

## LETTERS TO THE EDITOR

# Does Oxaliplatin increase radiotherapy-induced lung injury?

Dear Editor,

Lung toxicity of cancer drugs is well known. During the use of cancer drugs, pneumonia / fibrosis, noncardiogenic pulmonary edema and hypersensitivity related lung injury may develop. It has been reported that lung toxicity develops in approximately 10-20% of patients receiving chemotherapy. The reason why lung toxicity is so frequent is because all the blood passes through the lungs. Although lung toxicity is sometimes preventable, most are idiosyncratic and unpredictable. The most well-known drug is bleomycin. Furthermore, cytarabine, gemcitabine, docetaxel, etoposide, methotrexate, bortezomib, fludarabine, vinblastine, anthracyclines, thalidomide, lenalidomide, ifosfamide have been reported to cause lung toxicity. In recent years, oxaliplatin has been reported to cause lung toxicity [1-3].

The use of oxaliplatin in the last 5 years has increased rapidly. There are many side effects in patients receiving oxaliplatin, a platinum derivative. The most common side effects are neutropenia, gastrointestinal manifestations and peripheral sensory neuropathy. In recent years, drug-induced pulmonary embolism and lung fibrosis have begun to be reported [3]. However, there are not enough studies on this subject.

Many systemic chemotherapy agents are thought to cause pulmonary toxicity and therefore may increase radiation-induced lung injury. In this regard, doxorubicin, actinomycin-D, busulfan, bleomycin, gemcitabine, mitomycin, irinotecan and taxanes have been implicated. More modern agents such as docetaxel and gemcitabine have been shown to increase lung injury when used concurrently with radiotherapy [3-5]. When the literature was reviewed, there was no information about whether oxaliplatin increases toxicity due to radiotherapy. The lungs are dose-limiting organs during thoracic radiotherapy due to limited regeneration capacity. Currently, there is no fully accepted method of determining the possibility of developing pulmonary toxicity for each patient. However, with the development of three-dimensional planning systems, obtaining dose histograms gave the opportunity to examine

the detailed dose distribution [4]. Many risk factors such as low Karnofski performance status, low pulmonary function, history of smoking, changes in plasma TGF-beta level, fraction dose, and concurrent chemotherapy with radiotherapy were investigated [3].

As a result, clinicians should keep in mind the potential pulmonary toxicity associated with oxaliplatin, and should be more careful in terms of toxicity, especially in patients undergoing radiotherapy in the thoracic region. Prospective studies are needed to clarify this issue.

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# Adjuvant chemotherapy might show benefit in luminal B breast cancer patients with isolated locoregional recurrence

Dear Editor,

Isolated local or regional recurrence (ILRR) of breast cancer predicts a poor prognosis. No prospective rand-

omized trial of adjuvant chemotherapy for ILRR has been published in the past 30 years. Recently, Wapnir et al. [1] investigated the efficacy of chemotherapy (CT) for ER-negative and ER-positive ILRR of breast cancer in CALOR trial.

The final analysis of CALOR confirms that CT benefits patients with resected ER-negative ILRR and does not support the use of CT for ER-positive ILRR. The authors did not give detailed information about the efficacy of CT in luminal A and B tumors. Adjuvant CT has a critical role in many estrogen receptor (ER)-positive tumors with luminal B features. On the contrary, adjuvant CT does not have a role in breast cancer patients with luminal A features [2]. Therefore, adjuvant CT might show benefit in luminal B breast cancer patients with ILRR. This issue merits further investigation.

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# Telomerase activity in laryngeal squamous cell carcinoma

Dear Editor,

Concerning the histological types of Head and Neck Squamous Cell Carcinoma (HNSCC), laryngeal squamous cell carcinoma (LSCC) represents the predominant, most frequent malignancy. Aberrant cell proliferation -based on deregulated molecules involved in a cataract of genetic reactions- leads to a progressive malignant transformation. Among these proteins, telomerase plays a crucial role in this process. Human telomerase is a ribonucleoprotein enzyme that lengthens chromosome ends, which have been shortened during successive cycles of cell division. It consists of two main components, including an RNA subunit (h-TERC) located on chromosome 3 (3q26) that acts as template for telomeric DNA synthesis and a catalytic protein subunit (h-TERT). h-TERT gene is located on chromosome 5 (5p15.33) and its protein product acts as a telomerase reverse transcriptase [1]. Telomeres are short specific tandem DNA repeats (5-TTAGGG-3) located at the end of the chromosomes. By the end of each replication cycle, human telomeres in all somatic cells undergo progressive shortening and this event functions as a tumor suppressor mechanism by preventing the abnormal, excessive replication of the DNA molecule. So, telomerase expression acts as a regulator in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres.

Overactivation of telomerase leads to cell immortalization and this genetic event has been detected in significant proportions in carcinomas, as it happens in LSCC. Additionally, telomerase interacts with oncogenes such as c-myc (gene location: 8q24.12-q24.13) which activates it by inducing expression of its catalytic subunit and also with suppressor genes [2]. Mechanisms of increased cell proliferation in LSCC derived by h-TERT activation implicate a variety of factors. A study group analyzed the correlation between h-TERT and AP-1 transcription factor subunits c-Fos and c-Jun in transfected laryngeal carcinoma cells mediated by adenovirus (Ad-TERT) and TERT shRNA silencing adenovirus. They concluded that TERT

mRNA expression levels induced c-Fos and c-Jun mRNA in LSCC tissues and for this reason TERT enhances proliferation due to this pathway [3]. In conjunction with these molecular data, another study showed that h-TERC over expression based on gene amplification probably is an early genetic event in the development and progression of LSCC [4]. They analyzed not only pathologically proved LSCC tissues but also precancerous lesions, including severe dysplasia and *in situ* carcinoma by implementing fluorescent *in situ* hybridization (FISH). They observed that h-TERC gene amplification (increased intra-nuclear signal number) is associated with an initial mechanism of LSCC rise and development. Similarly, quite recently a study group explored the role of the short hairpin RNA expression vectors in targeting the messenger TERT RNA and protein expression in LSCC HEp-2 cell lines [5]. They concluded that the transfection of multiple short hairpin RNAs plasmids acts as a negative regulator in TERT expression inhibiting its mRNA and protein expression. This is a very important observation because reduced telomerase activity in LSCCs opens new horizons regarding novel targeted therapeutic strategies.

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## Trastuzumab-emtansine might affect the survival outcome by reversing increased platelet-to-lymphocyte ratio in HER2-positive metastatic breast cancer patients

Dear Editor,

A large number of studies have explored clinical and pathologic prognostic factors for patients with metastatic HER2-positive breast cancer with conflicting results. A recent study by Blanchette et al. [1] investigated factors influencing survival among 154 patients with HER2-positive metastatic breast cancer treated with trastuzumab. They found that older age, increased platelet-to-lymphocyte ratio (PLR), and serum alkaline phosphatase were identified as poor prognostic factors and ER positivity as a favorable prognostic factor for overall survival. In this study, 40 (27%) patients were treated with subsequent anti-HER2 directed therapies including 9 (6%) patients with trastuzumab-emtansine, 24 patients (16%) with lapatinib, and 7 (5%) patients receiving both trastuzumab-emtansine and lapatinib therapy. Trastuzumab-emtansine has been approved for use in patients with HER2-positive metastatic breast cancer who have failed prior therapy with trastuzumab and a taxane. Although well-tolerated in clinical trials, thrombocytopenia has been reported and platelet values should be monitored closely. Trastuzumab-emtansine had no direct effect on platelet activation and aggregation, but it did markedly inhibit megakaryocytes

differentiation via a cytotoxic effect [2]. Taken all together, patients who received trastuzumab-emtansine would have a more chance to reverse the increased PLR, which in turn might result in a better survival. This issue merits further investigation.

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## FDG PET targets dominantly stromal cells

Dear Editor,

The idea to target cancer associated fibroblasts (CAFs) by PET in malignant tumors by the Heidelberg group (Anastasia Loktev, 2018)[1] reopens the way of stroma targeting years later, after the use of phosphonates as markers of new bone formation by osteoblastic reactions in bone cancer [2].

Tumor microenvironment is currently a popular topic. Stromal cells represent the higher proportion of the mass of the majority of malignant tumors. Fibroblasts are a predominant, multifunctional cell type in connective tissue, depositing extracellular matrix and basement membrane components, regulating different events in associated epithelial cells, modulating immune responses

and mediating homeostasis. CAFs are in aberrantly high numbers and are distinct from normal fibroblasts. They constitute the major component of tumor stroma and play a crucial role in proliferation, invasiveness, metastasis, and angiogenesis in cancer. There is a bidirectional communication between cancer cells and their microenvironment. This intercommunication between cancer cells and stromal cells represents a relationship that influences cancer initialization, progression and prognosis [3].

Now it is accepted that the classical theory of Warburg effect cannot explain the phenomena related to the symbiotic couple of cancer and stromal cells [4,5]. The theory of the reverse Warburg effect elaborated by Lisanti and his coworkers is very promising and was validated by

experimental data. According to this theory, cancer cells corrupt the normal stroma, turning it to the aerobic glycolysis (Warburg effect) for quick production of ATP and the energy rich metabolites, pyruvate and lactate which are used by mitochondria of cancer cells for turning up the tricarboxylic acid cycle (TCA) and oxidative phosphorylation triggered by stromal cells (reverse Warburg effect) [5].

Consequently 18-FDG PET by targeting the increased glucose metabolism in tumors, targets predominately glycolysis in stromal cells and in a smaller degree oxidative phosphorylation in the mitochondria of cancer cells. Herein 18-FDG PET also is a marker of stromal cells and this is to take into account for interpret the findings of this procedure, especially concerning the response to therapeutic agents targeting cancer cells.

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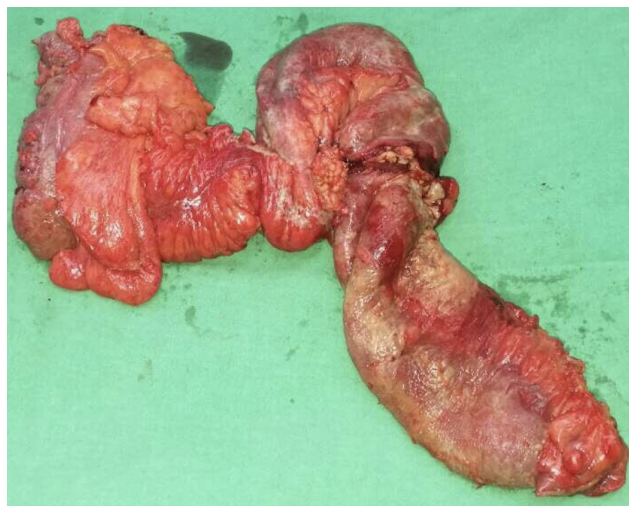
# Multidisciplinary management of complicated small bowel adenocarcinoma on the ground of Crohn's disease

Dear Editor,

Optimal management of small bowel adenocarcinoma (SBA) on the ground of Crohn's disease (CD) remains extremely challenging and necessitates multidisciplinary [1].

A 53-year-old man presented with acute abdomen. He had a history of CD of the terminal ileus diagnosed 40 years ago and several episodes of ileus. He underwent urgent laparotomy and a mass was revealed at the terminal ileum. Therefore, an enterectomy with a final ileum stoma along with lymph node dissection was performed (Figure 1). Histology demonstrated a ruptured SBA with seeding in the fat tissue of the adjacent mesocolon; the resected nodes were negative for malignancy.

The patient started adjuvant chemotherapy with capecitabine and oxaliplatin (XELOX). Treatment was interrupted on day 12 of cycle 1 due to grade 3 hiccups, grade 3 nausea (despite the administration of anti-emetics) and cough on liquid swallowing. However, no abnormality was found on the esophago-gastric imaging. In order to treat hiccup, we used metoclopramide, chlorpromazine and baclofen. Nausea was treated with intravenous aprepitant, while swallowing difficulty improved after treating the other toxicities. Furthermore, there was a high output of 3.5 lt from ileostomy despite the systemic use of loperamide. This led subsequently to electrolytic disturbances and creatinine increase. The patient was hospitalized for two months and managed conservatively. Due to the excessive toxicity observed with XELOX the patient underwent testing for DPD enzyme for 5FU toxicity, however no deficiency was observed. Therefore, although very uncommon, toxicity was mainly attributed to oxaliplatin.



**Figure 1.** Macroscopic appearance of the resected specimen.

The suboptimal management of ileostomy output led to the decision for ileostomy closure. Restaging revealed three intraperitoneal nodules highly suspicious for malignancy. These were excised along with ileostomy closure and two of them were found to be infiltrated. Postoperative complications included acute respiratory distress syndrome, septic shock, supraventricular tachycardia that necessitated intubation. Eventually, the patient recovered fully and was discharged after 50-day hospitalization.

Subsequently, the patient was treated with fluorouracil, irinotecan and folinic acid (FOLFIRI) and bevacizumab,

considering the metastatic disease. The treatment was chosen based on the previous oxaliplatin-related toxicity. The patient was restaged one-month post treatment completion with no evidence of disease. He is in great condition and with normal body weight.

Data from large series suggest a low frequency of CD-associated SBA (<2%), but reporting reasons may pertain to this [1,2]. Although the prognosis varies across studies [1], CD-associated SBA has an improved 5-year overall survival rate compared to de novo SBA (43% versus 34%,  $p=0.01$ ) [3]. Active follow-up and persistent obstructive symptoms may contribute to earlier diagnosis, as in our case. In this context, the value of endoscopy has been highlighted [4]. However, a prospective study revealed a suboptimal sensitivity of 33% and advised against the routine use for surveillance [5].

In conclusion, CD-associated SBA is usually detected at an early stage, which provides the opportunity for optimal therapeutic interventions. However, comorbidities and surgery- or chemotherapy-related complications may implicate the disease course and deteriorate the prognosis. Thus, the paradigm of multidisciplinary, personalized approach has to become a standard in clinical practice.

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# Breast cancer survivors might get more benefit if musical therapy is added to exercise

Dear Editor,

Complementary therapies include a broad range of mind and body practices, natural products and lifestyle modifications, and are commonly practised by breast cancer survivors. A growing number of well-conducted randomized controlled trials showed that selected therapies, including music therapy, may improve the management of symptoms of breast cancer and the adverse effects of treatment and might be associated with better survival. Furthermore, American Society of Clinical Oncology endorsed that music therapy is recommended for anxiety/stress reduction and depression/mood disorders in breast cancer patients [1]. Exercise is associated with significant reductions in the recurrence and mortality rates of several common cancers including breast cancer [2]. Exercise during and following treatment has been associated with reductions in breast cancer recurrence and disease-specific mortality rates of 30-60% [3]. Taken all together, music therapy during exercise might further decrease recurrence rate in breast cancer survivors. This issue merits further investigation.

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