JBUON 2021; 26(4): 1683-1691
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

LETTERS TO THE EDITOR

Hormonal status might affect outcome in women with HER2-positive ductal carcinoma *in situ* treated with radiotherapy alone or concurrent radiotherapy plus trastuzumab

Dear Editor,

Preclinical studies report that trastuzumab (T) can boost radiotherapy (RT) effectiveness. The data of adjuvant clinical studies show that the administration of trastuzumab as part of a multimodality approach (with radiation based on standard guidelines) results in improved outcomes, including lower locoregional recurrence [1]. Cobleigh et al [2] investigated the efficacy of radiotherapy (RT) alone vs concurrent RT plus T in preventing recurrence of ipsilateral breast cancer (IBTR) in women with HER2-positive ductal carcinoma *in situ* (DCIS) resected by lumpectomy. Stratification was by menopausal status, adjuvant endocrine therapy plan, and nuclear grade. They concluded that addition of T to RT did not achieve the objective of 36% reduction in IBTR rate but did achieve a modest but statistically nonsignificant reduction of 19%. The authors did not add hormonal status to stratification. Furthermore, Toss et al [3] evaluated clinicopathological features and treatment modalities associated with recurrence in DCIS and microinvasive carcinoma among 865 patients with DCIS or microinvasive carcinoma treated between 2003 and 2013. Only ER/PR negative DCIS were associated with significantly higher recurrence rate. Additionally, pCR rates in the hormone receptor positive subgroup were consistently lower than those in hormone receptor negative tumors in neoadjuvant treatment of invasive HER2-positive breast cancer receiving trastuzumab [4]. All together, hormonal status might affect outcome in patients wih HER2-positive DCIS treated with RT alone or concurrent RT plus T. This issue warrants further investigation.

References

1. Benderli Cihan Y. Do concurrent targeted treatments and radiotherapy cause additional acute side effects. J BUON 2018;23:1200-1.
2. Cobleigh MA, Anderson SJ, Siziopikou KP et al. Comparison of Radiation With or Without Concurrent Trastuzumab for HER2-Positive Ductal Carcinoma In Situ Resected by Lumpectomy: A Phase III Clinical Trial. J Clin Oncol 2021 Mar 19:JCO2002824. doi: 10.1200/JCO.20.02824. Epub ahead of print.
3. Toss A, Palazzo J, Berger A et al. Clinical-pathological features and treatment modalities associated with recurrence in DCIS and micro-invasive carcinoma: Who to treat more and who to treat less. Breast 2016;29:223-30.
4. Harbeck N. Neoadjuvant treatment of HER2-positive breast cancer: should therapy differ based on hormone receptor status? Ther Adv Med Oncol 2018;10:1758835918782356.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Cankaya, 06800 Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

Telomerase activity in nasopharyngeal 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 chromosome ends, which have been short¬ened during successive cycles of cell division. It con¬sists of two main components, including an RNA subunit (hTERC) located on chromosome 3 (3q26) that acts as template for telomeric DNA synthesis and a catalytic protein subunit (hTERT). hTERT 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. 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 [2]. Epstein-Barr virus (EBV) latent but persistent infection is predominantly implicated in its development and progression.

Some novel molecular studies have explained partially the impact of hTERT overexpression in NPC biological behavior. In one of them, researchers focused on the amount of hTERT mRNA levels in peripheral blood and circulating tumor cells (CTCs) detected in a series of NPCs by implementing real-time quantitative PCR (qPCR). They observed increased hTERT mRNA levels and CTCs in NPC compared to the healthy controls [3]. Furthermore, elevated levels of the molecule were correlated to advanced clinical (T) stage. They also reported an efficient activity of radio-chemotherapy in reducing hTERT mRNA level in peripheral blood and CTCs. Additionally; another study group analyzed the influence of hTERT overactivation in radio-resistant nasopharyngeal carcinoma cells (CNE-2R cell lines) exploring also the role of Wnt/β-catenin signaling deregulation. They reported the presence of a positive feedback loop between Wnt/β-catenin signaling and hTERT in CNE-2R cells. In fact, Wnt/β-catenin signaling induced hTERT expression in the corresponding cell cultures [4]. For these reasons they suggested that suppression of Wnt/β-catenin signaling activity leads to hTERT decreased expression, which is a promising approach for targeting radioresistant nasopharyngeal carcinoma cells with CSC-like traits. Interestingly, researchers analyzing also CNE-2R cell cultures by implementing an RNAi lentiviral vector specific to the hTERT gene, quantitative PCR, Western blot assays, and PCR-ELISA, confirmed that hTERT suppression led to decreased cell proliferation and increased cell apoptosis rates inducing the positive effect of radiosensitivity *in vitro* in the corresponding NPC cell lines [5].

References

1. Cao Y, Bryan TM, Reddel RR: Increased copy number of the TERT and TERC telomerase subunit genes in cancer cells. Cancer Sci 2008; 99:1092-9.
2. Zhao L, Fong AHW, Liu N, Cho WCS. Molecular subtyping of nasopharyngeal carcinoma (NPC) and a microRNA-based prognostic model for distant metastasis. J Biomed Sci 2018; 25:16-28.
3. Fu X, Shen C, Wang H, Chen F, Li G, Wen Z. Joint quantitative measurement of hTERT mRNA in both peripheral blood and circulating tumor cells of patients with nasopharyngeal carcinoma and its clinical significance. BMC Cancer 2017; 17:479-83.
4. Chen K, Chen L, Li L et al. A positive feedback loop between Wnt/beta-catenin signaling and hTERT regulates the cancer stem cell-like traits in radioresistant nasopharyngeal carcinoma cells. J Cell Biochem 2020;121:4612-22.
5. Chen K, Li L, Qu S et al. Silencing hTERT attenuates cancer stem cell-like characteristics and radioresistance in the radioresistant nasopharyngeal carcinoma cell line CNE-2R. Aging (Albany NY) 2020;12:25599-613.

Spyros Katsinis[1], Arezina Manoli[1], Sotirios Papouliakos[3], Evangelos Tsiambas[3]

[1]*Department of Otorhinolaryngology, Thoracic Diseases General Hospital "Sotiria", Athens, Greece.* [2]*Department of Otolaryngology GNA Hospital ''Gennimatas'', Athens, Greece.* [3]*Department of Cytology, 417 Hospital (NIMTS), Athens, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. Email: tsiambasecyto@yahoo.gr

Synchronous metastases of infiltrating lobular breast carcinoma to stomach and colon: rare but it does occur

Dear Editor,

Metastatic involvement of the peritoneum and gastrointestinal tract in breast cancer patients is rare [1,2]. Metastasis to the peritoneum-retroperitoneum was shown to be higher in infiltrating lobular breast carcinoma (ILC), i.e. 3.1% vs 0.6% for lobular and ductal breast cancer, respectively [1]. There are few studies which have collected such cases within the context of an analysis, in order to shed light on the optimal treatment strategies, prognosis and management of this rare presentation. The tendency of 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 [2]. A 65 year-old women was diagnosed with left breast cancer and underwent right modified radical mastectomy in December 2014. Her breast pathological stage was T3N3M0 with ILC with luminal B subtype. She received adjuvant chemotherapy (4 cyles of cyclophosphamide and adriamycin followed by 12 times weekly paclitaxel) and adjuvant radiotherapy. During adjuvant letrozole treatment, CEA increased steadily and FDG-PET/CT scan showed right tuber ischium metastasis in January 2019 and then she started receiving fulvestrant plus zoledronate. Due to gastrointestinal complaints and increased CEA levels, subsequent FDG-PET/CT scan was performed and revealed right ischium metastases and local focal FDG metabolic uptake in ascending colon in September 2019. Then, upper and lower endoscopies showed mucosal irregularities. Biopsies taken from both sites were compatible with metastatic ILC with luminal subtype. She started receiving capecitabine until

September 2020. At that time FDG-PET/CT scan was normal. However, due to elevation of CEA levels, treatment was switched to exemestane and everolimus. During this time, the patient complained of gastrointestinal discomfort and abdominal distention. However, another FDG-PET/CT scan was normal in March 2021 with elevated CEA level and then she received 2 cyles of gemcitabine till June 2021. The patient also lost weigt for about 10 kg within last 4 months. In June 2021, CEA tumor marker was still elevated with normal FDG-PET/CT. By the way, CA 125 tumor marker was also elevated. My physical examination currently showed abdominal distention with small nodules palpated in the peritoneal surface. An immediate CT scan was ordered and peritoneal biopsy was planned. Taken all together, ILC metastases might occur in atypical organ sites such as peritoneum or gastrointestinal tract. During the follow-up of high risk early-stage breast cancer patients with ILC histologic type, patients' complaints might guide us to consider possible metastatic rare organ site involvement. Last but not the least, CT scan should be preferred to FDG-PET/CT scan in order to show small implants in peritoneum due to breast cancer metastases.

References

1. Petekkaya I, Ayyildiz V, Kizilarslanoglu MC et al. Prognosis of breast cancer in patients with peritoneal metastasis. Breast 2012;21:420-1.
2. Altundag K. Infiltrating lobular breast carcinoma; is gastrointestinal endoscopy recommended for staging? JBUON 2019;24:2577.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Cankaya, 06800 Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

What is the best time for ^{18}F-FDG-PET evaluation in estrogen receptor-negative and HER2-positive breast cancer patients receiving neoadjuvant trastuzumab and pertuzumab?

Dear Editor,

Neoadjuvant dual HER2 blockade with trastuzumab and pertuzumab without chemotherapy has shown striking pathological complete response rates (20.5 to 36.3%) which is a validated surrogate endpoint for improved long-term survival. These findings resulted in further rationale for exploring chemotherapy-sparing approaches for patients with HER2-positive, early-stage breast cancer. Several studies have investigated possible predictive factors of pathological complete response to neoadjuvant treatment. Imaging procedure that could guide the response to preoperative therapy are of particular interest, especially the potential use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET scans [1]. Pérez-García and his colleagues evaluated early metabolic responses to neoadjuvant trastuzumab and pertuzumab using ^{18}F-FDG-PET and the possibility of chemotherapy de-escalation using a pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain trial) [2]. ^{18}F-FDG-PET identified patients with HER2-positive, early-stage breast cancer who were likely to benefit from chemotherapy-free dual HER2 blockade with trastuzumab and pertuzumab. ^{18}F-FDG-PET scans were done before randomisation and after two treatment cycles. Significantly higher pathological complete response rates were observed in patients with hormone receptor-negative tumours versus those with hormone receptor-positive tumours in group A (docetaxel, carboplatin, trastuzumab, and pertuzumab), but not in group B (trastuzumab and pertuzumab). Pathological complete response was not significantly different between hormone receptor positive and negative tumours both in ^{18}F-FDG-PET responders in group B and in ^{18}F-FDG-PET non-responders in group B. TBCRC026 phase II trial evaluated the correlation between early changes in standardized uptake value and pathological complete response in ER-negative, HER2-positive breast cancer receiving trastuzumab and pertuzumab pre-operatively [3]. Eighty patients with stage II or III, estrogen receptor-negative, HER2-positive breast cancer received four cycles of neoadjuvant trastuzumab and pertuzumab. ^{18}F-FDG-PET was performed at baseline and 15 days after trastuzumab and pertuzumab initiation. They found that early changes in SUV max predict response to trastuzumab and pertuzumab in estrogen receptor-negative and HER2-positive breast cancer. One of the differences between these two trials is that ^{18}F-FDG-PET was performed after two cyles of treatment in PHERGain trial and 15 days after trastuzumab and pertuzumab initiation in TBCRC026 phase II trial. It would be expected that earlier evaluation of response to trastuzumab and pertuzumab might predict who are likely to benefit from chemotherapy-free dual HER2 blockade with trastuzumab and pertuzumab in estrogen receptor-negative and HER2-positive breast cancer. This issue merits further investigation.

References

1. Kaya S, Aktas B, Tanrikulu Sismek E et al. Changes in ^{18}F-FDG-PET/CT tumor metabolism are not consistent with pathologic complete response in hormone-positive breast cancer. J BUON 2017;22:1191-8.
2. Pérez-García JM, Gebhart G, Ruiz Borrego M et al. Chemotherapy de-escalation using an ^{18}F-FDG-PET-based pathological response-adapted strategy in patients

with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial. Lancet Oncol 2021:S1470-2045(21)00122-4. doi: 10.1016/S1470-2045(21)00122-4. Epub ahead of print.

3. Connolly RM, Leal JP, Solnes L et al. Updated Results of TBCRC026: Phase II Trial Correlating Standardized Uptake Value With Pathological Complete Response to Pertuzumab and Trastuzumab in Breast Cancer. J Clin Oncol 2021:JCO2100280. doi: 10.1200/JCO.21.00280. Epub ahead of print.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Cankaya, 06800 Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

C-myc oncogene activation in pharyngeal-esophageal squamous cell carcinoma

Dear Editor,

C-myc proto-oncogene - the human cellular homologue of the v myc oncogene of avian myelocytomatosis retrovirus MC29 - which is located at chromosome 8 (8q24.12-q24.13) - is found to act as a strong transcription factor, implicated in the control of cell differentiation and apoptosis. Induction of this transcription factor 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 acts as a nuclear phosphoprotein that regulates cell cycle progression, apoptosis and cellular transformation. It activates transcription as part of a heteromeric complex with MAX protein. C-myc is also involved in direct human telomerase (h-TERT) activation by inducing expression of its catalytic subunit, h-TERT. h-TERT is a target of C-myc activity and some pathways linking cell proliferation and chromosome integrity in normal and neoplastic cells have already been confirmed [2]. C-myc amplification is observed frequently in solid malignancies of different histogenetic origin. Additionally, gross, structural chromosomal aberrations affect C-myc gene function in viral-mediated neoplasia such as Burkitt lymphoma translocations t(8;14), t(8;22) or t(2;8).

Concerning pharyngeal-esophageal squamous cell carcinoma, interactions between c-myc and other genes have been reported. Interestingly, long non-coding RNAs (lncRNAs) are implicated in c-myc activity regulation. One of them, the lncRNA BAALC antisense RNA 1 (BAALC-AS1) promotes cell proliferation by inhibiting the degradation enhancing accumulation of c-Myc [3]. Furthermore, c-myc increases BAALC-AS1 expression leading to a feedback loop between two molecules. Other critical genes that modify c-myc activity are CCAAT/enhancer binding proteins (CEBPs, including CEBPA, CEBPB, CEBPD, CEBPE, CEBPG, and CEBPZ). These genes are frequently up regulated by amplification in pharyngeal-esophageal squamous cell carcinoma. A study group showed that especially the CEBPG overactivates the PI3K-AKT signaling including c-myc [4]. Based on extensive molecular and protein analyses -due to c-myc expression patterns in pharyngeal-esophageal squamous cell carcinoma- there are controversial data about its prognostic significance in the corresponding patients. In a meta-analysis, the researchers concluded that c-myc oncogene over activation is strongly correlated to poor survival rates and advanced stage (increased metastatic potential, lymph node metastasis) [5]. C-myc overactivation seems to be critical for aggressive phenotypes in pharyngeal-esophageal squamous cell carcinoma and for this reason should be a reliable biomarker and also a target for anti-oncogene blocking regimens.

References

1. Leone G, Sears R, Huang E et al. Myc requires distinct E2F activities to induce S phase and apoptosis. Molec Cell 2001; 8: 105-13.
2. Tsiambas E, Stamatelopoulos A, Baltayiannis N et al. Evaluation of combined telomerase and c-myc expression in non-small cell lung carcinomas using tissue microarrays and computerized image analysis. J BUON 2005;10:533-9.
3. Zhang H, Wang Y, Zhang W, Wu Q, Fan J, Zhan Q. BAALC-AS1/G3BP2/c-Myc feedback loop promotes cell proliferation in esophageal squamous cell carcinoma. Cancer Commun (Lond). 2021;41:240-57.
4. Huang Y, Lin L, Shen Z et al. CEBPG promotes esophageal squamous cell carcinoma progression by enhancing PI3K-AKT signaling. Am J Cancer Res 2020;10:3328-44.
5. Shi X, Zhou R, Zheng L, Jiang M. Prognostic significance of C-MYC dysregulation in esophageal squamous cell carcinoma: a meta-analysis. Biomark Med 2020;14:599-609.

Dimitrios Tsounis[1], Evangelos Falidas[2], Antonella-Effrosyni Monastirioti[3], Evangelos Tsiambas[4]

[1]*Department of Gastroenterology, 251 AF Hospital, Athens, Greece;* [2]*Department of Surgery, Halkida General Hospital, Halkida, Greece;* [3]*ENT Department, ''Sotiria'' Thoracic Diseases General Hospital, Athens, Greece;* 4*Department of Cytology, 417 VA (NIMTS) Hospital, Athens, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD.
Email: tsiambasecyto@yahoo.gr

Triple-negative breast cancer metastasizing to gingiva

Dear Editor,

Malignant lesions in the oral cavity acount for 5-6% of all types of cancers. The most common primary organ sites were lung (24.2%), kidney (13.5%), skin (10.6%), and breast (8.7%) [1]. Triple-negative breast cancers (TNBC) account for 15% of breast carcinomas and, when present as early-stage disease, they are associated with higher rates of recurrence and early distant metastasis risk when compared to hormone receptor positive and human epidermal growth factor receptor (HER-2) positive breast cancers [2]. A 37-year-old female patient was diagnosed with bone-only metastatic TNBC in March 2019 and received dose-dense adriamycin-cyclophosphamide (AC) followed by dose-dense palitaxel plus denosumab and then underwent breast conserving surgery and sentinel lymph node dissection in July 2019 with stage pT1N1M0 and received adjuvant radiotherapy and 6 months of capecitabine. BRCA 1 and 2 were normal. She presented with multiple lung and bone metastases in April 2020 and PD-L1 was positive. She received gemcitabine and 8 cycles of cisplatin plus gemcitabine and atezolizumab. In October 2020, progression in lung metastases were observed and she started vinorelbine and cyclophospamide Per OS followed by eribuline in February 2021 due to progression of lung metastases. In June 2021, progression of lung and bone metastases were reported with newly appearing liver, brain and subrenal metastases. Liver biopsy was taken which showed metastatic TNBC. Tumor tissue from liver metastases was also sent for next generation sequencing. She started cranial radiotherapy. She then presented with a gingival mass located between upper-central incisor and upper-left lateral incisor of 0.9 cm in size. Punch biopsy from this lesion was diagnosed as metastatic TNBC with a highly proliferative carcinoma infiltration. Gingiva that is prone to inflammation may serve as a pre-metastatic niche for the attraction of circulating malignant cells. Metastatic soft tissue lesions may mimic reactive or hyperplastic benign diseases such as inflammatory fibrous hyperplasia and pyogenic granuloma, and unspecific sign to cause suspected malignancy [1].

References

1. Hirshberg A, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity - pathogenesis and analysis of 673 cases. Oral Oncol 2008;44:743-52.
2. Budakoglu B, Altundag K, Aksoy S et al. Outcome of 561 non-metastatic triple negative breast cancer patients: multi-center experience from Turkey. J BUON 2014;19:872-8.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Cankaya, 06800 Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

Discordance rates in hormone receptor status between primary and metastatic sites might incluence clinical outcome in women with hormone receptor-positive advanced breast cancer treated with first-line endocrine therapy

Dear Editor,

Endocrine therapy (ET) is used to treat hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer (ABC). However, most of the patients eventually progress. Polley and colleagues [1] developed and validated a web-based clinical calculator for predicting disease outcomes in women with HR+ABC who are candidates for receiving first-line single-agent ET. They reported that higher number of sites of metastases, measurable disease, younger age, lower body mass index, negative PR status, and prior endocrine therapy were associated with worse progression-free survival (PFS). Interestingly, the authors did not mention re-biopsy results from metastatic sites that migh change hormone receptor status. One study performed a meta-analysis including 39 studies assessing receptor conversion from primary breast tumors to paired distant breast cancer metastases [2]. For ERα, PR, and HER2, they found that random effects pooled positive to negative conversion percentages of 22.5, 49.4%, and 21.3%, respectively. Negative to positive conversion percentages were 21.5%, 15.9%, and 9.5%. Another study showed that during recurrent disease there was 50% discordance in the expression of ER, PR, and HER2 [3]. One would expect that discordance rates observed in hormone receptor status might incluence clinical outcome in women with HR+ ABC treated with first-line ET.

References

1. Polley MC, Dickler MN, Sinnwell J et al. A clinical calculator to predict disease outcomes in women with hormone receptor-positive advanced breast

cancer treated with first-line endocrine therapy. Breast Cancer Res Treat 2021 Jul 3. doi: 10.1007/s10549-021-06319-z.
2. Schrijver WAME, Suijkerbuijk KPM, van Gils CH et al. Receptor Conversion in Distant Breast Cancer Metastases: A Systematic Review and Meta-analysis. J Natl Cancer Inst. 2018;110:568-80.
3. Ilgun S, Sarsenov D, Erdogan Z et al. Receptor discordance rate and its effects on survival in primary and recurrent breast cancer patients. J BUON 2016;21:1425-32.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Cankaya, 06800 Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

SARS-CoV-2 infection in breast carcinoma patients

Dear Editor,

Rapidly global spread of Coronavirus Disease 2019 pandemic (COVID-19) -characterized by elevated rates of infectivity and mortality- increased the need and pressure for design and development of specific anti-SARS-CoV-2 targeted therapeutic strategies via monoclonal antibodies (mAbs) and also for massive production of safe and effective vaccines. In fact, Coronavirus-related Severe Acute Respiratory Syndrome (SARS-CoV) in 2002/2003, Middle-East Respiratory Syndrome (MERS-Cov) in 2012/2013, and especially the current 2019/2020 Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) tested the national health systems' endurance worldwide. SARS-Cov-2 virus belongs to lineage b of beta-CoVs demonstrating a strong phylogenetic similarity with BatCoVRaTG13 type. Concerning its genomic structure, a large non-segmented, positive-sense RNA molecule of approximately 30 kb has been detected and analyzed in conjunction with the corresponding RNA-dependent RNA-polymerase (Rd-Rp) that is essential for its replication in the cytoplasm of the target epithelial cells. Analyzing SARS-CoV-2 spherical virion's structure (diam~100nm), research groups have confirmed that there are four main proteins including the spike surface glycoprotein (S), the main or matrix protein (M), the envelope protein (E), and finally the nucleocapsid protein (NC), whereas a variety of non-structural proteins have been also identified. In fact, 16 non-structural proteins (NSP1–NSP16) that encode for the RNA-directed RNA polymerase, helicase, and other components required for virus replication and translation in target cell ribosome machinery have been reported, whereas the functional role of other seven accessory proteins (ORF3a–ORF8) remains under investigation [1].

Concerning the impact of SARS-CoV-2 infection on patients with solid malignancies, there are some very important new data. Especially in breast carcinoma cases, a systematic meta-analysis showed significant levels of mortality estimating the case-fatality rate (CFR)/rate of death, but lower compared to lung carcinoma and hematological malignancies, respectively [2]. Interestingly, deregulated metabolism in sub-groups of breast carcinoma patients seems to be a negative predictive parameter leading to elevated possibility of severe COVID-19 phenotype. A study group considered dyslipidemia (increased levels of phospholipids, cholesterol, sphingolipids, and eicosanoids) as a major risk factor in the incidence and severity of SARS-CoV-2 infection [3]. Additionally, specific molecular signatures of breast carcinomas (HER2/neu negative/estrogen receptors positive) that are treated with a combination of endocrine therapy and CDK 4/6 inhibitors (first/second-line regimens) seem to demonstrate increased risk in SARS-Cov-2 infected breast carcinoma patients due to neutropenia [4,5]. For this reason, there is a need for modifying the management and therapeutic strategies in these patients.

References

1. Finkel Y, Mizrahi O, Nachshon A et al. The coding capacity of SARS-CoV-2. Nature 2021;589:125-30.
2. Tagliamento M, Agostinetto E, Bruzzone M et al. Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2021; 163:103365-71.
3. Shakartalla SB, Alhumaidi RB, Shammout ODA, Al Shareef ZM, Ashmawy NS, Soliman SSM. Dyslipidemia in breast cancer patients increases the risk of SAR-CoV-2infection. Infect Genet Evol 2021; 92:104883-89.
4. Barba M, Krasniqi E, Pizzuti L et al. COVID-19 risk in breast cancer patients receiving CDK4/6 inhibitors: literature data and a monocentric experience. Breast J 2021; 27:359-62.
5. Altundag K. Triple-negative breast cancer patients with isolated lung metastases and concomitant COVID-19 infection; does cytokine storm result in better efficacy? JBUON 2020; 25:1664.

Athanasios Niotis[1], Konstantinos Manios[2], Odysseas Dimas[3], Evangelos Tsiambas[4]

[1]*Department of Surgery, 417 VA Hospital, Athens, Greece.* [2]*Department of Thoracic Surgery, "Sotiria" General Hospital, Athens, Greece.* [3]*2nd Department of Internal Medicine, "Gennimatas" General Hospital, Athens, Greece.* [4]*Department of Cytology, 417 VA Hospital, Athens, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD.
Email: tsiambasecyto@yahoo.gr

Higher incidence of osteonecrosis of the jaw in patients with multiple myeloma receiving zoledronic acid: is there any rational explanation?

Dear Editor,

The bisphosphonates and denosumab are associated with an oral disease known as osteonecrosis of the jaw (ONJ). In patients treated with zoledronic acid or denosumab for up to 36 months, the incidence is reported as 1-2%. The rates of ONJ appear to increase over time. The etiology of ONJ is unknown. Potential mechanisms are infection, immune dysfunction, inflammation, vascular effect, oversuppression of bone remodeling, drug interactions, and genetic predisposition [1]. In their article Van Poznak and colleagues [2] analyzed the cumulative incidence of ONJ at 3 years in patients receiving zoledronic acid for metastatic bone disease (MBD) from any malignant neoplasm. The SWOG S0702 trial enrolled 3491 evaluable patients, of whom 1120 had breast cancer, 580 myeloma, 702 prostate cancer, 666 lung cancer and 423 other neoplasms. Three-year cumulative incidence was highest in patients with multiple myeloma (MM) (4.3%) and lowest in those with breast cancer (2.4%). Furthermore, Hoff et al [3] reported incidence and risk factors for ONJ in 4019 patients treated with intravenous bisphosphonates between 1996 and 2004. In that study, the estimated cumulative incidence of ONJ at 3 years was 1.6% in breast cancer and 3% in MM. It is still unknown why ONJ is more common in MM. MM is a systemic disease, characterized by excessive numbers of abnormal plasma cells in the bone marrow. Bone marrow in mandibular and maxillary bones would be expected to be involved in patients with MM. However, these specific sites are infrequently involved in patients with breast cancer and other solid tumors with bone metastases. Since bisphosphonates accumulate specifically in active bone metastatic sites with increased osteoclastic activity, more bisphosphonates might be expected to accumulate in the jaw region in patients with MM than in patients with breast cancer and other solid tumors, leading to higher incidence of ONJ in patients with MM [4].

References

1. Van Poznak C, Reynolds EL, Estilo CL et al. Osteonecrosis of the jaw risk factors in bisphosphonate-treated patients with metastatic cancer. Oral Dis 2020 Dec 4. doi: 10.1111/odi.13746.
2. Van Poznak CH, Unger JM, Darke AK et al. Association of Osteonecrosis of the Jaw With Zoledronic Acid Treatment for Bone Metastases in Patients With Cancer. JAMA Oncol 2020 Dec 17:e206353. doi: 10.1001/jamaoncol.2020.6353. Epub ahead of print.
3. Hoff AO, Toth BB, Altundag K et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 2008;23:826-36.
4. Delibasi T, Altundag K, Kanlioglu Y. Why osteonecrosis of the jaw after bisphosphonates treatment is more frequent in multiple myeloma than in solid tumors. J Oral Maxillofac Surg 2006;64:995-6.

Kadri Altundag

MKA Breast Cancer Clinic, Tepe Prime, Cankaya, 06800 Ankara, Turkey.

Corresponding author: Kadri Altundag, MD.
Email: altundag66@yahoo.com

COVID-19 in pancreatic carcinoma patients

Dear Editor,

Severe Acute Respiratory Syndrome (SARS-CoV) in 2002/2003, Middle-East Respiratory Syndrome (MERS-CoV) in 2012/2013, and the current 2019/2020 Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) are causes of major public health disorganization testing also the national health systems' endurance worldwide. In particular, the current COVID-19 disease has become a global catastrophe targeting negatively the socio-economical status. Extensive molecular analyses have decoded all CoVs' genomic sequences concluding that although there are small specific differences at the RNA level referring to five only nucleotide sites, the group of 380 amino acid substitutions in 2019 novel CoV (2019-nCoV) provides not only structural divergence, but also more aggressive functional and clinicopathogenic characteristics in infected communities. Concerning its genetic substrate and protein morphology, its RNA molecule (a large positive-sense RNA genome of approximately 30 kb) is enclosed in a spherical-like glycoprotein envelope characterized by many spikes (S projections) on its surface that create a crown-like formation (corona). These modifications act as binding tools for the corresponding membrane receptors of the host epithelial cells. The main receptor-binding loci that CoVs selectively use for cell invasion are human angiotensin-converting enzyme 2 (hACE2), CD209L, and dipeptyl peptidase 4 (DPP4) [1]. SARS-CoV-2 aggressive mutational landscape increases the affinity levels on the binding cell membrane sites (functional receptors), and elevates intracellular viral replication rates, high transmissibility/infectivity, and finally severe disease phenotype (increased morbidity and mortality levels) in sub-group of infected patients with specific demographic, clinical and genetic/epigenetic signatures, such as chromosome X – linked genes [2].

Concerning the impact of SARS-CoV-2 infection on patients with solid malignancies, there are some very important new data. In malignancies with aggressive phenotypes, such as pancreatic carcinoma, there are new data regarding potential relation with the viral infection. A study group explored the risk of pancreatic adenocarcinoma following SARS-CoV family infection in an *in silico* study model. Specific viral genes including SARS-CoV, SARS-dORF6, SARS-BatSRBD, and also H1N1were analyzed [3]. Interestingly, the PTEN, CREB1, CASP3 and SMAD3 genes were found to be upregulated under the experimental SARS-CoV-2 infection. The authors concluded that pancreatic adenocarcinoma is maybe the most potential type of malignancy that could be raised after infection with SARS-CoV family. Another clinical study investigated the influence of SARS-CoV-2 infection on pancreatic adenocarcinoma patients. The authors observed that a sub-group of patients surgically treated by pancreatoduodenectomy exposed to the virus postoperatively demanded modified supportive care for preventing poor prognosis [4]. Furthermore, another experimental study explored the role of rintatolimod, a Toll-like receptor 3 (TLR3) agonist implicated in immune response reactions. The researchers used pancreatic cancer cells (HPACs) in order to identify potential influence of the agent on them and reported interferon signaling pathway overactivation followed by cytokines and chemokines overexpression in epithelial cells, and also angiogenesis-related upregulation [5]. They concluded that rintatolimod induced antiviral response to SARS-CoV-2 infected HPACs and probably provided strong prevention to the complicated severity of the disease in patients with solid malignancies, like pancreatic adenocarcinoma.

References

1. Wu A, Peng Y, Huang B et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microb 2020; 27:325-8.
2. Tsiambas E, Chrysovergis A, Papanikolaou V et al. Chromosome X riddle in SARS-CoV-2 (COVID-19) - related lung pathology. Pathol Oncol Res 2020; 26: 2839-41.
3. Sadrabadi EA, Bereimipour A, Jalili A, Gholipurmalekabadi M, Farhadihosseinabadi B, Seifalian AM. The risk of pancreatic adenocarcinoma following SARS-CoV family infection. Sci Rep 2021;11:12948-55.
4. Bacalbasa N, Diaconu C, Savu C, Stiru O, Balescu I. The Impact of COVID-19 Infection on the Postoperative Outcomes in Pancreatic Cancer Patients. In Vivo. 2021; 35:1307-11.
5. Mustafa DAM, Saida L, Latifi D et al. Rintatolimod Induces Antiviral Activities in Human Pancreatic Cancer Cells: Opening for an Anti-COVID-19 Opportunity in Cancer Patients? Cancers (Basel) 2021; 13:2896-901.

Dimitrios Tsounis[1], Loukas Manaios[2], Evangelos Tsiambas[3], Despoina Spyropoulou[4]

[1]*Department of Gastroenterology, 251 Armed Forces Hospital, Athens, Greece.* [2]*Department of Surgery, ''BIOCLINIC'', Athens, Greece.* [3]*Department of Cytology, 417 VA Hospital, Athens, Greece.* [4]*Department of Radiology, Medical School, University of Patras, Patras, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. Email: tsiambasecyto@yahoo.gr

Mismatch repair system deficiency in nasopharyngeal carcinoma

Dear Editor,

Nasopharyngeal carcinoma (NPC) is a unique, aggressive pathological entity included in the Head and Neck Carcinoma (HNC) family of malignancies that demonstrates specific molecular characteristics including also micro-RNA markers. Concerning its geographical distribution, its prevalence is observed in East Asia and Africa with the highest incidence rate in China. Concerning its histological origin, this malignancy is derived from the nasopharyngeal epithelia demonstrating a high invasive and metastatic potential correlated with poor prognosis. Keratinizing, non-keratinizing and Basaloid carcinoma represent its pathological variants that reflect the corresponding cytogenetic features [1]. Epstein-Barr virus (EBV) latent but persistent infection is predominantly implicated in its development and progression. In fact, EBV's oncogenic activity is mediated by the aberrant expression of specific critical proteins including LMPs and EBNA1 that promote specific genetic signatures even in micro-RNA level [2].

Microsatellites are referred to repetitive nucleotide sequences including usually 1 to 5 base pairs repeated for 15-30 times which normally are 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 the two strands. Insertion or deletion of these repeated nucleotide chains are identified also inside the introns of the genes. For all these molecular reasons, micro-satellite instability (MSI) is a biomarker for detecting DNA Mismatch Repair (MMR) deficiency in a variety of malignancies of different histogenetic origin. Hereditary non-polyposis colorectal cancer (HNPCC) - an autosomal dominantly inherited disorder of cancer susceptibility - demonstrates the highest levels of DNA MMR-depended MSI (~90% cases), whereas sporadic colorectal cancers (CRCs) only 15% [3]. Concerning NPC, specific genetic signatures involving DNA MMR deregulation combined with *BRCA2* germline rare variants and also somatic alterations have been identified by implementing integrative genomic analysis in a series of patients [4]. Interestingly, those aberrations were correlated to poor overall survival and progression-free survival. The study group suggested that both of them should be used as biomarkers providing a molecular-based patient stratification. Additionally, another study explored the role of

MMR deficiency combined with programmed cell death-1 ligand (PD-L1) protein. PD-1 gene (2q37.3) encodes for a cell surface membrane protein of the immunoglobulin super-family which is very important for novel targeted immunotherapy strategies in malignancies. They showed that a low percentage of MMR alterations in the examined NPCs demonstrated MMR deficiency, whereas PD-L1 high expression was frequent in tumor-infiltrating immune cells.

References

1. Zhao L, Fong AHW, Liu N, Cho WCS. Molecular subtyping of nasopharyngeal carcinoma (NPC) and a microRNA-based prognostic model for distant metastasis. J Biomed Sci 2018; 25:16-28.
2. Tsiambas E, Mastronikolis NS, Fotiades PP, Ragos V, Kavantzas N, Lazaris AC. Epstein-Barr Virus MicroRNAs in Nasopharyngeal Carcinoma. Pathol Oncol Res 2020;26:1347-8.
3. Li GM. Mechanisms and functions of DNA mismatch repair. Cell Res 2008; 18:85-98.
4. Dai W, Chung DL, Chow LK et al. Clinical Outcome-Related Mutational Signatures Identified by Integrative Genomic Analysis in Nasopharyngeal Carcinoma. Clin Cancer Res 2020; 2854-8.
5. Zhao L, Liao X, Hong G et al. Mismatch repair status and high expression of PD-L1 in nasopharyngeal carcinoma. Cancer Manag Res 2019; 11:1631-40.

Ioannis Stavrakis[1], Sofianiki Mastronikoli[2], Evangelos Tsiambas[3], Vasileios Ragos[4]

[1]*ENT Department, "Sotiria" General Hospital, Athens, Greece;* [2]*Brighton and Sussex Medical School, UK;* [3]*Department of Cytology, 417 GAH (NIMTS), Athens, Greece;* [4]*Department of Maxillofacial Surgery, Medical School, University of Ioannina, Ioannina, Greece.*

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. Email: tsiambasecyto@yahoo.gr