E10. Post-neoadjuvant treatment

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Neoadjuvant systemic therapy is considered today as a valid option for many patients with larger breast tumours, those who wish to be treated by breast conservation, or to monitor the efficacy of systemic treatment. With anthracycline-taxane based regimens, a pathological complete remission can be achieved in up to 20% of patients with HER2 negative disease, whereas with the addition of trastuzumab, pathological complete remission rates increase to above 40%.[1] These patients are known to have a favourable long term outcome, despite showing an aggressive tumour pattern at early diagnosis. However, for most patients with tumour residuals in the breast and/or regional lymph nodes after neoadjuvant chemotherapy, outcome is considerably poor. Response to neoadjuvant chemotherapy might therefore provide important information about how to plan subsequent post-neoadjuvant systemic treatment.

Management of post-neoadjuvant treatment differs strongly between the biological subtypes of breast cancer and is therefore discussed separately in the following:

Management in hormone-sensitive / HER2 negative disease

Pathological complete response to neoadjuvant chemotherapy is achieved in 10% of this subtype of breast cancer, and will be even lower if other patterns of the tumour signal low proliferation and high hormone responsiveness. Therefore, neoadjuvant chemotherapy is today not considered for patients with a luminal A type of tumour.

Patients with luminal B type tumours and a complete response show a low risk for relapse; however, patients with residual tumour at surgery still have a favourable long term outcome, as the overall prognosis of this group of patients is good.

These patients will all receive endocrine treatment with an aromatase inhibitor and/or tamoxifen irrespective of the response to neoadjuvant chemotherapy, referring to the same decision criteria as for patients being treated with adjuvant chemotherapy. In the future, it could be considered that patients with a pathological complete response might not need further endocrine treatment as well as patients with large residual tumours and tumour patterns signalling a higher degree of proliferation having a need for other treatment modalities.

Response to neoadjuvant endocrine treatment is also correlated with long term outcome. A maintained high tumour Ki67 level after short term endocrine treatment or at surgery was associated with a lower recurrence-free survival[2] and might therefore be helpful in deciding which patient needs further adjuvant chemotherapy.

Management of HER2 positive disease

Patients with tumours of this subtype receiving neoadjuvant chemotherapy and trastuzumab have a high chance of achieving a pathological complete remission, and, as demonstrated by the NOAH study[3] and the TECHNO study, the 3 year event free survival of these treatment sensitive patients ranges between 69% and 90% for locally advanced and operable tumours, respectively. Patients with residual disease at surgery showed a significantly worse long term outcome despite trastuzumab treatment being continued postoperatively to complete a 1 year total duration of trastuzumab treatment in both trials. This, again, raises two questions regarding the future management of these patients:

- Is it necessary to continue trastuzumab treatment in patients having achieved a pathological complete response in patients with operable tumours?
- Can we identify markers for resistance at the residual tumour tissue that help to decide which patient might benefit e.g. from a switch to another anti-HER2 agent?

Management of triple-negative disease

Management of patients with this breast cancer subtype differs from the others subtypes as current treatment options are limited. Triple-negative tumours show the highest sensitivity to neoadjuvant anthracycline-taxane based chemotherapy with pathological complete response rates of around 40%. Similar to the other subtypes, these sensitive patients show a significantly better outcome than patients with remaining residual disease.[4] However, until now, the only option available is to treat those unfavourable patients with more chemotherapy. However, if these patients have already received complete treatment

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with anthracyclines and taxanes, any additional chemotherapy regimen is experimental and so far shows no benefit in retrospective patient cohorts. Furthermore, we have demonstrated in the GeparTrio study that an early switch to a non-taxane-based treatment in clinical non-responders does not increase the chance of a response at surgery, and are therefore considering these patients as being, in general, chemo-resistant. Finally, it is expected that many of these patients will not tolerate further toxic treatments. Therefore, it is of great interest in this patient subgroup to investigate non-toxic approaches based on a mechanism of action different from that of cytotoxic agents.

Current approaches for new post-neoadjuvant treatments

Bisphosphonates

The NaTaN (Neo-Adjuvant Trial Add-oN) study, led by the German Breast Group, is a randomised, multicentre, open phase III study comparing the postoperative use of zoledronic acid versus no treatment in patients with histological tumour residuals after preoperative anthracycline and taxane containing chemotherapy for primary breast cancer. There is increasing evidence from a range of cell line experiments that zoledronic acid can inhibit tumour cell adhesion and invasion as well as evidence from two adjuvant zoledronic acid studies (ABCSG 12, ZoFast) showing a lower recurrence rate after 2–5 years of treatment. Between 2005 and 2009, 669 patients were randomised to either observation or 4 mg zoledronic acid treatment (every 4 weeks for the first six doses, then every 3 months for eight doses, and then every 6 months for five doses). In addition, patients with hormone sensitive tumours (ER and/or PgR positive) receive simultaneous endocrine treatment according to current treatment guidelines. The first interim efficacy analysis is expected in 2011.

Anti-vascular endothelial growth factor treatment

A phase II study 05-055, conducted by the Hoosier Oncology Group, explored the feasibility and toxicity of anti-angiogenesis therapy in the post-neoadjuvant setting.[5] Eligible patients had stage II–III breast cancer with residual invasive carcinoma at surgery following anthracycline-containing neoadjuvant chemotherapy. Treatment consisted of bevacizumab 15 mg/kg given every 3 weeks for 1 year, either alone, in combination with low-dose oral cyclophosphamide and methotrexate or with different capecitabine schedules. Concurrent endocrine and/or trastuzumab therapy was allowed but, when indicated, all patients completed radiation therapy prior to enrolment. A total of 161 patients were enrolled. The most common side effects were hypertension, arthralgia, headache and epistaxis; significant proteinuria, thromboembolic events and cardiac dysfunction were rare. Importantly, no new safety signals were identified. Overall, this pilot trial suggests that anti-angiogenic therapy with bevacizumab alone or in combination with chemotherapy after neoadjuvant chemotherapy, surgery and radiation is feasible and generally well tolerated.

Future directions

Apart from bisphosphonates and bevacizumab, various other new agents could be considered as candidates for clinical trials in the post-neoadjuvant setting, e.g. multi-tyrosine-kinase inhibitors, mTOR or PARP inhibitors. These trials will require a much smaller number of participants as their risk for relapse is much higher than in an unselected population. However, there will also always be the tendency to explore the efficacy of these agents as part of a neoadjuvant regimen, e.g. the GeparQuinto and NSABP-B40 studies are currently investigating the effect of bevacizumab. However, the post-neoadjuvant approach provides the unique possibility to restrict treatments only to those patients who still have an unfavourable prognosis even after receiving all kinds of established therapies.

Conflict of interest statement

None declared.

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