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Neoadjuvant Therapy of Breast Cancer – what role?

Terapêutica Neoadjuvante do Cancro da Mama – que papel?

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INTRODUTION

Breast cancer is a major public health problem for women throughout the world.

In the western countries, breast cancer is the most frequent cancer in women and the second most frequent cause of cancer death. In Portugal, in 2006, the National Cancer Registry reported an incidence of 5087 new cases of breast cancer and 1447 deaths caused by this disease ([1]).

Today we know that breast cancer is an heterogeneous disease with at least four subtypes as defined by gene expression profiling: luminal A and luminal B subtypes (typically estrogen (ER) and/or progesterone receptor (PR) positive), HER 2 gene-amplified subtype and basal like subtype (that typically lack ER, PR and HER 2, why it is often referred to as triple negative) ([2]). These different subtypes have different prognosis and different treatment algorithms.

Mathematical models suggest that both the adoption of screening mamography and the administration of (neo)adjuvant chemotherapy and/or tamoxifen have contributed to the observed decline in death rate from breast cancer since 1990 ([3]).

The multidisciplinary utilization of surgery, radiation therapy and systemic treatment constitute the backbone of the treatment of early (and locally advanced) breast cancer. However, the best strategy to integrate these three treatment modalities is still a subject of clinical research. Regarding systemic treatment with chemo, endocrine and anti-HER 2 therapy, its main objective is to eradicate micrometastatic disease to prevent future disease relapse.

NEOADJUVANT THERAPY IN EARLY BREAST CANCER

Neoadjuvant (also known as primary, induction or preoperative) therapy is defined as the therapy delivered before local treatment, usually surgery. Historically, neoadjuvant treatment of breast cancer was indicated for locally advanced and inflammatory disease ([4]). However, even early stage breast cancer is increasingly thought as a systemic rather than a local disease, and interest in the early use of systemic preoperative treatment has increased in recent years, supported by data from clinical trials.

This approach has several theoretical as well as clinical potential advantages over adjuvant therapy. First, it provides the opportunity to monitor clinical tumor response to treatment, allowing tailoring of alternative treatment options in case of absence of response

and avoidance of the toxicity associated with an ineffective treatment. However, the clinical usefulness of this strategy in operable breast cancer remains to be proven ([5]). Second, it is well documented that neoadjuvant chemotherapy increases the rate of breast conservation surgery in large operable breast cancer, without compromising disease-free and overall survival ([6, 7]), by tumor downsizing allowing the conversion of upfront mastectomies to wide tumor excisions (tumorectomy or quadrantectomy) performed after neoadjuvnat treatment. Furthermore, the extent of residual cancer burden in the breast and axillary lymph nodes after neoadjuvant therapy is a powerful prognostic marker ([6, 8]). Lastly, neoadjuvant clinical trials is the ideal clinical experiment to study tumor biology, predictive markers, mechanisms of drug resistance and new treatment approaches. Requiring fewer patients and shorter follow-up, looking at validated clinical endpoints such as pathological complete remissions (pCR), the results of neoadjuvant clinical trials may foresee the disease-free and overall survival results of confirmatory adjuvant trials requiring many more patients and longer follow-up ([9, 10]).

Recently, data from 12,000 patients enrolled in neoadjuvant randomized clinical trials with at least 5 years of patient follow-up, were analyzed to evaluate the relationship between pCR and disease-free and overall survival for the different intrinsic breast cancer subtypes. Based on these results the Food and Drug Administration (FDA) decided to accept pCR as a validated surrogate endpoint, which will likely expedite drug development and approval of new treatments for patients with early stage breast cancer ([10]).

NEOADJUVANT VERSUS ADJUVANT CHEMOTHERAPY

The concept of moving systemic treatment from after surgery (adjuvant) to before surgery (neoadjuvant) was proposed on the assumption that the earlier disseminated single tumor cells are killed, the less likely is the development of future distant metastases.

Randomized trials were conducted in the 1980s and 1990s, in patients with large but potentially operable tumors, comparing the same chemotherapeutic regimen given pre or postoperatively. The primary objective was to improve long-term outcome of patients due to an earlier exposure to systemic therapy. The largest and most important trial was the NASBP B-18 trial which compared four cycles of doxorubicin plus cyclophosphamide (AC) given either pre or postoperatively ([6]). In total, 1523 women were included. The trial showed no difference in disease-free survival (DFS: HR=0.93; 95% CI, 0.81 to 1.06; p=0.27) or overall survival (OS: HR= 0.99; 95%CI, 0.85 to 1.16; p=0.9) between the two arms. Patients achieving a pCR (in both arms) had a superior DFS and OS compared to patients not achieving a pCR (DFS: HR=0.47, p<0.0001; OS: HR =0.32, p< 0.0001). There was a trend in favor of neoadjuvant chemotherapy for OS and DFS in women youger than 50 years (DFS: HR=0.85, p=0.09; OS: HR=0.81, p=0.06). Similar results were achieved in 698 patients randomized in the EORTC 10902 trial to four cycles of 5-fluoruracil, epirubicin and cyclophosphamide (FEC) given either pre or postoperatively ([7]).

A meta-analysis published in 2005 including nine randomized trials and 3946 women documented no difference in DFS or OS between adjuvant and neoadjuvant therapy ([11]). The rate of local recurrence was higher in patients treated with neoadjuvant group, but this finding might be explained by foregoing surgery in some trials in patients who obtained a clinical complete response after administration of preoperative chemotherapy. Although the primary objective of earlier administration of systemic therapy – to improve PFS e OS – was not met, these trials establish that preoperative therapy does not jeopardize the outcome of patients with early stage breast cancer.

In the 2000s, the incorporation of taxanes into neoadjuvant chemotherapy regimens was investigated. Seven randomized trials of neoadjuvant taxane and anthracycline-based chemotherapy, including a total of 2455 patients, were included in a meta-analysis published in 2008 ([12]). Patients treated with

taxanes had a higher rate of breast conserving therapy (BCT) (absolute difference of 3,4%, p=0.012) as well as higher rate of pCR, but in this case, only for the sequential administration of antracyclines and taxanes. The incorporation of other chemotherapy drugs to antracycline and taxane-based combination chemotherapy regimens (cisplatin, vinorelbine or gemcitabine) has not been shown to improve PFS or OS ([13, 14, 15, 16]).

In many neoadjuvant trials pCR was shown to be a strong prognostic marker for better long term outcome. A more stringent definition of pCR, defined as absence of invasive cancer in the breast and axillary lymph nodes (rather than limiting this concept to no invasive carcinoma in the breast), is considered the most correct definition of pCR ([8]). The impact on prognosis of residual intraductal carcinoma (DCIS) is less well established ([17, 18]). The probability of obtaining a pCR with neoadjuvant chemotherapy is dependent on the subtype of breast cancer. While for her2-amplified and triple-negative breast cancer the percentage of pCR after antracycline and taxane-based combination chemotherapy (plus anti-her2 therapy, for this subtype) can range for 20% to more than 45%, the pCR rate in hormone receptor-positive her2-negative breast cancer is less than 10% ([18]). Indeed for triple-negative breast cancer, systemic chemotherapy induces the highest pCR rate, despite an overall worse prognosis for the whole group; however, the long term outcome of those reaching a pCR is very good, contrasting to a dismal prognosis for those with residual invasive cancer. This observation has been referred to as "the triple negative paradox" ([19]).

In a pooled analysis of 6377 patients treated in the German Breast Group (GBG) trials, pCR was not associated with prognosis in luminal A or luminal B breast cancer, whereas in patients with highly proliferative tumors like triple negative or her2-amplified tumors (HER2-positive and ER-negative) pCR could discriminate between good and poor prognosis patients ([18]). A Cochrane meta-analysis of 5500 patients enrolled in 14 randomized trials comparing preoperative with postoperative chemotherapy showed that the risk of death among patients who had a pCR was about half that of patients with residual cancer in the surgical specimen ([8]).

The administration of preoperative chemotherapy could allow tailoring further treatment to clinical anti-tumor response, based on the evaluation of the breast and regional lymph nodes ([5]). This approach was tested in two clinical trials by the GBG; however both trials showed that, in patients not responding to the initial 2 to 4 cycles of chemotherapy, the pCR rates remained low despite the modification of the chemotherapy, suggesting broad resistance to cytotoxic systemic therapy ([20, 21]).

NEOADJUVANT ANTI-HER 2 THERAPY

One year treatment with adjuvant trastuzumab, a monoclonal antibody against the external portion of the her2 trans-membrane cellular receptor, has a major impact on DFS and OS of her2-amplified early stage breast cancer ([22, 23]). Initial phase II trial of neoadjuvant trastuzumab, associated with antracycline and taxane-based combination chemotherapy, reported an unprecedented rate of pCR (66%) ([24]). The NOAH trial (of preoperative chemotherapy combined with and without trastuzumab) was the first randomized controlled trial to confirm this finding (pCR rate of 43% in the trastuzumab arm versus 22% in the control arm, p=0.002). This trial was also one of the first to document the relationship between higher pCR rate and improved outcome (3-year event-free survival of 70% in the trastuzumab arm versus 53% in the control arm, p=0.07)(9).

More recent trials have evaluated the incorporation of dual anti-her2 therapy, either by adding to trastuzumab the intracellular anti-her2 tyrosine kynase inibitor (TKI) lapatinib (NeoALTTO trial) or pertuzumab, a different monoclonal antibody against the extracellular dimerization domain of the her2 receptor (NeoSphere trial) ([25, 26]). Both trials reported higher pCR rates for combined her2 blockade (associated with single agent preoperative paclitaxel in Neo-

ALTTO and with docetaxel in NeoSphere) compared with the control arms of chemotherapy plus single anti-her2 blockade. In NeoALTTO the tpCR (total pCR, breast and axilla) rate was 51% with paclitaxel+trast uzumab+lapatinib, 29% with paclitaxel+trastuzumab and 24% with paclitaxel+lapatinib. Furthermore high pCR rates in the paclitaxel+trastuzumab+lapatinib arm were obtained in both her2+/ER-negative (61%) and her2+/ER+ (41%) tumors. Similarly, in Neo-Sphere the pCR rate was 46% with docetaxel+trastuzu mab+pertuzumab, 29% with docetaxel+trastuzumab and 24% with docetaxel+pertuzumab. Interest-ingly, NeoSphere included a fourth experimental non-chemotherapy arm of isolated preoperative trastuzumab+pertuzumab, which was associated with a pCR rate of 17%, despite the absence of chemo-therapy administration. Dual anti-HER2 blockade may soon become a new standard of neoadjuvant treatment for this breast cancer subtype. In fact, the FDA has recently approved preoperative treatment with pertuzumab.

A new formulation of trastuzumab, for subcutane-ous administration, has also been compared with the intravenous formulation in the neoadjuvant setting, with similar pCR rates and pharmacokinetic param-eters as well as similar toxicity profile ([27]). The ease of subcutaneous administration improves patient convenience and decreases health care resource utili-zation ([28]).

NEOADJUVANT ENDOCRINE THERAPY

Neoadjuvant endocrine therapy has been studied much less frequently than neoadjuvant chemotherapy. This may be due to a slower response to endocrine therapy and a less well established duration of such preoperative treatment. Hormone receptor-positive her2-negative breast cancer has a probability of less than 10% of reaching a pCR with neoadjuvant chem-otherapy. Both tamoxifen and aromatase inibitors have been studied in this setting, with response rates similar to those obtained with chemotherapy (partial responses up to 60%) but rare complete responses. Candidates to neoadjuvant endocrine therapy include patients with large operable or locally advanced breast cancer with other comorbidities that contra-indicate the administration of systemic chemotherapy.

SURGERY AFTER NEOADJUVANT THERAPY

Surgery should be performed after the patient recovers from the last chemotherapy dose and after all planned systemic chemotherapy has been deliv-ered. The extent of excision does not necessarily have to include the entire area of malignancy identified at diagnosis (before chemotherapy administration). Instead, the breast tumor site should be marked with a clip before initiating chemotherapy so that, in case of complete clinical response, the surgeon can iden-tify the tumor bed. In patients with no clinical axil-lary lymph node involvement at diagnosis, the ideal time to perform a sentinel node biopsy is controver-sial (before versus after neoadjuvant chemotherapy).

For hormone receptor-positive breast cancer, endocrine therapy should be initiated after complet-ing neoadjuvant chemotherapy. For her2-amplified tumors, trastuzumab therapy should be maintained for a year and should be maintained independent from the timing of surgery.

NEOADJUVANT THERAPY FOR LOCALLY ADVANCED BREAST CANCER (INCLUDING INFLAMATORY BREAST CANCER)

Locally advanced (LABC) and inflamatory breast cancer (IBC) are formal indications for neoadjuvant therapy in an attempt to downsize primary inoper-able breast tumors and/or bulky axillary disease, to make surgery possible and to improve local control and survival. Prior to the use of neoadjuvant chemo-therapy, long-term survival was uncommon.

The initial evidence to support the use of neoadju-vant chemotherapy came from a clinical trial where

LABC patients were treated with neoadjuvant chemotherapy, followed by mastectomy and radiotherapy, and compared with an historical control group treated with surgery and radiotherapy only ([4]). A 50% reduction or more in the size of the tumor (partial response) was achieved in 67% of patients and clinical complete responses were observed in 17%. Dramatic improvements in DFS were also noticed and neoadjuvant therapy assumed a determinant role in LABC/IBC treatment. The same principles of neoadjuvant systemic therapy of early-stage breast cancer should be applied to LABC.

FUTURE DIRECTIONS

Neoadjuvant treatment is the ideal setting to test new pharmacologic agents looking at pCR rate and identification of predictive markers of response. These studies may require sequential tumor biopsies (before, during and after neoadjuvant therapy) looking at early predictors of response or drug resistance and molecular interference with intracellular pathways. Tumor cell expression of Ki67 expression, a measurement of proliferative activity, determined after two weeks of treatment is such a predictor of neoadjuvant endocrine therapy and has been shown to correlate with survival ([29]).

Another area of research is how to address patients with residual tumor in the surgical specimen after systemic neoadjuvant treatment. This is mostly relevant for hormone receptor-negative breast cancer since the worst prognosis of patients that do not reach a pCR is well documented. Clinical trials are evaluating new systemic approaches in this scenario.

CONCLUSIONS

Neoadjuvant systemic therapy is the standard of care for patients with LABC and IBC. In early-stage breast cancer neoadjuvant therapy is also increasingly used and for some patients, should be the standard of care. Randomized prospective clinical trials have demonstrated equal efficacy, in terms of DFS and OS, of neoadjuvant compared to adjuvant therapy. Furthermore, clinical responses lead to a higher rate of breast conserving surgery and better cosmetic results with the neoadjuvant approach. These trials have also shown that pCR predicts prolonged DFS and OS.

Additionally, the neoadjuvant setting is the ideal clinical experiment to test new drugs, with early evaluation of efficacy looking at pCR rate and requiring fewer patients. Finally, serial biopsies of tumor tissue before, during and after preoperative treatment with evaluation of therapy-induced molecular changes, provide an excellent tool to study biomarkers, mechanisms of action and predictors of response or toxicity.

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