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LETTERS TO THE EDITOR

Infiltrating lobular breast carcinoma; is gastrointestinal endoscopy recommended for staging?

Dear Editor,

The tendency of infiltrating lobular breast carcinoma (ILC) cases to gastrointestinal tract (GIT) is higher than infiltrating ductal carcinoma cases. Most of the cases, however, develop during the follow-up of the disease rather than as synchronous presentation. Therefore, staging gastrointestinal endoscopy is not currently recommended for staging of ILC cases. However, any complaints related to gastrointestinal system might warn us of the possibility of ILC metastases to GIT. Interestingly, one study showed that the risk of secondary gastric cancer was higher among young women diagnosed with ILC [2]. Furthermore, gastric cancer and ILC metastasis to stomach might be misdiagnosed and we should be careful in this regard. Taken all together, ILC cases should not undergo gastrointestinal endoscopy during staging work-up.

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Some concerns about adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer

Dear Editor,

There has been no single standard treatment recommended for patients with small, node-negative, human epidermal growth factor receptor type 2 (HER2)-positive breast cancers. Tolaney et al. [1] reported 7-year follow-up analysis of adjuvant paclitaxel and trastuzumab (APT) trial for node-negative, human epidermal growth factor receptor 2 (HER2)-positive breast cancer. They showed that adjuvant paclitaxel and trastuzumab was associated with excellent long-term outcomes. In this phase II study, although patients with HER2-positive breast cancer with tumors 3 cm or smaller and negative nodes were enrolled, only 9% of all cases were having tumor size of 2.0 to ≥3.0 cm. Apparently, it is very difficult to draw a conclusion that APT was efficacious in this group. Secondly, hormone receptor positivity (67%) rate in all cases was higher compared to hormone receptor positivity (50-55%). in other adjuvant trastuzumab trials [2,3]. This might explain that recruiters might not be initiating to enroll hormone receptor negative patients into this study. Twenty-three events reported during follow-up. However, the authors did not describe any association between tumor size and number of events. As a whole, we have to be cautious to treat small HER-2 positive and node-negative tumors with APT, especially if tumor size is more than 2 cm and/or hormone receptor is negative.

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C-myc deregulation in pancreatic carcinomas

Dear Editor,

Oncogenes' overactivation combined with suppressor genes' downregulation represents a genetic mechanism providing genomic imbalance in solid malignancies. Among them, C-myc proto-oncogene -the human cellular homologue of the v-myc oncogene of avian myelocytomatosis retrovirus MC29 - which is located at chro¬mosome 8 (cytogenetic band: 8q24.12-q24.13), is found to act as a strong transcription factor, implicating in the control of cell differentiation and apoptosis. This gene encodes a nuclear phosphoprotein. Induction of this transcription factor by gene amplification promotes cell proliferation and transformation by activating growth-promoting genes, including the ornithine decarboxylase (ODC1) and CDC25A genes and also the E2F1, E2F2 and E2F3 genes [1]. The c-myc protein activates transcription as part of a heteromeric complex with MAX. Not only amplification but also C-myc translocation is involved in Burkitt lymphoma and multiple myeloma. C-myc is also involved in direct human telomerase activation by inducing expression of its catalytic subunit, h-TERT. Concerning pancreatic normal histogenesis and homeostasis, C-myc is highly expressed in pancreatic multipotent progenitor cells (MPC) but progressive silence of the gene leading to its protein low expression seems to be a critical event for pre-acinar to acinar normal maturation [2]. In fact, C-myc aberrant expression in pre-acinar cells leads to a disorganization of the differentiation mechanism in these cells. In pancreatic ductal adenocarcinoma (PDAC), C-myc overexpression is a relatively frequent gene abnormality with specific interest for developing novel targeted therapeutic strategies in subgroups of patients characterized by specific genetic signatures [3]. Interestingly, the role of programmed cell death-1 (PD-1) gene and its interaction with C-myc I PDACs is under investigation. The PDL1 (gene locus: 2q37.3) protein encodes a cell surface membrane protein of the immunoglobulin super-family. It acts as an immunoinhibitory receptor of the CD28 family, involved in tumor immune escape process. A combined C-myc/PDL1 protein expression analysis showed that probably there is a synergistic overactivation of the two molecules [4]. Based on this observation, development and application of novel agents -such as JQ1, which is an inhibitor of C-myc that also inhibits PD-L1 - is critical for subgroups of patients exhibiting specific genetic imbalances. Besides PDAC, C-myc deregulation is detected also in another type of pancreatic carcinoma, the pancreatic acinar cell carcinoma (PACCs). A combined protein (immunohistochemistry) and molecular (fluorescence in situ hybridization) analysis for expression levels and C-myc/chromosome 8 numerical imbalances showed that there are different protein expression patterns due to gene amplification combined or not with chromosome 8 polysomy [5].

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All-oral (vinorelbine plus capecitabine) combination regimen might be preferable to oral vinorelbine or weeky paclitaxel in estrogen receptor-positive, HER2-negative patients with visceral metastasis

Dear Editor,

For many metastatic breast cancer (MBC) patients, especially receiving third- or fourth-line chemotherapy, an active all-oral combination chemotherapy regimen that avoids the need for intravenous treatment administration visits at the clinic might be preferable. Aapro and colleagues compared first-line oral vinorelbine versus weekly paclitaxel in a phase II trial with 131 patients with MBC (NorBreast-231 trial) [1]. They reported that oral vinorelbine and weekly paclitaxel demonstrated similar disease control rates (DCRs) (~75%). Visceral involvement in all patients was 78-79% and equally distributed in both groups in this trial. Although international guidelines recommend monotherapy

for MBC [2], combination chemotherapy might be preferable in MBC with visceral metastases. It is worth to mention a recent phase II study (NorCap-CA223 Trial) that compared first-line all-oral (vinorelbin plus capecitabine [NORCAP]) versus taxane-based chemotherapy (gemcitabine plus paclitaxel or gemcitabine plus docetaxel) for HER2-negative MBC 3]. DCRs were similar in all groups. They concluded that all-oral NORCAP is an active first-line chemotherapy regimen and might be offered as an alternative to first-line taxane-based therapy for HER2-negative MBC, particularly if patients wish to avoid alopecia or frequent intravenous administrations. In conclusion, all-oral NORCAP regimen might be preferable to oral vinoreline or weeky paclitaxel specifically in MBC with visceral metastases. This issue merits further investigation.

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Strict definition of inflammatory breast cancer should be revisited

Dear Editor,

Inflammatory breast cancer (IBC) is a rare subtype accounting for up to 6% of all breast cancers. IBC is a highly aggressive subtype that leads to significant breast cancer-related mortality. The 5-year survival of patients with this cancer type is worse compared to other breast cancer types. However, the combinations of neoadjuvant chemotherapy, surgery and radiotherapy have led to an improvement in prognosis [1]. Interestingly, IBC is often misdiagnosed. A diagnosis of IBC is based on clinical findings that require erythema and dermal edema (peau d'orange) of at least one-third of the skin of the breast due to blockage of dermal lymphatics by tumor emboli. Dermal lymphatic involvement is neither required nor sufficient by itself for a diagnosis of IBC [2]. Furthermore, axillary lymph node involvement in patients with locally advanced non-IBC also might lead to skin edema on the same breast due to lymphatic blockage in the axilla misdiagnosed as IBC [3]. In conclusion, strict definition of IBC is emergently needed to promote the proper diagnosis and treatment of IBC.

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Interaction of brivudine with capecitabine: A case of serious toxicity

Dear Editor,

Brivudine, a medication for the treatment of herpes zoster, irreversibly inhibits dihydropyrimidine-dehydrogenase. 5-Fluorouracil (5FU) is a widely used chemotherapeutic drug, and is metabolized via the degradation pathway of pyrimidines [2,5]. The first enzyme in this pathway is dihydropyrimidine-dehydrogenase, which catabolizes 5FU in $5FUH_2$ [1,3,4]. Capecitabine is an oral-5FU prodrug that is hydrolyzed in the liver and other tissues in 5FU. Coadministration in a patient, of brivudine and 5FU or capecitabine, may lead to unacceptable toxicity, and in some cases to death [2,4]. Brivudine should be administered at least 4 weeks after 5FU or capecitabine therapy, in order to avoid toxicity from reduced 5FU catabolism.

We present a case of a 44-year-old female, with K-ras mutant, metastatic colon cancer, that received FOLFOX and bevacizumab as first-line chemotherapy, with partial response. After the completion of 12 cycles, maintenance treatment with capecitabine (1,250 mg/m^2 daily, continuously), and bevazizumab (7.5 mg/kg every 21 days) was initiated. No adverse events occurred during the first five

cycles. The patient received brivudine (125 mg daily) for herpes zoster on days 8-14, of the sixth cycle. During brivudine administration, capecitabine was not administered. However, accidentally, the patient received capecitabine again on day 16, for a total of 5 days. Four days later, the patient presented with stomatitis and dysphagia. A grade III stomatitis/esophagitis and thoracic-facial maculopapular rash were observed. From the laboratory test, the patient had initially grade I neutropenia (neutrophils, 1,800/μL), grade I anemia (hemoglobin, 10.4 g/L), and grade I thrombocytopenia (platelets, 75,000/μL). In the course of hospitalization, the patient showed severe and prolonged haematological and non-haematological toxicity: neutropenia (minimum neutrophils, 0/μL on day 7 of hospitalization). Anemia (minimum hemoglobin, 8.1 g/dL on day 10 of hospitalization). Thrombocytopenia (minimum platelets, 20,000/μL on day 9 of hospitalization). Thoracic and facial maculopapular rash, stomatitis/oesophagitis grade III. Diarrhea, grade III. Alopecia, grade II on day 3 of hospitalization.

The patient was symptomatically treated with prednisone 1mg/kg, intravenous hydration, broad-spectrum antibiotic therapy (piperacillin/tazobactam, teicoplanin), antifungal treatment (fluconazole), concentrated red-blood cells/platelet transfusions and filgrastim. Hospitalization was complicated with *C.Difficile* infection (treated with oral metronidazole). After 21 days of treatment, the patient fully recovered from hematological and gastrointestinal toxicity and was discharged in good overall condition.

Brivudine, a thymidine analogue, is an antiviral agent, active against herpes-simplex virus type-I and varicella-zoster virus (herpes-zoster). It is a potent and irreversible inhibitor of dihydropyrimidine-dehydrogenase. Insufficiency of this enzyme, may lead to severe toxicity [5]. The reduction in dihydropyrimidine-dehydrogenase activity is more than 90% and is restored after 18 days of discontinuation of brivudine [1,3,4]. A pharmacokinetic study in humans showed that brivudine resulted in a significant increase in the half-life of 5FU to 4-7 hours (instead of 8-20 min), and the drug concentration in the blood by 5-15 times [5]. There have been only a few cases reported in the literature, of drug-drug interaction, due to concomitant administration of brivudine, with either 5FU or capecitabine. Most of the cases experienced severe haematological and non-haematological toxicities, similar to those of our patient [1,3].

Consequently, coadministration of brivudine with 5FU or capecitabine is contraindicated. Treating physicians have always to be aware of this severe drug-drug interaction.

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Screening imaging of the brain might be considered in triple negative breast cancer patients receiving neo-adjuvant chemotherapy with a high-risk score features

Dear Editor,

Brain metastases (BM) represent a significant cause of morbidity and mortality among patients with breast cancer. Patients with human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer (TNBC) subtypes experience significantly higher rates of BM. Current breast cancer screening guidelines do not recommend routine assessment BM via imaging of the brain in breast cancer patients with localized disease [1]. Martin et al [2] characterized the incidence proportions and median survivals of patients with breast cancer and brain BM at the time of cancer diagnosis. They identified 968 patients with BM at the time of diagnosis of breast cancer, representing 0.41% of the entire cohort. Incidence proportions were highest among patients with hormone receptor (HR)-negative HER2-positive (1.1% among the entire cohort, 11.5% among patients with metastatic disease to any distant site) and TNBC (0.7% among the entire cohort, 11.4% among patients with metastatic disease to any distant site). Gabani and colleagues [3] developed a simple predictive model to stratify the risk of BM in TNBC patients receiving neo-adjuvant chemotherapy (NAC), surgery, and radiation therapy. They found that lack of downstaging and persistent lymph node positivity (high-risk group) after NAC are associated with development of BM in TNBC. These findings might support the consideration of screening imaging of the brain for patients with TNBC with a high-risk score. This issue merits further investigation..

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Efficacy of neoadjuvant endocrine therapy versus neoadjuvant chemotherapy in luminal A or luminal B breast cancer patients: Does it matter?

Dear Editor,

Neoadjuvant chemotherapy (NACT) is preferred in stage II/III triple-negative breast cancer (TNBC) or HER2-positive disease, in stage II/III ER-positive, if it is clear that chemotherapy will be administered and if optimal surgical treatment will be facilitated by NACT [1]. Neoadjuvant endocrine therapy (NET) is associated with similar response rates as NACT but with significantly lower toxicity, especially in hormone receptor-positive and HER2-negative breast cancer. LeVasseur and colleagues [2] investigated the efficacy of NET versus NACT in a matched cohort analysis of 176 ER-positive breast cancer patients. Clinical downstaging was more frequent with NACT (20/51, 39%) compared to NET (11/51, 22%; p=0.032). Of these, 2% achieved pathologic complete response (pCR) in each cohort. The authors concluded that significantly higher rates of downstaging were achieved with NACT compared to NET when patients were matched. However, the authors did not analyze ER-positive breast cancer patients according to luminal A or luminal B subgroups. Haque et al [3] analyzed response rates and pCR by breast cancer molecular subtype following NACT. 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. These results might show that NET might be preferred especially in luminal A patients among ER-positive breast cancer patients.

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Regular daily consumption of cruciferous vegetables may be effective for prevention and treatment of breast cancer by reactivating PTEN tumor suppressor

Dear Editor,

Many targeted agents used to treat cancer today block proteins produced by oncogenes that encourage cancer cells to grow. Another class of proteins important to cancer development are tumor-suppressor proteins, like PTEN and p53. These proteins normally act to stop abnormal cell growth, but they can lose this function in cancer cells. If they could be turned back "on" with drugs, such an approach would be another option to treat cancer. PTEN is a critical tumor suppressive phosphatase that is active in its dimer configuration at the plasma membrane. Polyubiquitination by the ubiquitin E3 ligase WWP1 (WW domain-containing ubiquitin E3 ligase 1) suppressed the dimerization, membrane recruitment, and function of PTEN. Pharmacological inhibition of WWP1 triggered PTEN reactivation and unleashed

tumor suppressive activity [1]. Interestingly, the authors identified indole-3-carbinol, a compound found in cruciferous vegetables, as a natural and potent WWP1 inhibitor. Many cancer types, including breast, frequently lose some of their PTEN function as they grow. Consequently, proteins that are normally kept in check by PTEN (a signaling pathway) can become overly active and can drive uncontrolled cell growth. In conclusion, these findings suggest that regular daily consumption of cruciferous vegetables might be a potential therapeutic strategy for breast cancer prevention and treatment through PTEN reactivation and this issue merits further investigation in human studies.

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