ONCOLOGIC

C029
EVALUATION OF SYNTHETIC CHALCONES ON CELL VIABILITY OF HUMAN LEUKEMIA CELL LINES

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P-glycoprotein is a member of the ATP-binding cassette transporter family which is involved in the multidrug resistance of cancer cells to several anti-cancer drugs.
To synthesize and to determine the effects of selected chalcones on viability of human leukemia cell lines and in particular P-glycoprotein-overexpressing K-562/ADR cells.
Chalcones were synthesized by a Claisen–Schmidt condensation of 2-hydroxyacetophenones and benzaldehydes and their structures were determined by spectroscopic analyses. HL-60, U-937, MOLT-3, K-562 and K-562/ADR cells were grown in RPMI 1640 medium and cytotoxicity was analyzed by colorimetric MTT assay. Cell cycle phase distribution and reactive oxygen species were determined by flow cytometry. The evaluation of apoptosis was carried out by fluorescent microscopy, flow cytometry and DNA fragmentation. Caspase activity was determined using colorimetric substrates, processing of caspases and release of mitochondrial proteins by Western blot.
We evaluated the antiproliferative activity of seventeen synthetic chalcones against human leukemia cell lines and found that 2′-hydroxy-6′-benzyloxy-4-bromochalcone was the most potent, showing IC50 values of approximately 5 mM, including the multidrug resistant K-562/ADR. This compound induced apoptosis in a concentration- and time-dependent manner and blocked cell cycle progression at the S phase. Cell death was found to be associated with the release of mitochondrial pro-apoptotic proteins, the cleavage and activation of caspases and an increase of intracellular reactive oxygen species generation.
The selected chalcone effectively induces cell death in leukemia cells that overexpress P-glycoprotein and could be a potential candidate for developing novel anti-cancer agents.

C070
ADDING PERTUZUMAB IN NEOADJUVANT TREATMENT OF PATIENTS WITH HER2$^+$ BREAST CANCER IN SPAIN: A COST OFFSETS STUDY

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Pertuzumab (Perjeta®) has recently been approved in Europe as part of the neoadjuvant treatment for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer (BC). We aimed to calculate the cost-offsets of avoiding locoregional and metastatic recurrences in a Spanish setting due to the addition of pertuzumab to the neoadjuvant treatment.
We developed a budget impact analysis to assess the cost-offsets of adding pertuzumab to the neoadjuvant therapy based on the reduction of metastatic and locoregional events. Cost savings have been estimated based on PFS rate at year 5. A conservative approach was considered: for locoregional recurrence, 12 months of trastuzumab adjuvant treatment was included; for mBC, direct costs (drugs, diagnosis, hospitalizations, follow-up visits) were estimated by a clinical expert panel, for first- and second-line only. Indirect costs have also been for the population under 65 years only for mBC. Clinical data used were that the addition of 4 cycles of Pertuzumab in neoadjuvant shows significant improvements in pCR and long term benefit (PFS: 5% increase at year 5).
The average cost calculated for a locoregional event was 24 and 153k€ for a mBC event (137k€ direct; 16k€ indirect). For a cohort of 100 patients, the accumulated cost-offsets for avoided events was estimated to be 636k€.
Based on PFS the benefit of adding Pertuzumab to the neoadjuvant therapy could be translated into cost-savings in further lines, that may off-set around 50% of the drug cost. This percentage should be higher when taking into consideration beyond 2 l of treatment for mBC event.

C072
BRCA2-DEFICIENT CELLS ARE HYPERSENSITIVE TO CYTOTOXICITY AND DNA DAMAGE INDUCED BY THE SOY ISOFLAVONE GENISTEIN

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Genistein is a soy isoflavone whose consumption has been associated with a decreased risk of breast cancer. However, several studies suggest that this polyphenol may increase the risk of this cancer. Cancer is a disease caused by the accumulation of DNA damage and experimental data have shown that genistein induces DNA damage in cells. This genotoxicity has been associated to topoisomerase poisoning activities and induction of double-strand DNA breaks. Since BRCA2 is an important protein implicated in repair double-strand DNA breaks and the presence of mutations in the BRCA2 gene is known to increase the risk of several cancers it is important to evaluate the cytotoxicity and DNA damage induce by genistein in BRCA2-deficient cells.
BRCA2-deficient cells (VC8) and BRCA2-complemented VC8 (VC8B2) cells were used. Cytotoxicity activity of genistein was evaluated by clonogenic survival assay. DNA damage was studied by an immunofluorescence assay in which γH2AX and its colocalization with 53BP1 foci was measured.
We found that BRCA2 deficient cells were more sensitive to the cytotoxicity of genistein. Using the focus assay and antibodies against gamma-H2AX and 53BP1 proteins, we also observed that genistein induced higher levels of gamma-H2AX. Higher levels of gamma-H2AX colocalizated with 53BP1, indicative of double-strand breaks, were also seen. Genistein induced higher levels of double-strand breaks in BRCA2-deficient cells.
These data suggest that people with genetic defects in BRCA2 may be more sensitive to the cytotoxicity and DNA damage induced by genistein. Genistein could induce carcinogenic activity, especially in people born with mutated BRCA2.