoter of cell migration, and inhibitor of apoptosis [1]. Normally VEGF cytokine induces endothelial proliferation and increases vascular permeability, whereas deregulation of its upstream regulators, such as HIF-1a, a transcription factor responsible for the regulation of oxygen homeostasis, leads to a tumour-associated angiogenesis by its overexpression. Under hypoxic conditions, HIF-1a is activated through PI3 kinase – AKT and MAPK–ERK pathways, binding with its complementary factor HIF -1a to the promoters of genes that mediate glycolysis and angiogenesis, such as VEGF [2]. Aberrant secretion of VEGF due to hypoxia, activation of oncogenes, and even EGFR or an abnormal hormonal activity leads to an uncontrolled binding to specific receptors such as VEGFR-1or VEGFR-2.

Nasopharyngeal Carcinoma (NPC) is a unique, aggressive pathological entity included in the Head and Neck Carcinoma (HNC) family of malignancies. Concerning its histological origin, the malignancy is derived from the nasopharyngeal epithelia demonstrating a high invasive and metastatic potential mainly correlated with poor prognosis. Keratinizing, non-keratinizing and Basaloid carcinoma represent its pathological variants that reflect the corresponding cytogenetic features [3]. Epstein-Barr virus (EBV) latent but persistent infection is predominantly implicated in its development and progression. Concerning VEGF implication in NPC, it seems that the molecule influences mechanisms including the epithelial-mesenchymal transition (EMT). A study group showed that VEGF over activation leads to increased metastatic potential (cancerous cell migration and invasion) in VEGF-VEGFR2 signaling transduction pathway –an autocrine feedback loop- by regulating EMT and matrix metalloproteinase (MMP) over expression [4]. Besides VEGF-VEGFR2 interaction, VEGF

involvement in down-stream intracellular pathways such as PI3/AKT/mTOR is observed in NPCs. VEGF-mTOR interaction plays a crucial role in NPC biological behavior. A study group co-analyzing the two molecules reported that VEGF reduced expression is associated with low cell proliferation and enhanced apoptotic levels, whereas the corresponding activation of the mTOR pathway increased autophagy and radiosensitivity in NPC after VEGF depletion [5]. VEGF is not only an important pro-angiogenic factor, but modifies critical signaling pathways and affects specific intracellular mechanisms in NPCs. Sub-group of patients suffering by NPC with specific VEGF-related gene signatures should be eligible for targeted therapeutic strategies.

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Pets might reduce side-effects related to chemotherapy in patients with cancer

Dear Editor,

Animals have had great importance in human life. There is an innate human biological tendency to interact and form close associations and emotional bridges with other forms of natural life, especially with animals. Human behaviour towards animals is complex and involves psychological and cultural factors. Companion animals can contribute to the establishment of a human-animal relation that is behaviourally and neurohormonally similar to the mother-baby relationship. Recognition of the positive aspects of this mutual interspecies relationship has provoked some scholars to investigate the use of animals in promoting human health [1]. Associated with this, a patient of mine diagnosed with breast cancer shared her experience with her cat: "It hurts me deeply to talk about my experience with my cat which has had a cancer surgery on March 28, 2021. I noticed a lump on her back, in fact she showed it to me by meowing gently. While she was being operated, I recalled what she did when I had the fourth chemotherapy cycle. It was a very difficult time because right after I was given the medication, I would vomit several times a day and could not eat or drink anything. Nor could I speak or walk properly. On the sixth day, I could not go to the bathroom when I felt a terrible nausea and just had to vomit on the floor. My cat jumped on the bed in panic. Then I fell over the pillow. She lay down on the pillow, too, resting her back on my face. I could not breathe so I pulled back, but she also pulled back and insisted on pressing her body against my face. We both fell asleep. The point is her lump is exactly where my mouth touched her back. Last week a friend told me that cats are protective and heal people. I am not sure if this is true. I hope not because it is unbearable to think that she took on all the burden and sacrificed herself to save me! I hope I will, God willing, win the fight to save her".

In conlusion, pets can be a great source of comfort and companionship during cancer treatment. In fact, research has shown that pet therapy can have often obvious benefits during chemotherapy if appropriate safety measures are taken. Having a pet by your side can decrease feelings of loneliness, promote a sense of well-being, and even reduce the need for pain medications [1].

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Low-dose metronomic eribulin in metastatic breast cancer: Is this real metronomic therapy?

Dear Editor,

Metronomic chemotherapy is the frequent administration of chemotherapy drugs at doses below the maximum tolerated dose and with no longer drug-free break in metastatic breast cancer (MBC) and other solid tumors. It thus results in a sustained low blood level of the drug without significant toxic side effects. The rationale behind the use of metronomic chemotherapy for longer duration is to decrease adverse drug reactions and to target both endothelial cells and tumor cells which are at proliferating stage. Therefore, metronomic chemotherapy is defined as repeated administration of anti-neoplastic drugs at comparatively low doses frequently and without long drug-free period [1,2]. Chalasati and colleagues conducted an open-label, multi-center, single arm phase II study of metronomic eribulin in patients with MBC whose disease has progressed following at least one prior regimen of chemotherapy in the metastatic setting [3]. All patients were treated with metronomic eribulin (0.9cmg/m^2 administered intravenously on days 1, 8, and 15 of a 28-day cycle). They concluded that metronomic weekly low-dose eribulin is an active and tolerable regimen with significantly less myelosuppression, alopecia, and peripheral neuropathy than is seen with the approved dose and schedule, allowing longer duration of use and disease control, with similar outcomes compared to the standard dose regimen. However, this study design did not meet criteria for metronomıic treatment. In that study, patients received eribulin on days 1, 8, and 15 of a 28-day cycle. Patients did not receive eribulin every week, giving instead 14 days off between day 15 and day 28. It would be more convenient to give eribulin at lower dose on weekly schedule without longer drug-free period like weekly paclitaxel. This issue merits further investigation.

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Histologic subtypes in chemotherapy vs. sacituzumab sovitecan groups might affect progression-free and overall survival in metastatic triple-negative breast cancer

Dear Editor,

Patients with metastatic triple-negative breast cancer have a poor prognosis. Although immunotherapy has shown promising first-line clinical activity, single-agent chemotherapy remains standard for previously treated (beyond first-line) metastatic triple-negative breast cancer. However, chemotherapy is associated with low response rates and short progression-free survival [1].Sacituzumab govitecan is an antibody–drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2, which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker. Bardia et al reported that progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer [2]. The authors did not give detailed information about tumor subtypes. Histologic heterogeneity (metaplastic breast cancer vs. medullary breast cancer vs others) in triple negative breast cancer significantly affect the survival outcome [3]. Therefore, inequal distribution of histologic subtypes in both groups might affect progression-free and overall survival. This issue merits further investigation.

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