Zoledronic Acid and the Mevalonate Pathway: An Opportunity to Overcome Resistance in Hormonal HER2 positive Breast Cancer

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The Human Epidermal growth factor Receptor-type2 (HER2) positive breast characteristics and treatment

The HER2 positive breast cancer subtype exhibits a distinct behaviour from the others, usually accompanied with early relapse, including a higher percentage of brain metastasis [1]. Therefore, it remains a challenge in clinical practice [2]. On the other hand, anti-HER2 target therapy has dramatically changed the course of the disease [3]. In neoadjuvant, adjuvant and metastatic setting, the advent of trastuzumabe and pertuzumab, both monoclonal antibody which binds to HER2 receptor in different domains on tumoral cells inhibiting it progression synergistically with cytotoxic chemotherapy, has improved several endpoints such as pathological complete response rate, relapse-free, progression-free and overall survival [4]. Beyond trastuzumab and pertuzumab combination, an antibody– drug conjugate (ADC) like trastuzumab emtansine (T-DM1) and an irreversible pan-HER tyrosine kinase inhibitor (TKI) such as neratinib meliorated the previous endpoints [5,6]. However, many patients still develop disease recurrence or progressive disease and die.

The current effort from scientists and clinicians is improve the results of anti-HER therapy and mainly its resistance [7]. There is a bidirectional crosstalk between HER2 and estrogen pathway [8]. Anti-HER2 targeting can up-regulate estrogen pathways and additionally estrogen pathway activation can reduce anti-HER2 activity [9]. Differences in responses are expected to occur depending on the positivity of hormonal receptors, justifying humbled performances of HR-positive subtype when compared to HR- negative in terms of pathological response rate in clinical trials as shown by Schedin 2018. Strategies to overcome resistance in HER2- positive breast cancer includes TKIs [10], and combinations of anti-HER2 therapy with other agents like immune checkpoint inhibitors [11], CDK4/6 inhibitors [12], and PI3K/AKT/mTOR inhibitors [13]. While the raise of cyclin inhibitors in pre-clinical models seems to be promising [14] and several studies are ongoing, other attempts has generally failed in demonstrating improvements such as standard therapy combination with hormonal agents in neoadjuvant setting [15].

Furthermore, absence of significant overall survival benefit and a humbled benefit if progression-free survival was reported in metastatic setting when hormonal agents are combined with anti-HER2 requiring other strategies [16,17].

Crosstalk's between HER2 and Mevalonate Pathway

Pre-clinical evidence revealed the previously unknown crosstalk between the estrogen, HER2, Notch and the mevalonate pathway [18]. HER2 protein initiates a cascade of phosphorylation's when activated [19]. Then interaction between core promotion and maintaining cell survival pathways occurs [20], such as the mitogen-activated RAS-RAF-protein kinase (MAPK)/extracellular signal-regulated kinase (MEK)-ERK and the phosphoinositide 3-kinase (PI3K)-PTEN-AKT, as schematic shown by in the figure 1 from Goltsov et al 2018 paper [21].

Zoledronic Acid Combination and the Its Potential Benefits

Zoledronic acid (ZOL) is a bisphosphonate which promotes clinical benefits in breast cancer [22,23]. In preclinical scenario, it demonstrated apoptotic, anti-proliferation [24] and anti-angiogenic effect [25], reduction of invasion and cell migration [26], immunogenic effect [27] and act synergistically with chemotherapy [28,29]. When the farnesyl pyrophosphate synthetize activity is inhibited by ZOL affecting the mevalonate metabolism, a GTPases proteins prenylation do not occurs, interfering with RAS activity, resulting in a potential anti-tumoral activity [30]. The Zo-NAnTax trial [31], is a proof of concept phase II study that explores this
potential therapeutic benefit based on drug repositioning [32] from our group. HER2-positive locally advanced breast cancer patients were treated with four cycles of anthracycline/cyclophosphamide (AC) plus zoledronic acid (ZOL), followed by four cycles of docetaxel with trastuzumab plus ZOL (ACZOLx4 + THZOLx4) pre-operatively. The primary endpoint in this trial was pathologic complete response (pCR) and most relevantly the secondary molecular end-points might potentially translate this pre-clinical to clinical evidence. The study was finished however results are to be published.

Conclusion
HER2-positive breast cancer treatment is a challenge, however the crosstalk between the estrogen, HER2, Notch and the mevalonate pathways represents a window of opportunity to improve resistance in this subset of tumours.

References