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Evaluation of TOP2A and HER2/neu in malignant pleural mesothelioma

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Introduction & Aim: Malignant Pleural Mesothelioma (MPM) is an aggressive tumor. Most of MPM cases present at advanced stage and treatment options are mainly palliative chemotherapy and best supportive care. The current lines of chemotherapy are limited and ineffective hence there is an urgent need to improve patient outcomes. This requires better understanding of genetic alterations and biomarkers driving MPM to improve diagnostic, prognostic and therapeutic strategies. TOP2A and HER2/neu were thoroughly investigated and proved to be predictive factors in breast cancer and other solid tumors. We aimed at investigation of TOP2A and HER2 expression in malignant pleural mesothelioma, for better understanding of the involvement of different biomarkers in this aggressive type of cancer and the possibility of introduction of new treatment strategies accordingly.

Methods: Thirty-four cases of MPM with full data that were referred to NCI, Cairo University, Egypt from 2011 to 2015 were enrolled in the study. We investigated protein over expression of TOP2A using immunohistochemistry as well as gene amplification of TOP2A and HER2 genes using FISH technique and correlated the results with different clinic-pathological data and survival using ROC curve, Chi-square and Kaplan-Meier tests.

Results: Our study included 34 cases of MPM. Median age was 51 years. Sixteen (47%) cases were females. Nineteen (55%) cases were stage-1 and 2. Twelve (35%) cases underwent major operations, Extrapleural Pneumonectomy (EPP) or Pleurectomy and Decortication (P/D). Thirty (88%) cases received chemotherapy, mainly platinum based chemotherapy combined with ALIMTA (if available) or Gemcitabine. Eight (23%) cases received radiotherapy either adjuvant in multimodality treatment or palliative for pain and bone metastasis. All cases were evaluated for TOP2A by immunohistochemistry with cutoff value=0.825. Twenty-two (64%) cases were TOP2A positive. All patients with progressive disease were TOP2A negative (p= 0.012). Thirteen (72%) out of 18 male cases were TOP2A negative. Eleven (73%) out of 15 stage-3 and stage-4 cases were TOP2A negative. Eight (88%) out of 9 biphasic cases were TOP2A negative. Nine (81%) out of 11 TOP2A positive cases were epithelioid (p=0.08). There was a statistical significant correlation between Time to Progression (TTP) and TOP2A expression (p=0.012). There was a difference between over-expression of TOP2A immunohistochemically and amplification by FISH technique, as only 5 (14%) out of the 34 evaluated cases showed TOP2A amplification. There was a statistical significant correlation between better PFS (p=0.005), OS (p=0.024) and TOP2A amplification by FISH. However, these significant correlations were not proved using multivariate analysis. As regard HER2neu, 3 (0.08%) out of the 34 evaluated cases were HER2neu positive. There was a trend between HER2neu non-amplified cases and earlier stage (p=185). Most of the HER2neu amplified cases were males.

Conclusion: Our preliminary studies revealed favorable prognosis of MPM cases with TOP2A expression. TOP2A should be evaluated by immunohistochemistry and not only by FISH technique as there is obvious disconcordance between the two techniques, the former succeeded in identification of more cases with TOP2A overexpression. We recommend performance of a pilot study using anthracyclines in addition to standard chemotherapy regimen in MPM cases to evaluate the benefit of these types of drugs.

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