C27 Estrogen receptor mutation: a new strategy to overcome endocrine resistance

A. Moretti[1], L. Lupini[2], I. Carandina[3], C. Bassi[2], L.R. Martella[3], F. Lancia[3], F. Daniel[3], L. Belluomini[3], I. Toma[3], E. Bannò[3], C. Nisi[3], L. Da Ros[3], P. Querzoli[4], M. Negrini[2], A. Frassoldati[3]

[1]UO Oncologia Clinica, Azienda Ospedaliero-Universitaria S. Anna, Ferrara; [2]Dipartimento di Morfologia, chirurgia e medicina sperimentale Università di Ferrara, Ferrara; [3]UO Oncologia Clinica, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara; [4]UO Anatomia Patologica, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara

Background: Around 75% of breast tumours express estrogen receptor (ER+). Endocrine therapy (ET) is a cornerstone in the treatment of both early and metastatic disease, but its effectiveness is limited by the developing of acquired resistance and more rarely by de novo resistance. Understanding the mechanisms of resistance to ET represents a challenge. Recently acquired mutations in ESR1, have been associated with resistance to aromatase inhibitor (Ai) therapy in hormone-refractory metastatic breast cancer (MBC).

Materials and methods: We retrospectively collected data of 85 patients (pts), treated at our Institution between 2007 and 2015, diagnosed with ER+ HER2- MBC, previously exposed to ET both in adjuvant or metastatic setting, whose tissue samples were available from primary (N = 40) and metastatic tumor (N = 45). We performed sequencing of DNA tissue to detect hotspot ESR1 mutations at codons 536-538 using Sanger sequencing and next-generation sequencing (NGS). Moreover, we collected blood samples from 7 pts to detect ESR1 mutational status in circulating cell free DNA (ccf DNA) using E-Ice-COLD for the amplification of ESR1 region and droplet digital PCR (ddPCR) or NGS to analyse the amplicons.

Results: We detected no mutations in primary tumor and 6 somatic mutations in 45 of metastatic specimens (overall 13,3% frequency). In our population, the most frequent mutation was the Y537S (3 pts) and in 2 pts D538G: all data were confirmed at NGS analysis. In one case a Y537C mutation was detected using only Sanger method. Blood samples from 7 patients were collected a long time away from the biopsy of metastatic lesions, after exposition at further lines of therapy. In 2 pts respectively L536H and Y537S mutation has been detected in plasma and none mutation in metastasis, in 1 pts a Y437C was found in metastasis but not in ccf DNA, 1 pts presented Y537S both in plasma and metastatic tissue and 3 pts either in plasma or in tissue were ERS1 wild-type. We observed an increase incidence of ESR1 mutations according to the number of endocrine lines administrated: 8,8% in pts with one line, vs 33% in pts with more than 3 lines of ET.

Conclusions: With the limitation of the retrospective nature of the study and the small population, our data confirm that ESR1 mutations are frequent in patients who

progress after ET with Ai. Their early detection and monitoring in plasma across metastatic history might help in the choice of best treatment.

doi:10.1093/annonc/mdx424 | vi33