IMMUNUNOHISTOCHEMICAL PROGNOSTIC FACTORS IN HIGH-GRADE ENDOMETRIAL NON-ENDOMETRIOID CARCINOMAS (HG-NECS). A PRELIMINARY REPORT

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Introduction. Endometrial carcinoma (EC) is the most prevalent gynecological cancer, with an increasing incidence of aggressive histotypes and mortality in recent years. Beside dichotomic classification in type I and II, recently ECs may be re-classified in molecular prognostic groups. In the present study EC potential prognostic factors were investigated by immunohistochemistry, especially in high grade endometrial non-endometrioid carcinomas (HG-NECs).
Materials and methods. In our study, we considered all high-grade endometrial non-endometrioid carcinomas surgically managed in IRCCS Ospedale Policlinico San Martino from 2013 to 2018, with available follow-up. Surgical specimens have been routinely processed and stained with immunohistochemical technique for Estrogen Receptor (ER), Progesterone Receptor (PR), Ki67, p53, E-cadherin, β-Catenin, Bcl2 and Cyclin D1 for each case. We evaluated the percentage of positive tumor cells (%) for all antibodies, distinguishing it in low and high rate according to the distribution in the study population. Follow-up was reported for disease-free survival (DFS) and overall survival (OS).
Results. 33 cases were eligible. Regarding histotype, 13 ECs were mixed, 9 serous, 6 MMMT, 3 undifferentiated and 2 clear cell carcinoma. About International Federation of Gynecology and Obstetrics (FIGO) stage: 19 ECs were at stage I-II and 14 at stage III-IV. 12 patients suffered from relapsing disease (RLP; mean follow-up 24.6 months); 8 patients died for the disease (DOD; mean follow-up 26,6 months). RLP demonstrated a significantly higher Bcl2 expression (38.2% vs. 8.1%; p=0.003), as well as DOD patients, for whom p reaches a borderline significance value though (34.4% vs. 13.1%; p=0.08). Moreover in DOD patients, neoplasms showed a higher mitotic index evaluated with Ki67 (75% vs. 67%; p=0.02). Patients affected by tumors with high expression of Bcl2 (Bcl2>10%) demonstrated a significant worse disease free survival (DFS) (HR=9.11 95%CI: 2.6-32.4; p=0.0006) and overall survival (OS) (HR=7.63 95%CI:1.7-34; p=0.0084). Also patients with low PR-expressing neoplasia (PR≤10%) had a significant worse DFS (HR=3.74 95%CI:1.2-11.9; p=0.02). OS in these patients had no clear significance value (HR=3.15 95%CI:0.73-13.53; p=0.12).
Conclusions. HG-NECs represent a heterogeneous group of endometrial aggressive neoplasms with a worrisome prognosis and often an advanced stage at presentation. Bcl2 and PR may represent promising immunohistochemical markers to identify a sub-group of patients having an even worse prognosis requiring a careful, close follow-up and eventually an improving post-surgical management.

PATOLOGIA PLEUROPOLMONARE

GRP78 AND PD-L1 EXPRESSION IN MESOTHELIOMA: A POSSIBLE LINK BETWEEN ER STRESS, UPR AND IMMUNECHECKPOINT INHIBITORS.

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Objective. Mesothelioma is a rare pleural and peritoneal malignancy related to asbestos exposure and with poor prognosis. First-line treatment consists of pemetrexed and platinum-based chemotherapy. Despite huge efforts made, therapies for mesothelioma continue to be challenging and the outcome for patients remains disappointedly poor.There is, therefore, an unmet need to identify more reliable diagnostic and/or prognostic markers and to highlight novel molecular targets clAim. ing efficient and tailored therapies.
GRP78, also referred to as BiP, is a molecular chaperone of the endoplasmic reticulum (ER) that aids proper folding of nascent polypeptides. When unfolded proteins accumulate, GRP78 triggers unfolded protein response (UPR), restoring cell homeostasis. Increased expression of GRP78 and mild UPR is constitutive activated in cancer cells, hindering apoptosis, and promoting cell survival, favoring the insurgence of chemoresistance and worsen patient outcome. We have already found that mesothelioma cells display mild constitutive UPR and overexpression of GRP78.
PD-L1 expression is actuallyused as a predictive biomarker forimmune checkpoint inhibitors, being incorporated into multi-parametric predictive therapeuticapproach in numerous tumors. PD-L1 is expressed in a substantial proportion of mesothelioma cases, as measured by FDA-approved companion assays for widely used immunotherapeutic drugs.
Interestingly, a recent study opens up the possibility that PD-L1 protein expression at the surface of cancer cellsmight be correlatedwith the protein levels of UPR proteins. This correlation prospect that PD-L1 expression on the surface of tumor cells might be linked to the UPR and cell proteostasis in general. Thisinteractioncould be targeted by some clinically approved drugs, which were recently reported to target PD-L1 for protein turnover by ER-associated degradation.
Materials. 15cases of mesothelioma have been selected (13 epiteliomorphic and 2 biphasic types). GRP78 (EPR4040 AbcammAb) has been tested through immunohistochemical method on formalin-fixed paraffin embedded bioptic samples. PD-L1 monoclonal antibody Ventana SP263 has been detected on Ventana Benchmark Ultra.
Results. All the cases considered were intensely positive for GRP78, with a valued score 2+ (5 cases, high granular cytoplasmatic positivity, Fig. 1) and 3+ (10 cas-