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LETTERS TO THE EDITOR

Targeting m-TOR gene in pancreatic carcinoma

Dear Editor,

The mammalian target of rapamycin (m-TOR) seems to be a very promising marker for handling patients with solid malignancies, especially at the basis of applying targeted therapeutic strategies. The m-TOR gene that encodes for the corresponding protein (289 kDa) is located on chromosome 1 (cytogenetic band: 1p36.22) [1]. The molecule acts as a down-stream serine-threonine kinase. It comprises mainly two distinct multi-protein complexes: m-TOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [2]. It regulates cell growth and metabolism depending on the availability of nutrients, growth factors and stress. Additionally, plays a central role in development and aging, whereas due to its deregulation it is implicated in a variety of carcinoma rise and progression. The protein is a main part of the phosphatidylinositol 3-kinase (PI3K)/ tumor suppressor phosphatase and tensin homologue deleted on chromosome ten (PTEN)/protein kinase B (Akt)/m-TOR pathway. In fact, the PI3K/AKT/PTEN/m-TOR signaling transduction pathway regulates many critical cell functions including cell proliferation, protein synthesis and survival. Concerning pancreatic cancer, which is one of the most lethal gastrointestinal malignancies and the fourth leading cause of cancer associated cases of mortality worldwide, oncogenes over activation –including k-ras and also m-TOR genes- and suppressor genes down regulation are main genetic abnormalities [3]. Novel targeted therapeutic approaches are based on small genetic entities such as RNAs. In a specific type of molecular analyses the study group focused on tripartite motif containing 59 (TRIM59) molecule. They showed that in pancreatic cancer the TRIM59 aberrant expression was increased and correlated to a poor survival of these patients. Furthermore, small interfering RNAs-that affect negatively TRIM59- were observed to inhibit cancer cell proliferation and migration. So, targeting the TRIM59 pathway and thus blocking the mTOR glycolysis-signaling pathway may potentially prove to be able to better treat pancreatic cancer [4]. Similarly, inhibition of another gene -zeste homolog 2 (EZH2) - that interacts with PI3K/AKT/PTEN/m-TOR signaling transduction pathway seems to be a very promising anti-m-TOR process. GSK343, an EZH2 inhibitor, led to decreased pancreatic cancer cell viability, cell proliferation, and increased apoptosis [5]. In fact, the GSK343 molecule down-regulated AKT/mTOR signaling pathway, inducing autophagy in the corresponding cancerous pancreatic cells.

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Behcet's disease and breast cancer

Dear Editor,

It has been reported that autoimmune diseases may increase the cancer incidence. However, the relation between Behcet's disease (BD) and breast cancer (BC) is unclear. Guven and colleagues [1] investigated cancer incidence in a large cohort of BD patients to compare with the data of the same age and gender groups. Totallys, 451 adult cases with BD were included. Eleven cancer cases were observed during a median follow-up of 124 months. They reported that BD patients had approximately 3-fold increased cancer risk compared with corresponding age and sex groups. Among 11 cancer cases, two female patients were diagnosed with BC during follow-up. However, the authors did not give detailed information about these cases. Recently, we investigated BD cases in a large breast cancer dataset with 4800 patients [2]. A total of 12 female BC patients with a diagnosis of BD were identified from a cohort (0.25%, 12/4800). All had early BC at the time of BC diagnosis, with a median age of 47 years (range: 38-51). Another noteworthy finding

of this research was that BC patients with BD were likely to be at earlier ages at BC presentation. All patients underwent curative surgery for BC. In the adjuvant setting, chemotherapy, radiotherapy, and endocrine treatment were administered in 11 (91%), 10 (83.4%), and 9 (75%) patients, respectively. Nine (75%) patients had a hormone-positive tumor, hence received adjuvant aromatase inhibitor (18%) or tamoxifen (63%). All patients received colchicine for BD. The clinical symptoms in 11 patients with BD were observed to be improved following the BC treatment. We did not observe any negative effect of BD on BC or *vice versa*. Chemotherapy regimens (such as cyclophosphamide, adriamycin) and taxane or hormonotherapy such as tamoxifen may safely be given in BC patients with BD using colchicine treatment.

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Telomerase reverse transcriptase mutations in thyroid carcinoma

Dear Editor,

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 the chromosome ends, which have been short¬ened during the successive cycles of cell division. It con¬sists 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) (Figure 1). 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. Concerning telomerase -especially h-TERT- gene aberrant expression, a broad spectrum of genetic (amplification, point mutations) and also epigenetic (promoter methylation and micro-RNA imbalances) alterations have been already identified [2].

In thyroid carcinoma, h-TERT over activation is frequently detected and seems to be correlated with an aggressive phenotype. Mutational landscape regarding the gene includes mainly h-TERT promoter point mutations (C228T, C250T) that modify negatively the neoplasm's differentiation. Anaplastic thyroid carcinoma tissues harbor elevated levels of mutations compared to papillary or follicular thyroid carcinoma ones [3]. Despite h-TERT mutations, another important observation in these malignancies at the molecular field is the frequent co-existence of multi-mutations in oncogenes, such as k-ras and BRAF. Interestingly, studies that focused on the impact of synchronous BRAF V600E and h-TERT promoter mutations in papillary thyroid carcinoma concluded that there are significant genetic events leading to an aggressive phenotype due to high stage (extrathyroidal and distant lymph node metastases) and poor response rates to targeted therapeutic regimens [4]. Additionally, another study detected increased h-TERT promoter mutational potential not only in papillary but also in follicular thyroid carcinoma with high or moderate grade of differentiation [5]. In these cases, mutated telomerase was also associated with advanced stage, node and distant metastases and poor survival combined with elevated recurrence disease rates. Based on all of these updated molecular data it seems that the role of h-TERT over activation via gene promoter mutations in thyroid carcinoma is crucial and should be considered a significant biomarker and a potential therapeutic target in handling the corresponding patients.

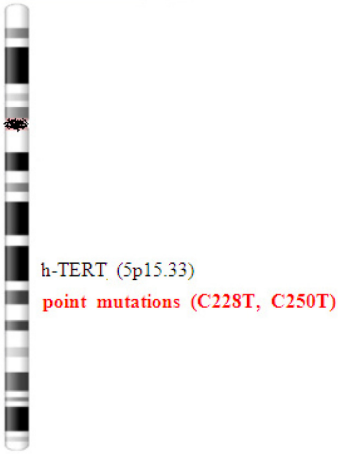

Figure 1. Ideogram of h-TERT gene on chromosome 5 (5p15.33) demonstrating specific gene promoter mutations in thyroid carcinoma.

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Is there any associaton between disease-free interval and discordant rates in estrogen, progesterone, and human epidermal growth factor receptor 2 status between primary and metastatic breast cancer?

Dear Editor,

The estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) statuses sometimes showed discordance between the primary tumor and metastatic lesions in metastatic breast cancer [1]. Walter and his colleagues [2] retrospectively compared ER, PR, and HER2 receptor profiles in biopsies of primary breast cancer and corresponding metastatic lesions in 541 patients to assess individual changes throughout tumor progression and location-specific discordance rates and reported statistically significant discordance rates of 14% and 32% were found for ER and PR. HER2 status was statistically insignificantly discordant in 15% of the patients. The authors recommended that metastatic lesions should be biopsied in accordance with current guidelines. However, the authors did not define any association between disease-free interval (DFI) and discordant rates. It would be expected that metastatic patients diagnosed after longer DFI might have higher chance of receptor discordance rates. Tumor biology in metastatic tumors might have more mutations as DFI prolongs. This proposal was not defined in the current literature. This issue merits further investigation.

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MicroRNAs in HBV-dependent hepatocellular carcinoma

Dear Editor,

Hepatocellular carcinoma (HCC) is one of the most important and leading causes of death worldwide. Hepatitis B virus (HBV) persistent infection is considered as one of the main causes of non-neoplastic (chronic hepatitis), pre-neoplastic (cirrhosis), and malignant (HCC) phenotypes regarding liver pathology. Natural history of a significant proportion of persistent HPB carriers leads to chronic hepatic disease, neoplastic and finally malignant transformation in affected hepatic parenchyma [1]. Because of HCC aggressive biological behaviour and poor response rates to novel targeted therapeutic strategies, there is an increasing need for specific molecular markers identification, necessary for early detection and evaluation of the response rates to the applied treatment protocols. MicroRNAs (miRNAs-miRs) could serve as potential biomarkers for the early detection and prognosis of HCC. miRNAs are considered as novel significant markers for discriminating patients based on their molecular characteristics. miRs are short, non-coding RNAs consisting of 20-25 nucleotides located at intra- or inter-gene regions. Functional miRs mediate a positive regulation of posttranscriptional gene silencing. Their deregulation in cancer cells due to genetic (mutations, translocations), epigenetic (DNA hypermethylation of tumour suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations leads to a loss of miRs-mediated

repression of target miRs. Interestingly, a biphasic role of miRs in cancers of different histogenetic origin has been confirmed. In some of them, their upregulation correlates with an increased ongogenic activity, whereas in others the same miR type acts as a suppressor agent [2].

Novel molecular analyses have shown that there is a variety of miRs potentially implicated in HBV-mediated carcinogenetic process. A study group analyzed the impact of miR-122 in HBV patients suggesting that its deregulation is a crucial epigenetic event in the progression of HCC [3]. Additionally, similar studies focused on the impact of miRs in cancer cell proliferation combined or not with apoptosis in HCC patients. A study group co-analyzing the expression of miR-325-3p and another agent, aquaporin 5 (AQP5), by implementing a quantitative Real Time Polymerase Chain Reaction (qRT-PCR) assay in HepaC cell cultures concluded that overexpression of miR-325-3p inhibited drastically cell proliferation and in parallel induced cell apoptosis. In this study, a significant relation between miR-325-3p and AQP5 was also assessed, based on the observation that the specific miR negatively modifies the expression rates of AQP5 [4]. Similarly, the expression of another miR (miR-125a-5p) seems to be effective for cell proliferation inhibition in HBV-related HCCs. A study group analyzing experimentally HepaC cultures for miR-125a-5p expression observed that the miR directly reduced mRNA and protein levels of ErbB3 gene that is implicated in signaling transduction in HCC. They concluded that miR-125a-5p promotes cell apoptosis and inhibits cell proliferation in HCC cells. Interestingly, it significantly decreased the secretion of HBsAg and HBeAg in the corresponding cell cultures [5].

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Effect of a switch of aromatase inhibitors to another aromatase inhibitor or tamoxifen on musculoskeletal symptoms in breast cancer; Which is the best?

Dear Editor,

Aromatase inhibitors (AIs) are standard of care in the adjuvant setting of postmenopausal women with hormone receptor positive breast cancer. Despite their beneficial effects on survival outcomes in breast cancer, musculoskeletal symptoms are common side effects which may lead to drug discontinuation and decreased AIs adherence among patients. The optimal treatment in its management has not yet been established. Switching to another aromatase inhibitor or to an alternate anti-endocrine therapy (tamoxifen) was also included based on guideline recommendations [1]. Ernst and colleagues [2] evaluated in their retrospective study AI symptom management practices in179 women with breast cancer who received AI therapy. Among 179 women prescribed an AI, 82% had at least one symptom and 46% had multiple symptoms. Seventy-seven patients (52%) received guideline-based treatments or guideline-based treatments in combination with non-guideline based treatments. Switching to another aromatase inhibitor or to an alternate anti-endocrine therapy (tamoxifen) was also included based on guideline recommendations. In this study, nearly three-quarters of patients who received guideline-based symptom palliation switched AIs as one or more of their interventions to palliate symptoms of the initial AI. However, the authors did nor mention switching details. This approach was assessed in the Articular Tolerance of Letrozole (ATOLL) study which was a prospective, non-randomized and multicenter trial [3]. ATOLL study demonstrated that switching to another AI could be more tolerable and beneficial in terms of controlling the joint symptoms. Also the outcomes of a previous study suggest that switching to another AI or a final switch to tamoxifen may be a reasonable method in the management for difficult cases [4]. Current guidelines did not give detailed information which one is more eficacious and feasible; switching from non-steroidal AI to steroidal AI or another non-steroidal AI or from AI directly to tamoxifen. Therefore, this issue merits further investigation.

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Pressurized intraperitoneal aerosol chemotherapy in gastric cancer with peritoneal metastasis

Dear Editor,

Gastric cancer is the fifth most common cancer and the second most common cause of death from cancer worldwide. Peritoneal carcinomatosis develops in more than half of gastric cancer patients. It has a poor prognosis with median survival of 3-5 months if left untreated [1]. Despite modest survival advantage, systemic chemotherapy is a well-practiced therapeutic option for gastric cancer with peritoneal metastasis in a patient with good performance status and the best supportive care is the optimal option in a terminally ill patient [2]. The willingness to cure or delay the disease course lead to invention of new surgical armamentaria like cytoreduction surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC). CRS/HIPEC has shown a curative treatment potential in a select group of patients who have isolated low burden peritoneal disease in gastric cancer [3]. However, the majority of patients do not fit in the strict selection criteria of CRS/HIPEC. Hence, PIPAC, a new surgical technique to administer chemotherapy drugs directly to the peritoneum under well-defined pressure is being used for these patients by the oncologists. PIPAC has better drug penetration and uniform distribution over the peritoneum than HIPEC. The applied pressure in PIPAC acts by counteracting the elevated intratumoral interstitial fluid pressure and enhancing drug uptake of tissue by convection mechanism. PIPAC has acceptable local toxicity and does not increase the systemic concentration of chemotherapy. So, the typical side effects of systemic chemotherapy like alopecia, myelosuppression, nephrotoxicity, neurotoxicity, hepatotoxicity, and cardiotoxicity are not clinically evident after PIPAC. The literature data about PIPEC deal with heterogeneous disease populations with different clinicopathological parameters and the results of these studies should be analyzed with caution [4]. The extrapolative results of PIPAC for a specific condition like gastric cancer with peritoneal metastasis does not evaluate the true efficacy value. PIPAC is used as a palliative "surgical" procedure to improve the quality of life, or at least to stabilize it from further deterioration. It is suitable for the patients who do not respond to systemic chemotherapy/immunotherapy but having a reasonable performance status and not having gross ascites, bowel obstruction, perforation or extra-abdominal metastatic disease. PIPAC with low-dose cisplatin and doxorubicin might be effective and safe in selected patients with peritoneal metastasis from recurrent, platinum-resistant metastatic gastric cancer [5]. The clinical benefits of PIPAC are not defined in the pleural effusion of gastric origin. PIPAC is still in the infancy stage because of a limited role in gastric cancer with peritoneal metastasis for prophylactic and palliative intent. Large multicentre, prospective, randomized studies exclusive with gastric cancer patients are warranted for the safety, feasibility, reproducibility, and effectiveness of PIPAC.

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Revisiting the concept of non- and minimally invasive interventions in early glottic cancer part I; radiotherapy is associated with worse post-interventional dysphagia than trans-oral laser microsurgery

Dear Editor,

Treatment options for early glottic cancer (EGC) include trans-oral laser microsurgery (TLM) and radiotherapy, as single treatment modalities, whilst their combination has also been utilized. The related 5-year survival is estimated to be as high as 90% [1]. Yet, due stress has been laid over the last two decades not only on the disease, but also in the impact of the proposed treatment on some of the most essential physiological functions, such as speaking, swallowing and breathing, in order to provide realistic patient expectations [2,3].

In a prospective study conducted at Attikon University Hospital, 108 patients treated for EGC with TLM (n=64), radiotherapy (n=14), or both (n=30), filled in the Eating Assessment Tool 10 (EAT-10), a validated questionnaire used for the early assessment of dysphagia [4], one and two years after their intervention. The EAT-10 consists of 10 domains, which assess medical, functional, and quality-of-life (QoL) issues, which may relate to the postoperative status of ECG patients; the questionnaire has been appropriately validated for the Greek language [5]. The non-parametric Wilcoxon Signed Rank test was used to perform the statistical analysis of data, as the respective distributions were not normal.

Both TLM and radiotherapy were associated with post-interventional dysphagia, which, however, attenuated between the first and second post-interventional year (p=0.000) (Figures 1A and 1B). Correlation analysis of both treatment modalities to socio-demographic parameters showed positive correlation between the attenuation of dysphagia and the patients' age, in the TLM group only (Spearman's r=0.454, p=0.000). TLM resulted in better post-interventional swallowing, than radiotherapy in the first (p=0.000) and second (p=0.000) post-interventional years, as the latter required increased effort/vigilance in swallowing liquids (p=0.000), and solids (p=0.000), whilst demonstrating worse food sticking during eating (p=0.000). The worse performance of radiotherapy compared with TLM was rather consistent, as it persisted at the end of the second post-interventional year (p=0.000). Finally, the addition of TLM to radiotherapy resulted in increased effort/vigilance in swallowing liquids, and this effect was worse in the second compared with the first post-interventional year (p=0.035).

Hence, the obtained results indicate that the concept of non- (radiotherapy), or minimally invasive (TLM) intervention, is not entirely accurate in ECG, as both treatment modalities bear a certain detrimental impact on post-interventional swallowing. Post-interventional dysphagia occurs irrespective of socio-demographic parameters in EGC patients, with the exception of age in patients receiving TLM, which tends to alleviate it. Post-interventional dysphagia should be taken into account during pre-interventional counselling, as it may exert leverage on various medical and QoL aspects of patients' lives (i.e. physical ability, social life, psychological well-being, financial implications).

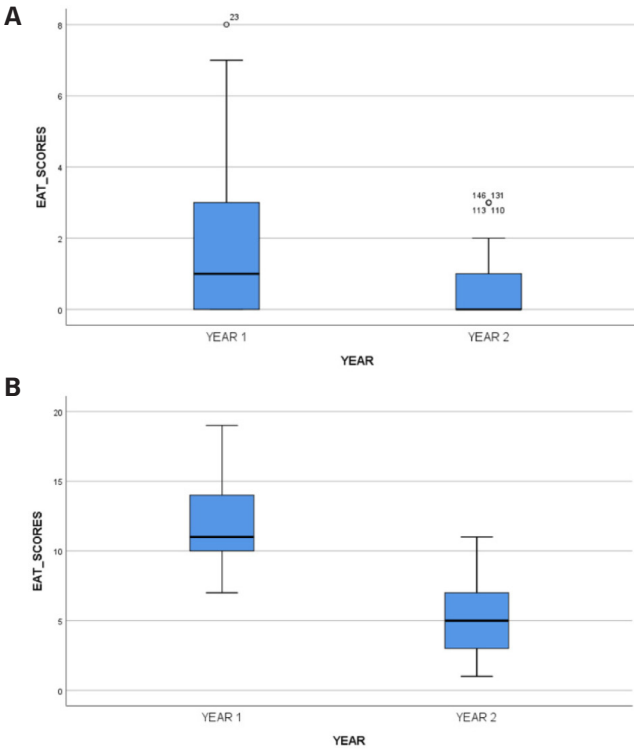

Figure 1. Box-plots depicting the attenuation of dysphagia between the first and second post-interventional year (**A:** TLM group, **B:** radiotherapy group).

In addition, though theoretically non-invasive, radiotherapy results in worse post-interventional dysphagia than TLM, demonstrating a more detrimental effect on the swallowing functionality of the preserved larynx (i.e. increased effort/vigilance in swallowing liquids, and solids, food sticking and coughing/choking whilst eating). Finally, the addition of TLM to radiotherapy impairs with the fine swallowing functionality of the preserved larynx (increased effort/vigilance in swallowing liquids), and this effect is deteriorating over time.

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