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P33.-Preclinical assays of EM1 calcitriol analogue alone and in combination with paclitaxel

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Triple Negative Breast Cancer (TNBC) lacks the molecular targets commonly used to treat hormone receptor- and HER2- expressing BC and, thus, mortality and morbidity remains high. Therefore, novel candidate molecular targets or drugs are needed to treat this subtype of tumors. We have previously reported that the vitamin D analogue EM1 elicited strong antitumor effects, specifically by targeting the metastatic process, in the LM3 hormone-independent BC cell line and animal model. Hence, the aim of the present study was to continue the preclinical assays by evaluating the antineoplastic effects of EM1 alone or in combination with paclitaxel in TNBC-cell lines and patient-derived xenografts (PDXs). The results show that EM1 decreases the viability of the TNBC cell line 4T1 ($p<0.001$) and cells derived from the primary tumors PDX410, PDX575 and PDX549. Instead, no effect was observed in the cell viability of PDX570. In addition, the expression of the vitamin D receptor (VDR) was studied in these PDX-derived cells, showing high levels of the receptor in EM1-responding cells (PDX410 and PDX575) and lower levels in non-responding cells (PDX570). In addition, EM1 reduced the migration rates of 4T1 and MDA-MB231 cells ($p<0.001$) and the invasion rates of 4T1 cells ($p<0.001$). Also, a preliminary experiment using 4T1 cell line implantation in Balb/C mice showed a significant decrease in the number of lung metastases ($p=0.0024$) following 30-day treatment with EM1, although no reduction in the growth of the primary tumor was obtained. The subsequent combination assays showed that EM1 and paclitaxel do not display antagonistic effects in the cell count of BC cells. Altogether, these results show that EM1 exerts antitumor activity in TNBC and its effects do not antagonize those of paclitaxel. Moreover, EM1 and paclitaxel could exert strong antitumor action by targeting complementary processes.