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LETTERS TO THE EDITOR

Predictive markers for trastuzumab-associated cardiac dysfunction in patients with early-stage human epidermal growth factor receptor 2–positive breast cancer receiving trastuzumab

Dear Editor,

Trastuzumab is used in the treatment of patients with human epidermal growth factor receptor 2 (HER2) –over-expressing breast cancer. Trastuzumab-related cardiac dysfunction (TRCD) is different from anthracycline-induced cardiotoxicity. TRCD is commonly reversible. Left ventricular ejection fraction assessment is standard for cardiac monitoring in routine practice and does not predict early TRCD signs. New markers for prediction of TRCD are needed [1]. Zardavas et al. [2] explored the prognostic value of cardiac markers (troponins I and T, N-terminal prohormone of brain natriuretic peptide [NT-proBNP]) to identify patients at increased risk for TRCD in patients with early-stage HER2–positive breast cancer receiving trastuzumab (HERA substudy). The authors reported that elevated troponin I or T before trastuzumab is associated with increased risk for TRCD. Associated with this, a recent study by Beer et al. [3] investigated new biomarkers associated with doxorubicin- and trastuzumab-induced cancer therapeutics-related cardiac dysfunction (CTRCD) using high-throughput proteomic profiling and they found that high baseline immunoglobulin (Ig) E levels are associated with a lower risk of CTRCD, pointing out the immune system as a potential mediator of CTRCD. As a conclusion, evaluation of baseline Ig E level in addition to the aforementioned cardiac markers may robustly identify patients at increased risk for TRCD.

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Athens Eye Hospital Ocular Oncology multidisciplinary team providing combined treatments for patients with choroidal melanoma: 3 years results

Dear Editor,

Management of ocular choroidal melanoma involves either conservative treatments (aiming to kill the tumor and to save the eye and vision) or radical treatment-enucleation (amputation of the eye). The majority of these patients receive care in specialized ocular oncology centers worldwide, that offer both conservative and radical treatments by multidisciplinary ocular oncology teams. Conservative treatments became more popular since the Collaborative Ocular Melanoma Study (COMS) [1] showed similar efficacy and equal survival rates between patients receiving enucleation and plaque brachytherapy. These globe-salvaging treatments are further divided into radiotherapies, phototherapies and local resection techniques. Radiotherapies (Plaque Brachytherapy and Proton beam

irradiation) are the most popular treatments with excellent rates of local tumor control, while phototherapies are only used for small tumors. Local resection techniques are technically very demanding (there is a need for hypotensive anesthesia), have lower rates of local tumor control but few surgeons worldwide elect to perform these operations for young patients with large melanomas in an attempt to avoid radiation-induced ocular complications, aiming also to achieve maximum functioning vision.

Until recently the management of choroidal melanoma patients in the Balkan countries was confined to enucleation, or if the tumor allowed and the patient wished to save the eye, then referral to ocular oncology units in Central and North Europe followed (where all the therapeutic modalities could be offered). Few cases were managed by stereotactic radiotherapy in Turkey [2]. In April of 2014 an ocular oncology team in Athens-Greece started consistently managing choroidal melanoma patients by conservative and radical treatments. The team comprises of eye surgeons trained in Ocular Oncology and combined treatments (such as brachytherapy combined with local resection) could also be offered in certain cases. First choice of treatment for choroidal melanomas up to 7.5 mm height is plaque brachytherapy (as long as the tumor does not approach the optic disc closer to 3 mm), since it is technically straightforward and effective. The plaque is sutured to the sclera overlying the tumor and removed few days later once the required dose of at least 100 Gy has been delivered to the tumor apex. Thicker tumors are mostly managed with enucleation. Combined treatments are reserved for certain cases, for example, if the tumor does not show satisfactory shrinkage or secondary complications appear, then adjuvant local resection is performed.Treatment plan and decision is thoroughly discussed with the patient and patients' fears or thoughts are significantly considered by the ocular oncology team. When diagnostic uncertainty exists, aspiration biopsy (either with a fine needle, 25g, or with a vitreous cutter) is performed, that allows not only accurate diagnosis, but also prognostication.

Preliminary results were reported on the International Annual Ocular Oncology Group (OOG) Meeting in Athens [3]. Local tumor control after Plaque Brachytherapy up todate was achieved in 18 of 19 cases (94.7%) with the majority of the patients saving their eye and attaining useful vision. Local recurrence and subsequent hepatic metastasis was observed in 1 out of 19 cases. Of note, patients undergoing plaque brachytherapy tolerated well these treatments as they report in quality of life questionnaires (EORTC) designed for patients with ocular tumors.

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Preliminary study on the role of secondary surgery in ovarian cancer patients. Experience of a tertiary institution

Dear Editor,

Ovarian cancer is the third most common cancer and the second cause of death among gynecological cancers worldwide [1]. In Romania, according to the North-Western Cancer Registry, the incidence and mortality of ovarian cancer are continuously increasing [2]. The vast majority of patients continue to be diagnosed in advanced disease stages (IIIC and IV), with a poor prognosis, which has not significantly changed over time, despite the progress in the therapeutic management of the disease.

The role of surgery in relapsed ovarian cancer is a controversial topic; according to some authors, surgery offers a survival benefit compared to medical therapy alone, without significantly increasing comorbidity. In the DESKTOP OVAR trial, Harter et al. showed that only complete resection was associated with significantly prolonged survival in recurrent ovarian cancer, compared to patients with suboptimal debulking (45.2 vs 19.7 months; $p<0.0001$) [3]. However, patient selection is still arbitrary

and influenced by the center's choice instead of standard selection criteria.

In a meta-analysis, Bristow et al. concluded that among patients who underwent surgery for recurrent ovarian cancer, the proportion of patients with complete surgical resection was independently associated with overall post-recurrence survival time, and the main purpose for these patients should be resection of all macroscopic disease [4].

Regarding the prediction of optimal cytoreduction, Angioli et al. elaborated a predictive score for secondary cytoreductive surgery in recurrent ovarian cancer (SeC-Score), which includes four variables (residual tumor at primary cytoreduction, preoperative CA-125 and HE4, ascites), combined into a multivariate logistic regression model, with a reported sensitivity and specificity of 82% and 83%, respectively (PPV=0.79, NPV=0.81) [5]. Nevertheless, choosing between debulking surgery and chemotherapy is made by explorative laparotomy.

We retrospectively analyzed 162 patients with advanced stage IIIB, IIIC or IV epithelial ovarian carcinoma, admitted to and treated in the "Prof. Dr. Ion Chiricuta" Oncology Institute between 2001 and 2010, for recurrent ovarian cancer. Of these, 58 patients underwent surgery followed by chemotherapy, and 104 received chemotherapy alone. Of all patients treated by surgery for recurrence, 63% had peritoneal carcinomatosis and 22.2% had ascites. In the group of patients surgically treated for cancer recurrence, the presence of ascites was statistically significantly correlated with the presence of peritoneal carcinomatosis ($p<0.04$). With respect to overall survival depending on the therapeutic approach of recurrence, there were statistically significant differences between the patients treated by surgery followed by chemotherapy compared to the patients receiving chemotherapy alone (52 months vs 40 months, $p=0.0025$).

In conclusion, our study, like other retrospective studies published in the literature, supports this surgical approach to relapsed ovarian cancer patients, provided that an optimal debulking is obtained. This data should be confirmed by the results of ongoing prospective clinical trials (DESKTOP III (NCT01166737), GOG 213 (NCT00565851) and SOCceR (NTR3337)).

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Histopathological definition of medullary breast cancer should be revisited

Dear Editor,

The diagnosis of medullary breast carcinoma (MBC) is usually defined by histologic diagnostic criteria proposed by Ridolfi et al. [1]. These histopathologic characteristics include lymphoplasmacytic infiltration, noninvasive microscopic circumscription, syncytial growth pattern >75%, and grade 2 or 3 nuclei. The Ridolfi criteria still remain the most generally acceppted criteria in daily practice and all population-based studies concerning medullary breast carcinoma. However, reproducibility of pathological diagnosis for MBC is known to be poor. Furthermore, positive estrogen receptors (ER) and progesterone receptors (PgR) were reported in up to 30–40% of the cases, and overexpression of human epidermal growth factor receptor 2 (HER2) in ~10% of tumors diagnosed as medullary subtype [2]. Paradoxically, gene expression profiling results showed that MBC is classified as a subgroup of basal breast cancers supposed to be known as triple negative breast cancer [3]. Furthermore, one recent study found that MBCs have a favorable prognosis compared with invasive ductal cancers. In this study, outcome was better in MBC patients restricted to the group having ER-negative and poor grade tumors compared to invasive ductal cancers

[4]. Therefore, histopathological diagnosis of MBC might be better defined when lack of hormone receptor expression and HER2 overexpression are added to the Ridolfi criteria.

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Ileal perforation following cetuximab and FOLFIRI chemotherapy in a patient with ascending colon cancer with peritoneal carcinomatosis

Dear Editor,

Cetuximab is used in combination with FOLFIRI (irinotecan, 5-fluorouracil [FU], and leucovorin) for patients with metastatic colorectal cancer carrying the wild-type KRAS gene. Unlike bevacizumab therapy, pneumatosis or bowel perforation following cetuximab administration has rarely been reported as a serious adverse event [1-5]. Here, we present a case of ileal perforation following cetuximab and FOLFIRI chemotherapy in a patient who had ascending colon cancer with peritoneal carcinomatosis and was treated with aspirin and clopidogrel for atrial fibrillation.

A 78-year-old man was admitted to the Colorectal Department for panperitonitis. Two weeks prior to admission, the patient had completed the third cycle of cetuximab (500 mg/m2) and FOLFIRI (irinotecan: 180 mg/m2) chemotherapy. Three months prior to admission, the patient had been diagnosed with ascending colon cancer with peritoneal carcinomatosis and undergone an extended right hemicolectomy. The patient had atrial fibrillation and had been taking aspirin and clopidogrel for the past year. During laparotomy, a perforation in the ileum was noted at 10 cm proximal from the previous ileocolic anastomosis. The perforated ileum was resected and an end ileostomy was created. A gross examination revealed that there were multiple large, superficial and irregularly shaped ulcers covered with green-colored necrotic material on the ileal mucosa, and the ileal wall was multifocally necrotic. A microscopic examination revealed acute suppurative inflammation with perforation and focal necrosis. The patient was discharged on postoperative day 27. Further chemotherapy was cancelled. Five months later, the patient was placed in hospice care due to an unresolved small bowel obstruction from peritoneal carcinomatosis.

There is anecdotal evidence for pneumatosis (or intestinal perforation) after cetuximab therapy (Table 1). In the literature, age has varied from 52 to 78 years [1,2,4,5], and the primary tumors have been either colorectal cancer [1,2,4] or non-gastrointestinal cancer [3,5]. Different clinical presentations, such as pneumatosis [2,3,5] or perforation [1,4], and different cetuximab doses and schedules, such as 250 mg/m2 weekly [5] or 500 mg/m2 biweekly [2], have been reported. Treatment duration also varied from 1 to 24 cycles [1-5], and diverse agent combinations have been used. To date, the mechanism underlying intestinal perforation following cetuximab therapy is not clearly understood. Disrupted mucosal integrity or increased luminal pressure induced by bacterial overgrowth have been suggested as potential contributors to the development of pneumatosis. In addition, predisposing medical conditions, such as preexisting ulcers or infectious enteritis, may also contribute to the development of intestinal perforation. In our patient, a pathological examination showed acute suppurative inflammation with perforation and focal necrosis compatible with infectious enteritis. Our patient had been taking antiplatelet agents due to atrial fibrillation. Antiplatelet agents rarely cause gastrointestinal hemorrhage or perforation; accordingly, in this patient, antiplatelet agents may have played a role in the development of the ileal perforation. Thus, in patients undergoing cetuximab and FOLFIRI chemotherapy, comorbidities and primary tumor types should be carefully examined. Although rare, physicians should alert patients to the risks of pneumatosis or intestinal perforation before undergoing cetuximab treatment.

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Table 1. Literature reports with respect to pneumatosis (or intestinal perforation) following cetuximab therapy

Study	*Sex/ age*	*Primary tumor*	*Previous laparotomy*	*Clinical presentation*	*Treatment*	*Cetuximab dose (mg/m²), schedule*	*Chemotherapy duration*	*Agent combinations*
Clemente [1]	M/58	Rectosigmoid colon	No	Pneumatosis followed by jejunal perforation	Surgery	NR	1 cycle	Cetuximab, oxaliplatin, Tegafur-uracil and folinic acid
Yoon [2]	F/55	Rectum	Yes	Pneumatosis	Conservative	500, biweekly	6 cycles	Irinotecan
	M/52	Sigmoid colon	No	Pneumatosis	Conservative	500, biweekly	8 cycles	Oxaliplatin, 5-FU, leucovorin
	M/72	Rectum	Yes	Pneumatosis	Conservative	500, biweekly	24 cycles	Irinotecan
Shinagare [3]	NR	Tongue	NR	Pneumatosis	NR	NR	1 month	NR
Ozturk [4]	M/65	Sigmoid colon	No	Small bowel perforation	Surgery	NR, 4 weekly	1 cycle	Irinotecan
Miller [5]	M/71	Head and neck	NR	Pneumatosis	Conservative	250, weekly	2 cycles	5-FU, cisplatin
	M/66	Maxillary sinus	NR	Pneumatosis	Conservative	250, weekly	1 cycle	NR
Current study	M/78	Ascending colon	Yes	Ileal perforation	Surgery	500, biweekly	3 cycles	Irinotecan, 5-FU, leucovorin

NR: not reported; FU: fluorouracil, M: male, F: female, NR: not reported

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A young woman with metastatic colon cancer presenting with elevated serum beta human chorionic gonadotropin

Dear Editor,

Serum β human chorionic gonadotropin (β-hCG) is generally connected with pregnancy and can be detected in gynecologic or rarely in non-gynecologic tumors [1]. In non-gynecologic tumors, elevated serum β-hCG is associated with poor prognosis and usually occurs in women in the reproductive age with lung tumors [1,2]. In the literature, urinary tract malignancies, sarcomas, gastric carcinoma and breast cancer are associated with high serum β-hCG [1]. To the best of our knowledge, there is only one case with metastatic colon cancer presented with elevated serum β-hCG [3].

A 35-year-old multiparous woman in good health had a right abdominal pain in the past 6 months. During her evaluation by a gynecologist, high serum β-hCG level was detected (600 miu/ml) but intrauterine and ectopic pregnancy had been ruled out. However, her serum β-hCG level had consistently increased and her abdominal pain had continued. A chest and abdominal computed tomog-

raphy scans showed multiple masses in the liver and a solid mass in the right colon. Colonoscopy and biopsy of the mass revealed colon adenocarcinoma (CK-20+, CDX-2 +, CK-7-) with poor differentiation. Also high serum carcinoembryonic antigen (CEA) level (400 ng/ml) and KRAS 12th codon mutation were detected.

She was administered oxaliplatin 130 mg/m^2 and capecitabine 2000 mg/m^2 for 3 cycles without response and her β-hCG and CEA levels continued to increase (from 600 to 1400 mIU/ml and from 400 to 1200 ng/ml, respectively). The patient died of disease 3 months from diagnosis.

The most frequent high serum β-hCG producing non-gynecologic tumors in women of the reproductive age are lung tumors and detection of serum β-hCG indicates poor prognosis in the non-gynecologic tumors. Also serial serum β-hCG measurements may be useful to monitor the treatment response and progression of disease. The current case demonstrated that elevated serum β-hCG was not associated with a pregnancy and gynecologic tumors. We should be aware that increased serum β-hCG may be associated with conditions other than pregnancy and may be the first sign of a primary non-gynecologic tumor.

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