POSTER SESSION 12: New treatment strategies

P12.2

Neoadjuvant biphosphonate in breast cancer

Selma Sakhri

Medical Oncology, Algeria, Algeria

Introduction: Clinical studies have demonstrated synergistic antitumor effects of chemotherapy (CT) and zoledronic acid (AZ). In the essay Neo - AZURE, to determine whether the addition of AZ to neoadjuvant chemotherapy gives compléte histological responses. We report a prospective evaluation comparing compléte pathological response between different sub - biomolecular groups.
Methods: from 2012 to 2014, 432 patients received neoadjuvant chemotherapy + AZ. The main objective is the complete histologic response. Secondary endpoints were clinical response according to RECIST criteria, estimate the overall survival of patients targeted by the study, assess bone density before and at the end of chemotherapy, the side effects associated with the treatment protocol, and Quality life
Results: histologic complete response with zoledronic acid was 40.13% .the higher in the subgroup Her2 / luminal (RH ± Her2 +) and under Her2 + (HR-Her2 +) and the lowest rate was observed in the triple negative group as classified by Sataloff, overall survival was 45.77 months for subgroups (Her2 / luminal and in Her2 + group) vs 44.11 months for triple negative group.
Conclusion: These data suggest a possible direct antitumor effect of AZ in combination with CT .The studies were recently published in the Proceedings of the American Academy of Sciences (PNAS) shows that bisphosphonates namely zoledronic acid the ability to block the abnormal growth of signals transmitted via the HER receptors, these studies demonstrated that the same can inhibit zoledronic acid tyrosine kinases in case of secondary transfer and thereby potentiate and treat breast cancer became resistant primary treatment.

Keywords: antitumor activity; breast cancer; neoadjuvant chemotherapy; pCR; zoledronic acid

P12.3

Maintenance treatment of Uracil and Tegafur in responders following first-line fluorouracil-based chemotherapy in metastatic gastric cancer

Wenhua Li, Xiaodong Zhu, Xiaoying Zhao, Huijie Wang

Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China

Background: Maintenance therapy proves to be effective in advanced lung and breast cancer after initial chemotherapy. However, its role in gastric cancer is not clear. The purpose of this phase II study was to evaluate the efficacy and safety of Uracil and Tegafur (UFT) maintenance in metastatic gastric cancer patients following the first-line fluorouracil-based chemotherapy.
Methods: Metastatic gastric cancer patients with stable disease or a better response after the completion of first-line chemotherapy were randomized to oral UFT (360mg/m2 × 2 weeks) every 3 weeks until disease progression/intolerable toxicity or to observation (OBS). The primary endpoint was progression-free survival (PFS); the secondary endpoints were overall survival (OS) and safety.
Results: The trial was closed after the interim analysis of the 58 enrolled (120 planned) patients. Median PFS was not significantly improved in the UFT group compared with the OBS group (3.2 months versus 3.6 months, P = 0.752). Similarly, UFT maintenance did not prolong median OS compared with OBS (14.2 months for both, P = 0.983). However, subgroup analysis showed that patients with low hemoglobin (< 120 g/L, n = 32) had a shorter PFS after the maintenance therapy (1.9 months in 17 patients of UFT group versus 3.6 months in 15 patients of OBS group, P = 0.032), whereas patients with normal hemoglobin (≥ 120 g/L, n = 26) benefit from the UFT maintenance (7.1 months in 12 patients of UFT group versus 2.4 months in 14 patients of OBS group, P = 0.008). Similar trend was also observed in the OS analysis. Patients with normal baseline hemoglobin had a better survival trend after the maintenance therapy (23.6 months versus 10.5 months, P = 0.09), whereas patients with low hemoglobin did not (14. 0 months versus 21.2 months, P = 0.106). Grade 3 to 4 toxicities in the UFT group were anemia (3.4%), thrombocytopenia (3.4%) and diarrhea (6.9%).
Conclusions: This trial did not show superiority of UFT maintenance in non-selected patients responding to fluorouracil-based first-line chemotherapy. The normal hemoglobin level at baseline is a predictive biomarker for favorable patient subsets from the maintenance treatment. Safety profile of UFT was acceptable.

P12.4

The discovery of novel synthetic lethal compounds for the treatment of E-cadherin deficient tumours

Henry Beetham, Augustine Chen, Parry Guilford

The University of Otago, Dunedin, New Zealand

The cell-cell adhesion protein E-cadherin (CDH1) is a tumour suppressor that is frequently mutated in a range of sporadic and hereditary cancers including hereditary diffuse gastric cancer (HDGC). The lifetime risk of developing advanced diffuse-type stomach cancer in individuals with pathogenic CDH1 germline mutations is approximately 70%. Additionally, female mutation carriers have an elevated lifetime risk of developing lobular breast cancer (LBC) of between 40-60% (1).
At present, prophylactic total gastrectomy is the single option to abolish an inherited risk of gastric cancer and is recommended by the age of 20 years. HDGC is characterized by multiple foci of stage T1a signet ring cell carcinomas which are relatively indolent and develop after downregulation of the 2nd CDH1 allele (2). We hypothesise that the loss of CDH1 within these early stage foci could be specifically targeted with drugs using a synthetic lethal approach (3) before they progress through the musclaris mucosa and invade the submucosa.
To identify novel synthetic lethal compounds for the treatment of cancer arising from E-cadherin loss, we performed a three-staged 114,000 hit-like compound screening campaign on an isogenic pair of human mammary epithelial cell lines with and without CDH1 expression (4). The metabolism-based celltiter-blue assay and a high content imaging approach were employed to determine the impact of the compounds on cell viability and cell cycle phase distribution. This approach identified 84 lead-like compounds which were found to belong to 16 distinct pharmacophore groups. Validation of these groups identified 13 novel compounds as being highly selectively lethal to E-cadherin deficient cells, demonstrating that E-cadherin loss creates druggable vulnerabilities within tumour cells. These novel synthetic lethal compounds are now being validated in more complex in vitro and in vivo models and their targets identified.
Overall this work provides novel leads for the chemoprevention and treatment of both sporadic and familial LBC and DGC.

1. van der Post, et al. J. Med. Genet. 52, 361–374 (2015)
2. Humar, et al. Cancer Res 69, 2050–2056 (2009)
3. Telford, et al. Mol. Cancer Ther. 14, 5 (2015)
4. Chen, et al. BMC Cancer 14, 552 (2014)