probably directly responsible for the increase in proliferation of HER2-positive cells. The inhibition of drainage-fluid-induced proliferation in HER2-over-expressing cells by antibodies directed against HB-EGF and TGFα, confirmed the role of EGF-like ligands in proliferation.

Although HB-EGF and TGFα do not bind directly to HER2, they do bind to both HER1 and HER4,[30] and hence it is possible that the cooperation between HER2 and these two receptors (HER1 and HER4), which are expressed by breast carcinoma cells at moderate levels, drives growth stimulation.

The incomplete inhibition of drainage-fluid-induced proliferation upon treatment with a combination of antibodies against HB-EGF and TGFα shows that other factors are also present in drainage fluid. These other growth factors—such as TGFβ, which has been shown to be present in surgical wounds[31]—might be responsible for HER2-independent cell proliferation, since drainage fluid and postsurgical serum both induced proliferation of HER2-negative cells, although at significantly lower levels than in HER2-positive cells.

The EGF-like growth factors HB-EGF and TGFα, and their ability to induce HER2-positive cell proliferation, showed a correlation with the cellular damage induced by surgical resection. Thus, invasive surgery, resulting in extensive blood coagulation with a correspondingly high number of platelets releasing growth factors, might induce proliferation of tumour cells expressing the appropriate growth factor receptors. Such factors entering the bloodstream, as shown by the increase in EGF in postsurgical serum, might rescue micrometastatic foci of tumour cells overexpressing HER2 from dormancy. This initial induction of proliferation could, in turn, induce the endocrine or paracrine secretion of growth factors that continue to stimulate tumour growth.

The results of a randomised clinical trial comparing mastectomy and quadrantectomy showed that early distant relapses in node-positive patients were more frequent in the mastectomy than the quadrantectomy group. This difference, which disappeared later on during follow-up, is consistent with an acceleration of metastatic burden in the first years after invasive surgery.[32]

In conclusion, our data suggest that any surgical treatment undertaken in a patient with cancer, even those other than the removal of the primary tumour, could lead to promotion of tumour recurrence. Nevertheless, the observation that the humanised anti-HER2 monoclonal antibody trastuzumab impairs postsurgically-induced tumour proliferation points to a new therapeutic intervention that exploits the ability of this reagent to inhibit HER2-related growth.

Contributors

E Tagliabue participated in protocol design, data collection, and writing of the manuscript. R Agresti participated in protocol design and sample collection. M L Carcangiu participated in data collection and independent outcome assessment. C Ghirelli participated in data collection. D Morelli participated in data collection and independent outcome assessment. M Campiglio participated in protocol design and data collection. M Martel participated in data collection. R Giovanazzi participated in data collection. M Greco participated in protocol design and independent outcome assessment. A Balsari participated in protocol design and writing of the manuscript. S Ménard coordinated the study and participated in the protocol design, statistical analysis, and writing of the manuscript.

Conflict of interest statement

None declared.

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