EDITORIAL
DOI: 10.29289/259453942018EDIT283

NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER: TIME FOR AN APPRAISAL

Quimioterapia neoadjuvante em câncer de mama: tempo para uma avaliação

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Neoadjuvant chemotherapy (NC) has been established as standard treatment for locally-advanced breast cancer (LABC) based on randomized clinical trials (RCT) performed in the 1980s and 1990s[1]. We all know the story: NC is not better (nor worse) than adjuvant chemotherapy in terms of prognosis; it leads to downstaging and surgery downsizing in 30–40% of the cases (albeit with a slight increase in the risk of local recurrence); it is an interesting platform for the research of biomarker and new drugs; it increases the accuracy of prognostic assessment (e.g., patients who achieve pathological complete response (PCR) have an excellent prognosis)[2].

However, there were also some frustrations. For instance, NC failed to deliver the promise of becoming an *in vivo* assessment of chemotherapy sensitivity and guidance. In GeparTrio[3], switching agents in patients resistant to anthracyclines and taxanes failed to improve responses — suggesting that either we had no good alternative agents at the time, or tumours truly display multi-agent chemotherapy resistance.

However, these historical data must be addressed in light of current understanding of cancer biology. No molecular classification was available at the time; based on knowledge from current molecular signatures[4], we can assume that at least 2/3 of the patients included in these trials had tumours that did not need and would not respond to chemotherapy. What would have been the outcome of these trials if these patients had been excluded? Unfortunately, this question will never be answered, but one has to admit the possibility that a benefit from upfront administration of chemotherapy could have emerged. Interestingly, there is indirect evidence that early exposure to chemotherapy could favourably affect outcomes in cases of more aggressive biology[5].

Modern understanding of cancer biology established that the molecular subtypes respond differently to chemotherapy, with PCR rates in the range of 10–20%, 30–40% and 50–60% for luminal (herein defined as Her2 negative/ER Positive), triple negative and Her2 positive disease, respectively. There is general agreement that optimal chemotherapy should include anthracyclines and taxanes. Attempts to include a third cytotoxic agent have largely failed. In the last decade, the interest switched to target therapies — and this eventually led to the definitive separation of Her2 positive from Her2 negative disease in clinical trials and, more recently, also a tendency of triple negative disease being investigated separately from other subtypes.

Currently, chemotherapy for high risk luminal breast cancer (BC) should include anthracyclines (doxo or epirubicin) and taxanes (docetaxel, paclitaxel or albumin-bound paclitaxel). The treatment of triple-negative disease is similar, though there is some controversy over the value of adding carboplatin to taxanes for this particular subtype. This is based on data from phase II RCT that showed gains in PCR in the range of 13–14%[6,7], with unclear impact on outcome at this time. Of note, carboplatin clearly adds toxicity, especially haematological and fatigue. Counterintuitively, BRCA 1/2 genotyping has not been shown to be discriminative of benefit from carboplatin in this setting[7]. The antiangiogenic agent bevacizumab, which had shown activity in the metastatic setting, failed to improve responses both in luminal and triple negative disease. Finally, in a recent metanalysis, dose-dense administration of chemotherapy (every two weeks with growth factor support) has been shown to be more effective than conventional chemotherapy in the adjuvant setting[8], and there is a strong argument to also apply this data to the neoadjuvant setting. Although there is a stronger rationale for this concept in triple negative disease, in this metanalysis the benefit was not restricted to this molecular subtype.

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Conflict of interests: nothing to declare.

In Her2 positive disease, the incorporation of trastuzumab has increased PCR rates to the rage of 30–50% and it has become standard treatment. More recently, phase II RCT have shown further gains with the addition or pertuzumab, leading PCR rates to the range of 50–60%[9]. These trials were not powered to depict disease-free survival (DFS) and overall survival gains, but the recent demonstration of a DFS advantage with pertuzumab in the adjuvant setting (especially in node positive disease) provides support for using this agent as a component of the neoadjuvant schedule, especially in locally-advanced tumours.

After almost three decades of NC research, two new tendencies must be addressed. First, the strategy that explores PCR as biomarker to determine the need for additional (postoperative) treatment. In a Japanese RCT, 900 patients with Her2 negative (1/3 triple negative) LABC who failed to achieve PCR with anthracyclines and taxanes were randomized to receive eight cycles of capecitabine vs nil[10]. This trial reported significant reduction in recurrence events with the investigational agent — which appeared to be more robust in triple negative disease. Despite significant criticism (clearly, this trial must be replicated in the occident before becoming standard treatment), it was the first ever to report a benefit from this strategy; of note, it has also gained support from a recent American Society of Clinical Oncology (ASCO) panel. More importantly, this landmark study opens new avenues for this strategy, with further RCT now investigating "rescue therapy" with agents such as T-DM1, palbociclib, non-cross resistant cytotoxic chemotherapy, and immunotherapy. Should this strategy succeed in BC, there will be growing pressure for the use of NC, in order to identity treatment-resistant patients that could still be "rescued".

Second, NC raises concerns over the risk of overtreatment. Currently, this can occur in at least two situations. In Her2 positive disease, patients operated upfront with tumours of 3cm or less and negative lymph nodes can be safely treated with a simplified, well-tolerated regimen or 12 weeks of paclitaxel with concurrent trastuzumab (given for a total duration of 12 months)[11]. After seven years of follow-up, distant DFS was higher than 98%, implying that any more intensive treatment (e.g., more aggressive/longer chemotherapy, pertuzumab) is unjustifiable. Therefore, the indication of NC to patients with T1/small T2, node negative disease poses a real risk of overtreatment and should be employed with caution. Of note, treatment de-escalation remains an active area of investigation, with ongoing trials also investigating chemotherapy-free schedules and shorter trastuzumab durations in this setting.

Another situation is luminal BC. The new genomic signatures have revolutionized the management of these patients, showing that chemotherapy is unnecessary for the majority of them. Commercially available platforms such as Oncotype Dx and others reliably identify patients with more advanced cancers and low risk scores who have very low risk of recurrence[4,12]. This new knowledge has led to an update in the AJCC staging system, suggesting that patient with previous stage II and III disease holding a low risk signature have a prognosis similar to stage I. Therefore, NC poses the greatest risk of overtreatment when employed in luminal cancers, and this is particularly valid for postmenopausal women.

So where do we go from here with NC? There are conflicting indications — suggesting that NC could either grow in importance (the "rescue strategy" after non-PCR) or diminish (treatment de-escalation trials in Her2 positive disease, genomic signatures gradually eliminating chemotherapy in luminal cancers). We will need to wait for the outcome of ongoing clinical trials to better understand these tendencies. In the meantime, caution is recommended when indicating NC for luminal and very early stage Her2 positive cancers — overtreatment has been under scrutiny in oncology. In triple negative disease, NC remains an excellent choice, regardless of disease stage.

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