Editorial Commentary

Neoadjuvant nab-paclitaxel in breast cancer: who stands to benefit?

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In the treatment of early breast cancer, the addition of a sequential taxane following an anthracycline-based regimen has improved patient outcomes (1), with studies suggesting that weekly solvent-based paclitaxel given after an anthracycline regimen significantly reduces the risk of relapse (2,3). Phase II data exists in favour of incorporating weekly paclitaxel into anthracycline-based neoadjuvant regimens (4,5). Furthermore, and more broadly, the efficacy of paclitaxel in combination with anthracyclines (epirubicin/cyclophosphamide; doxorubicin/cyclophosphamide/fluorouracil) has been demonstrated in several phase III neoadjuvant trials (6,7), establishing these combinations as standard-of-care. In the metastatic setting, nanoparticle albumin-bound (nab)-paclitaxel given weekly at 150 mg/m^2 has been shown to be superior to docetaxel 100 mg/m^2 given on a 3-weekly schedule (8), posing the question as to whether nab-paclitaxel is a better choice of taxane in the early setting, compared to solvent-based paclitaxel.

The Gepar-Septo GBG-69 trial initially reported in 2016 (9). This randomised, phase III study randomised patients with untreated early breast cancer to receive neoadjuvant therapy in the form of weekly nab-paclitaxel 150 mg/m^2 (later amended to 125 mg/m^2) for a total of 12 weeks, versus weekly paclitaxel 80 mg/m^2 over 12 weeks. Both arms subsequently received standard epirubicin/cyclophosphamide on day 1 for four 3-week cycles, and patients with HER2-positive disease also received concurrent trastuzumab and pertuzumab. The primary endpoint of GBG-69, pathological complete response (pCR), was reached with a significantly larger proportion of the nab-paclitaxel arm achieving pCR (38% versus 29% for paclitaxel). Exploratory analyses suggested that this pCR benefit was confined largely to patients with triple-negative disease (48% pCR rate for nab-paclitaxel, versus 26% in those who received paclitaxel; P=0.00027). Comparatively, there was no statistically significant difference in pCR rate observed in patients with hormone receptor-positive and/or HER2-positive disease according to study arm. It is also notable that significant pCR improvements in patients were not observed in the neoadjuvant ETNA study (NCT01822314), regardless of tumour subtype (10). ETNA—which, unlike GBG-69, only enrolled patients with HER2-negative early disease—reported a statistically insignificant improvement in pCR rate of 22.5% after NAB-paclitaxel versus 18.6% for paclitaxel overall (OR 0.77; 95% CI, 0.52–1.13, P=0.19).

GBG-69 has recently reported again: after a median follow-up of 49.6 months, the 4-year rate of invasive disease-free survival (iDFS) has been reported as significantly better in the nab-paclitaxel group compared to that of those in the paclitaxel arm (84.0% versus 76.3% respectively; HR 0.66; 95% CI, 0.51–0.86, P=0.002) (11). Statistically significant benefit in favour of nab-paclitaxel was also noted in the overall population in terms of endpoints of event-free survival (EFS) and disease-free survival (DFS), but no analogous benefit was shown in distant disease-free survival

(DDFS) or overall survival, data for the latter not having reached maturity at time of reporting.

Safety data from the original report of GBG-69 showed nab-paclitaxel was more frequently associated with serious adverse events (26% versus 21% for paclitaxel, P=0.057), with a more frequent occurrence of haematological and non-haematological toxic effects alike. Dose reductions occurred in 30% of patients assigned to the nab-paclitaxel arm, versus 12% in the paclitaxel group (P=0.0001). In particular, peripheral sensory neuropathy (all grades) occurred in 85% of patients treated with nab-paclitaxel, versus 65% in patients on the paclitaxel arm (P<0.0001). Long-term follow-up of time to resolution of peripheral sensory neuropathy from grade 2–4 to grade 1 showed a prolonged duration for patients who received 150 mg/m^2 of nab-paclitaxel prior to study amendment, compared to those who received the modified 125 mg/m^2 dose (median of 12.7 versus 6.4 weeks, respectively). Weekly paclitaxel 80 mg/m^2 given 3 weeks out of every four took a median rate of 7.0 weeks to reach neuropathic resolution, which was not statistically different to the rate of resolution associated with the nab-paclitaxel 125 mg/m^2 regimen (P=0.74). Collectively this suggests that whilst the administration of nab-paclitaxel is temporally associated with a greater risk of immediate toxicities and subsequent dose reductions, there does not appear to be a long-term functional impact on enduring symptoms that may dissuade the clinician from considering nab-paclitaxel (at 125 mg/m^2) above paclitaxel as a treatment option.

In neoadjuvant trials, the primary endpoint of pCR is often viewed as a surrogate for long-term disease-free benefit, and serves as a direct—albeit temporally short-term—reflection of the efficacy of the treatment rendered. A previous pooled analysis of 11,955 patients enrolled across 12 international trials suggested the association between pCR and long-term outcome is greatest in patients with triple negative disease, and those with hormone receptor-negative, HER2-positive cancer treated with trastuzumab (12). However, trial-level analysis demonstrated little association between pCR and EFS and/or overall survival, and so this concept should still be approached with caution.

Overall, the iDFS benefit from nab-paclitaxel observed in GBG-69 appears most evident in patients with HER2-negative disease. This provides an interesting contrast with the ETNA study, which, unlike GBG-69, did not show a statistically significant benefit from nab-paclitaxel in terms of pCR. Similarly, differences in 5-year EFS observed in the two arms of ETNA failed to reach statistical significance (84.8% for paclitaxel versus 87.3% for nab-paclitaxel, P=0.245) (13). In the TNBC cohort of GBG-69, pCR rates were considerably higher in patients receiving nab-paclitaxel (48% versus 26% for paclitaxel, P=0.00027), which later translated to EFS benefit within this group. However, in clinical practice, guidelines are now suggesting that consideration be paid to dose-dense regimens (particularly for highly proliferative disease) as well as the addition of carboplatin in TNBC (14). This leaves unanswered the question as to whether nab-paclitaxel would be a feasible or beneficial option in the setting of a dose-dense or platinum-containing regimen, particularly in view of recent findings of trials such as GeparSixto, which demonstrated that the addition of carboplatin to neoadjuvant non-pegylated liposomal doxorubicin plus solvent-based paclitaxel resulted in improved DFS in patients with TNBC (15).

The absence of a statistically significant benefit in favour of nab-paclitaxel in the HER2-positive subgroups may be viewed as an indication of the relative strength of clinical benefit bestowed by anti-HER2 agents, nullifying benefit that might be offered by subtle alterations in the taxane-agent backbone. Although significantly better iDFS was observed in patients receiving nab-paclitaxel who did not achieve pCR in GBG-69, it must be noted that trials such as KATHERINE (16) and CREATE-X (17) present an increasingly significant role for adjuvant therapies in the setting of residual disease following neoadjuvant management. Similarly, recent interim findings from KEYNOTE-522 also suggest potential for immunotherapy-based neoadjuvant treatment and post-operative maintenance in early triple negative disease (18). These collective data, and more forthcoming, may in time displace the relative importance regarding neoadjuvant chemotherapy choice alone in clinical practice, with greater long-term benefits perhaps found with the introduction of new agents to the neoadjuvant regimen, and/or the addition of adjuvant therapy, particularly in patients who do not achieve pCR initially.

Whilst pCR rates were overall low and showed no benefit for nab-paclitaxel within patients with endocrine receptor-positive, HER2-negative disease in the original report of GBG-69 (16% for nab-paclitaxel versus 12% for paclitaxel, P=0.23), intriguingly, this group showed a consistent benefit in favour of nab-paclitaxel in terms of iDFS, EFS and DFS in the updated data. As such, in patients with luminal-like disease, wherein initial pCR does not appear to predict long-term survival outcomes, and wherein patients largely uniformly receive standardised adjuvant management in

the form of endocrine therapy, neoadjuvant nab-paclitaxel may be worthy of consideration. This premise may extend beyond just those patients with luminal B-like disease, which is classically understood to be more chemo-sensitive with less potential for benefit from endocrine therapy than luminal-A subtypes, as notably, overall, patients with tumours with lower proliferative indexes (Ki67 ≤20%) demonstrated a better iDFS when treated with nab-paclitaxel, despite no initial evidence of a pCR benefit.

In the overall population of GBG-69, the type of taxane received on trial did not significantly influence the rates of DDFS (HR for overall group 0.78; 95% CI, 0.59–1.03, P=0.084), in contrast to the strong indication that nab-paclitaxel was beneficial in the overall group in terms of iDFS (HR 0.66; 95% CI, 0.51–0.86, P=0.002). The estimation of DDFS excluded consideration of loco-regional recurrence and invasive disease in the contralateral breast: occurrences largely determined by surgical approach and adjuvant radiotherapy (details of which are not included in survival analysis), and arguably critically less-so by systemic chemotherapy. Such recurrences can often still be salvaged with curative intent, in contrast to distant disease which is still largely regarded as an incurable scenario. Once loco-regional recurrence is removed from analysis in GBG-69 (and thus, by extension, any unreported potential advantage derived from loco-regional treatment is indirectly discounted), no advantage from nab-paclitaxel is observed in terms of recurrence at distant sites. This is perhaps counter-intuitive, in that the perceived predominant benefit of systemic chemotherapy in the neo(adjuvant) setting is to reduce rates of subsequent incurable distant recurrence, and so one may expect that any true advantage of one chemotherapy regimen over the other should also be borne out in DDFS rates. It may be that the data from GBG-69 is still too immature to detect a DDFS advantage in patients with luminal-like disease assigned to the nab-paclitaxel arm (HR 0.75; 95% CI, 0.51–1.10, P=0.139), given that distant recurrences commonly occur well beyond 5 years follow-up in this population. It is also important to acknowledge the limitations of this sub-analysis, given the smaller proportion of patients who incurred recordable events (249/957 patients in the overall modified intention-to-treat population reported an event; 57% of these denoted distant relapse of disease). However, it is notable that the TNBC group—a cohort in whom disease recurrence classically tends to occur in the earlier years of follow-up—also showed no significant benefit in terms of DDFS according to treatment arm (HR 0.81; 95% CI, 0.48–1.36, P=0.420), despite demonstrable benefit both in terms of pCR and EFS. As analysis of GBG-69 at a later time point was not foreseen, it is possible that the effect of nab-paclitaxel in this setting will not be fully appreciated in the context of survival from distant recurrence events.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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