A Prospective, Single-Arm, Phase II Trial of Apatinib Combined With Nab-Paclitaxel and Carboplatin for The Neoadjuvant Treatment of Triple-Negative Breast Cancer

Tianyu Zeng
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Jue Wang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Wei Li
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Yiqi Yang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Fan Yang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Mengzhu Yang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Chunxiao Sun
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Xiang Huang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Yan Liang
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Ziyi Fu
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Xiaoming Zha
Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital
Yongmei Yin (ymyin@njmu.edu.cn)
the First Affiliated Hospital of Nanjing Medical University https://orcid.org/0000-0003-3335-369X
Jun Li
the First Affiliated Hospital of Nanjing Medical University

Research

Keywords: Apatinib, Neoadjuvant treatment, Triple negative breast cancer, Pathological complete response, Nab- paclitaxel, Carboplatin.

Posted Date: August 31st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-812315/v1

Abstract

Background: Pathological complete response (pCR) is essential for improvements of prognosis in triple-negative breast cancer (TNBC). We evaluated the efficacy of apatinib combined with nab-paclitaxel and carboplatin in patients in this phase II clinical trial.

Methods: Women with hormone receptor- and human epidermal growth factor receptor 2 (HER2)-negative, stage II/III breast cancer received six cycles of 75 mg/m2 docetaxel, carboplatin (AUC = 5) and 15 mg/kg bevacizumab every 21 days. The primary end point was pathological complete response (pCR) in the primary breast and axillary lymph nodes (ALN).

Results: Thirty-two patients were recruited into the clinical trial, the vast majority of the patients had stage III tumors (65.6%) and the median longest tumor size was 3.5 cm. The pCR rate was 43.8% (n = 14); clinical response rate 93.8% (n = 30); complete response rate 21.9% (n = 7); partial response rate 71.9% (n = 23); stable disease 6.2% (n = 2). After surgery, 7 (63.6%) of the 11 patients without axillary lymph node metastasis achieved a pCR. The median target lesions in breast reduced to 1.2 cm after the third cycle treatment and 0.9cm after the last cycle. Most frequent grade 3/4 adverse events were thrombopenia (40.6%, n = 13) and neutropenia (25%, n = 8).

Conclusions: Neoadjuvant apatinib, combined with albumin paclitaxel and carboplatin resulted in an encouraging pCR rate in locally advanced breast cancer and no major safety concerns during the therapy.

Clinical trial registration: NCT03650738

Background

Challenges were existed in treatment of triple-negative breast cancer (TNBC) owing to the short of appropriate targets(1). With the absence of hormone receptor and human epidermal growth factor receptor 2 (HER2), definitive therapy such as antihormonal treatment and anti-HER2 monoclonal antibody were improper(2, 3).

Aggressive nature and frequent visceral metastases of TNBC leads to the poor prognosis of patients, including short disease-free intervals (DFS), progression free survival (PFS) and overall survival (OS)(4–6). As a result, pathological complete response (pCR) after neoadjuvant therapy was pursued to achieve comparable survival outcomes in patients with TNBC(7, 8). Currently, data from clinical studies support that neoadjuvant therapy plays an important role improving the pCR rates and long-term prognosis(8). Clinically, only about one-third of stage II-III TNBC patients achieve pCR after anthracycline and taxane-based neoadjuvant chemotherapy (NAC)(9, 10). More than half of TNBC patients still have invasive lesions remaining after NAC, which leads to clinical on the rapid metastasis and recurrence(7, 8). Therefore, increasing the pCR rate after NAC is the top priority for improving the prognosis of TNBC patients, and it has also become an urgent clinical problem that needs to be resolved.

Nab-paclitaxel: the first chemotherapy drug based on a nanotechnology platform that does not require solvents, with active transport mechanism. After endocytosis, it is transported by endothelial cells and aggregated to the tumor site by albumin(4). At the same dose, the accumulation of drugs in tumor tissues after nab-paclitaxel administration is more efficient than paclitaxel, and shows better tumor/normal tissue selectivity(11, 12). Several randomized controlled studies compared the efficacy and safety of nab-paclitaxel and paclitaxel/docetaxel, and the results suggested that the pCR rate of the TNBC subgroup was 41% (95% CI 38%-45%)(13, 14). Compared with paclitaxel treatment, it can obtain higher pCR rate and significantly reduce the incidence of allergic reactions.

Most TNBCs exhibit a "BRCAness" phenotype due to BRCA1/2 gene mutations or other molecular changes(15, 16), and usually have defects in the DNA repair mechanism, so they are particularly sensitive to DNA damaging agents. Platinum belongs to DNA damaging agent that kills tumor cells by inducing double-stranded DNA breaks(17). CALGB 40603(18) and GeparSixto(19) have shown that the pCR rate can be as high as 75% after the introduction of platinum in the neoadjuvant scheme. On the other hand, angiogenesis associated genes are frequently activated in TNBC, and inhibiting angiogenesis may be another strategy for TNBC treatment. The GBG44 and NSABP B-40(20) study published in 2012 showed that the combined use of anti-angiogenesis therapy in neoadjuvant chemotherapy increased the pCR by about 4%-11%, opening up a new treatment for anti-vascular targeted therapy for TNBC. Apatinib, by highly selective competition for the ATP binding site of VEGFR-2 in cells, block downstream signal transduction and inhibit tumor tissue angiogenesis, have demonstrated good results in patients with advanced breast cancer in previous research(21, 22), but currently lack experience in the application of neoadjuvant therapy.

Here, we performed a single-arm, randomized, phase II trial for patients with Stage IIb-IIIc breast cancer, aiming determining whether the addition of apatinib to neoadjuvant chemotherapy increase the rate of pCR.

Methods

Patients

Eligible patients were female, age ≥ 18 years, diagnosis with stage II-III triple negative breast cancer by histopathology, no systemic anti-tumor treatment, at least one measurable lesion (according to RECIST v1.1(23)), Eastern Co-operative Oncology Group Performance Status 0–1, expected survival time ≥ 3 months, laboratory tests meet the following criteria: absolute count of blood neutrophils ≥ 1.5×10^9/L, platelet count ≥ 100×10^9/L, hemoglobin ≥ 90g/L, serum total bilirubin, combined bilirubin ≤ upper normal limit (UNL) ×1.5, alanine aminotransferase, aspartate aminotransferase ≤ UNL×2.5, serum creatinine ≤ UNL, endogenous creatinine clearance ≥ 60 ml / min (calculated using the Cockcroft-Gault formula).

Patients with major surgery within 4 weeks prior to enrollment or surgical wounds have not healed, or embolization and bleeding occurred within 4 weeks preceding enrolment, or malignant tumors of other histological origins in the past 5 years (except for cured cervical carcinoma in situ and basal cell carcinoma or squamous cell carcinoma) were ineligible. Severe cardiovascular disease including hypertension (BP ≥ 160/95mmHg) uncontrolled by medical treatment, unstable angina, history of myocardial infarction in the past 6 months, congestive heart failure > NYHA II, severe heart rhythm Abnormalities and pericardial effusions must be excluded, as were those suffering severe infection or mental illness, poor compliance.

This trial was executed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, as was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2018-SR-115).

All the patient volunteers and signs an informed consent form (ClinicalTrials.gov identifier: NCT03650738).

Treatment

Patients received six cycles of 260 mg/m^2 albumin paclitaxel and carboplatin (AUC = 5–6) intravenously, once every 21 days, in combination with apatinib 250mg oral, continuous dosing. Patients with progressive disease by clinical or radiological confirmation or intolerable toxicity were withdrawn from the study. Regular follow-ups were conducted to evaluate safety and effectiveness. If the toxicity recovery does not meet the criteria for subsequent chemotherapy, the start of the subsequent cycle can be postponed appropriately, but the delay cannot exceed 14 days.

Study end points

The primary end point of the study was pCR rate, defined as absence of invasive breast cancer in the primary breast and ALN. Secondary endpoints were toxicity.

Assessment

Tumour and axillary nodal status were evaluated as baseline, and after cycles 3 and 6 by radiological imaging tests. Physical examination about target lesion and regional lymph nodes were carried out at every cycle. Breast MRI was used to assess clinical complete response following Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Toxic effects were supervised on an ongoing basis and graded according to Common Terminology Criteria for Adverse Events, version 3.0.

Statistical design

Patients were included in the intent-to treat (ITT) population received all the 6 cycles of apatinib, nab-paclitaxel and carboplatin. Statistical analysis was conducted using SPSS software (version 21.0). The

enumeration data are expressed in percentage, and the measurement data are expressed as mean ± standard deviation (SD).

Results

Baseline characteristics

From September 2018 to August 2020, 33 patients were recruited at the First Affiliated Hospital of Nanjing Medical University and 32 patients completed the planned treatment course that were included in all efficacy and safety analyses. One patient declined further treatment after cycle 4 due to vascular diseases (aortic intramural hematoma) and received Breast conserving surgery, the pathology showed that the invasive cancer tissue was significantly reduced, and only a few residual cancer cells were scattered and distributed.

Baseline demographics and disease characteristics of the 32 eligible patients are shown in Table 1. Based on breast MRI, most patients had stage III tumors (65.6%) and the median longest tumor size was 3.5 cm (Table 1).

Table 1
Baseline characteristics of patients.

Characteristics	ITT population(N = 32)
Female, n (%)	32
Median age, years (range)	49(20–65)
ECOG	
0	19 (59.4)
1	13 (40.6)
Median largest Tumour diameter, cm (range)	3.4 (2.0-9.8)
Clinical T stage, n (%)	
cT2	24(75.0)
cT3	6(18.7)
cT4	2(6.3)
Clinical N stage, n (%)	
cN0	11(34..4)
cN1	2(6.3)
cN2	19 (59.4)
AJCC clinical stage, n (%)	
IIB	11 (34.4)
IIIA	19 (59.4)
IIIB	2(6.3)

Efficacy

Table 2 shows the rate of pCR in both breast and axillary lymph nodes was 43.8% (95%CI: 26.4%-62.3%). At the time of surgery, 7 (63.6%) of the 11 patients without axillary lymph node metastasis and 7 (33.3%) patients had axillary lymph node metastasis achieved a pCR (Fig. 1A, Table 2).

Table 2
Summary of therapy efficacy

N(%) [95% CI]	ITT(N = 32)
pCR	14(43.8)
pCR(without ALNs)	7(63.6)
pCR(ALNs)	7(33.3)
Clinical response	
CR	7(21.9)
PR	23(71.9)
SD	2(6.3)
PD	0

Based on breast MRI and RECIST, clinical responses were observed in 30 patients (93.8%), including 7 (21.9%) complete responders and 23 (71.9%) partial responders (Fig. 1B, Table 2).

Following surgery, besides a pCR rate of 43.8%, most of patients exhibited a ypT stage of T1. Efficacy results about tumor shrinkage size are shown in Fig. 2. The median target lesions in breast reduced to 1.2 cm after the third cycle treatment and 0.9cm after the last cycle.

Follow-up is ongoing and the data of disease-free survival (DFS) and overall survival (OS) are not yet published.

Saety

All 32 patients were included in the safety analysis during the treatment period and there were no intolerable AEs after corresponding treatment (Table 3).

Table 3
Treatment-emergent adverse events for patients.

No. (%) of patients	Grade 1	Grade 2	Grade 3	Grade 4
Haematological	-	-	-	-
Leukopenia	3	8	2	5
Neutropenia	6	5	2	6
Anaemia	10	12	2	-
Thrombopenia	6	9	9	4
Non-haematological				
Hypertension	2(6.3)	4(12.5)	3(9.4)	-
hand-foot-skin reaction	7(21.9)	-	-	-
Diarrhoea	8(25.0)	1(3.1)	-	-
Nausea	8(25.0)	4(12.5)	-	-
Vomiting	5(15.6)	-	1(3.1)	-
Mucositis	4(12.5)	1(3.1)	1(3.1)	-
Stomatitis	2(6.3)	1(3.1)	1(3.1)	-
Asthenia	18(56.3)	2(6.3)	-	-
Paraesthesia	12(37.5)	6(18.8)	-	-
cephalalgia	3(9.4)	1(3.1)		
Presyncope	5(15.6)	2(6.3)		
Anorexia	11(34.4)	3(9.4)		
Cough	2(6.3)	-	-	-
Alopecia	-	18(56.3)	-	-
Rash	5(15.6)	1(3.1)	2(6.3)	-
Pyrexia	3(9.4)	-	-	-
Constipation	1(3.1)	-	-	-

Haematological toxicity was the predominant toxic response and happened in 28 (85.7%) patients for all grades. 9 patients experienced hypertension and 7 patients suffered from hand-foot-skin reaction which

are apatinib-related adverse events. The most frequently reported grade 3/4 toxicity were thrombopenia, neutropenia, leukopenia and hypertension.

The chemotherapy dose reduction or delay was calculated (Fig. 3A-C), most commonly because of myelosuppression and abnormal liver function. In total, all the patients received all six cycles of therapy and underwent breast surgery.

Discussion

Although anthracycline and taxane-based neoadjuvant chemotherapy has been the mainstay for TNBC, 30–40% of early stage TNBCs recurred despite receiving the neoadjuvant regimen. Studies such as WSG-ADAPT TN(24) suggest that taxane combines with carboplatinum regimen but neoadjuvant therapy can increase the pCR rate of TNBC. GeparSixto(19) showed that adding platinum to TNBC neoadjuvant therapy can bring longevity benefits, but the results of the CALGB40603(18) study are the opposite. Therefore, due to lack of long-term survival and evidence-based medicine reports, whether platinum can be used for neoadjuvant therapy has always been controversial.

Results of our study showed that apatinib combined with albumin paclitaxel and carboplatin as neoadjuvant regimen is a safe and well-tolerated, demonstrating a 43.8% pCR rate in patients with stage II-III TNBC. This data compares favourably with recent published data for neoadjuvant therapy in early TNBC, including a pCR rate of 41% in patients received albumin paclitaxel in the Impassion031 trial(25) and 40.6% in patients with treatment of nab- paclitaxel and carboplatin in NeoTRIP trial. While the increasing pCR rate were observed combining with immunotherapy in the KEYNOTE522(26) and Impassion031 trial(25), it is conceivable that controversy over the addition of immune check point inhibitors would persist due to negative result of the NeoTRIP trial and the urgent need of biomarkers that predict pCR.

Hypothesis of anti-angiogenic therapies play a specific role in populations of patients with highly proliferative disease. Patients involved in our study were almost locally advanced tumors either with large tumor sizes or a considerable number of lymph node metastases. To the best of our knowledge, no other article has reported data on the combination of neoadjuvant apatinib and chemotherapy exclusively in patients with TNBC. As an oral drug, apatinib in convenient to receive treatment and more economical than other anti-angiogenic therapy. In so doing, we have already explored the curative effect of low dose apatinib (250mg) in patients with advanced HER2-negative breast cancer and proposed patients may benefit more from the therapy, as well as recent research published. Therefore, we attempt to determine whether the addition of apatinib to neoadjuvant chemotherapy produce higher pCR. Previously reported research on the combination of neoadjuvant anti-angiogenic and chemotherapy has shown varied results(20, 27–29). The difference in terms of pCR rate among the studies could be almost attributed to the patient populations, baseline stage of breast cancer and the combined chemotherapy regimen. The GeparQuinto trial(19) presented a significant improvement in pCR rate combining with bevacizumab in TNBC (39% vs 28%, p = 0.003). Meanwhile, the NSABP B-40 trial(20) demonstrated a numerical increase

of pCR rate in patients with TNBC without statistical significance (52% vs 47%, p = 0.34). Similarly, the KCSG BR-0905(29) shared a comparable pCR rate of 42% in TNBC with those studies. Significantly,these data could be attributable to the relatively early-stage patients included in their research and the pCR rate of patients without axillary lymph node metastasis in our research was as high as 63.6%, so caution should be exercised when making comparisons to others.

Another growing attention is apatinib-related postoperative wound complications. Antiangiogenic therapy may increase the risk of postoperative complications, including wound dehiscence and slow recovery, especially patients received breast reconstruction with tissue expanders. A minimum of 21 days between surgery and the last therapy had been recommended to avoid postoperative wound complications in our study and recorded few wound complications with neoadjuvant apatinib indeed. Furthermore, other adverse events reported in our study were all manageable. The most frequently reported grade 3/4 toxicity were thrombopenia, neutropenia, leukopenia and hypertension and a clear upturn was observed following treatment or dose reduction.

The main limitations of our study are the lack of a control arm and the relatively small sample size. A future neoadjuvant study incorporating more information for prospective detection of patients to explore the biomarkers that can simultaneously predict the reaction efficacy and potential toxicity has crucial clinical value.

Apatinib combined with nab-paclitaxel and carboplatin showed an encouraging anti-tumor activity in patients with TNBC resulting in high pCR rate and tolerable side effects toxicity. Our study adds to the evidence supporting the addition of apatinib to neoadjuvant therapy for TNBC, especially locally advanced cancer and provides further rationale for efficient neoadjuvant therapy for patients with relatively severe breast cancer.

Conclusion

Analyses of this phase II study proved that neoadjuvant treatment containing apatinib, nab paclitaxel and carboplatin is efficient in patients of high tumor burden with TNBC, which is a safe and well-tolerated. We demonstrated the pCR rate in patients with stage II-III TNBC is 43.8%and patients without axillary lymph node metastasis among them is as high as 63.6%. We propose that patients with high tumor load may benefit from the neoadjuvant treatment of apatinib combined with nab-paclitaxel and carboplatin.

Abbreviations

TNBC
Triple-negative breast cancer
pCR
Pathological complete response
HER2

Human epidermal growth factor receptor 2
ALN
Axillary lymph nodes
DFS
Disease-free intervals
PFS
Progression free survival
OS
Overall survival
NAC
Neoadjuvant chemotherapy
RECIST
Response Evaluation Criteria in Solid Tumors
UNL
Upper normal limit
ITT
Intent-to treat

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2018-SR-115). All human samples and biopsies were collected after obtaining a written informed consent.

Consent for publication

Not Applicable.

Availability of data and materials

The data analysed during the research are included in this study or are available on reasonable request.

Competing interests

The authors declare that there is no competing interests.

Funding

This study was financially supported by the National Key Research and Development Program of China (ZDZX2017ZL-01), High-level innovation team of Nanjing Medical University (JX102GSP201727), Wu Jieping Foundation (320.6750.17006), Key medical talents (ZDRCA2016023), 333 Project of Jiangsu

Province (BRA2017534 and BRA2015470), The collaborative innovation center for tumor individualization focuses on open topics (JX21817902/008) and Project of China key research and development program precision medicine research (2016YFC0905901)

Authors' contributions

XZ and YY designed this study. TZ, JW and WL carried out the main research procedures, wrote the manuscript and made the figure. FY, MY, CS, XH, YL and ZF collected the data, performed the statistical analysis and revised the manuscript.

Acknowledgements

Not applicable.

References

1. Yu KD, Ye FG, He M, Fan L, Ma D, Mo M, et al. Effect of Adjuvant Paclitaxel and Carboplatin on Survival in Women With Triple-Negative Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020;6(9):1390–6.
2. Venkitaraman R. Triple-negative/basal-like breast cancer: clinical, pathologic and molecular features. Expert Rev Anticancer Ther. 2010;10(2):199–207.
3. Hoadley KA, Siegel MB, Kanchi KL, Miller CA, Ding L, Zhao W, et al. Tumor Evolution in Two Patients with Basal-like Breast Cancer: A Retrospective Genomics Study of Multiple Metastases. PLoS Med. 2016;13(12):e1002174.
4. Winer EP, Lipatov O, Im SA, Goncalves A, Munoz-Couselo E, Lee KS, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(4):499–511.
5. Wang X, Wang SS, Huang H, Cai L, Zhao L, Peng RJ, et al. Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-Free Survival Among Patients With Early-Stage Triple-Negative Breast Cancer Who Had Received Standard Treatment: The SYSUCC-001 Randomized Clinical Trial. JAMA. 2021;325(1):50–8.
6. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021;384(16):1529–41.
7. Zetterlund L, Celebioglu F, Hatschek T, Frisell J, de Boniface J. Long-term prognosis in breast cancer is associated with residual disease after neoadjuvant systemic therapy but not with initial nodal status. Br J Surg. 2021;108(5):583–9.
8. Huang M, O'Shaughnessy J, Zhao J, Haiderali A, Cortes J, Ramsey SD, et al. Association of Pathologic Complete Response with Long-Term Survival Outcomes in Triple-Negative Breast Cancer: A Meta-Analysis. Cancer Res. 2020;80(24):5427–34.

9. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30(8):1279–88.
10. Nabholtz JM, Abrial C, Mouret-Reynier MA, Dauplat MM, Weber B, Gligorov J, et al. Multicentric neoadjuvant phase II study of panitumumab combined with an anthracycline/taxane-based chemotherapy in operable triple-negative breast cancer: identification of biologically defined signatures predicting treatment impact. Ann Oncol. 2014;25(8):1570–7.
11. Adams S, Dieras V, Barrios CH, Winer EP, Schneeweiss A, Iwata H, et al. Patient-reported outcomes from the phase III IMpassion130 trial of atezolizumab plus nab-paclitaxel in metastatic triple-negative breast cancer. Ann Oncol. 2020;31(5):582–9.
12. Gennari A, Sun Z, Hasler-Strub U, Colleoni M, Kennedy MJ, Von Moos R, et al. A randomized phase II study evaluating different maintenance schedules of nab-paclitaxel in the first-line treatment of metastatic breast cancer: final results of the IBCSG 42 – 12/BIG 2–12 SNAP trial. Ann Oncol. 2018;29(3):661–8.
13. Schettini F, Giuliano M, De Placido S, Arpino G. Nab-paclitaxel for the treatment of triple-negative breast cancer: Rationale, clinical data and future perspectives. Cancer Treat Rev. 2016;50:129–41.
14. Futamura M, Oba M, Masuda N, Bando H, Okada M, Yamamoto Y, et al. Meta-analysis of nanoparticle albumin-bound paclitaxel used as neoadjuvant chemotherapy for operable breast cancer based on individual patient data (JBCRG-S01 study). Breast Cancer. 2021;28(5):1023–37.
15. Domagala P, Hybiak J, Cybulski C, Lubinski J. BRCA1/2-negative hereditary triple-negative breast cancers exhibit BRCAness. Int J Cancer. 2017;140(7):1545–50.
16. Lips EH, Mulder L, Oonk A, van der Kolk LE, Hogervorst FB, Imholz AL, et al. Triple-negative breast cancer: BRCAness and concordance of clinical features with BRCA1-mutation carriers. Br J Cancer. 2013;108(10):2172–7.
17. Chang HR, Glaspy J, Allison MA, Kass FC, Elashoff R, Chung DU, et al. Differential response of triple-negative breast cancer to a docetaxel and carboplatin-based neoadjuvant treatment. Cancer. 2010;116(18):4227–37.
18. Golshan M, Cirrincione CT, Sikov WM, Berry DA, Jasinski S, Weisberg TF, et al. Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: surgical results from CALGB 40603 (Alliance). Ann Surg. 2015;262(3):434–9. discussion 8–9.
19. von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, Rezai M, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014;15(7):747–56.
20. Bear HD, Tang G, Rastogi P, Geyer CE Jr, Liu Q, Robidoux A, et al. Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): secondary outcomes of a phase 3, randomised controlled trial. Lancet Oncol. 2015;16(9):1037–48.

21. Liu J, Liu Q, Li Y, Li Q, Su F, Yao H, et al. Efficacy and safety of camrelizumab combined with apatinib in advanced triple-negative breast cancer: an open-label phase II trial. J Immunother Cancer. 2020;8(1).
22. Zhu A, Yuan P, Hu N, Li M, Wang W, Wang X, et al. Phase II study of apatinib in combination with oral vinorelbine in heavily pretreated HER2-negative metastatic breast cancer and clinical implications of monitoring ctDNA. Cancer Biol Med. 2021.
23. Morse B, Jeong D, Ihnat G, Silva AC. Pearls and pitfalls of response evaluation criteria in solid tumors (RECIST) v1.1 non-target lesion assessment. Abdom Radiol (NY). 2019;44(2):766–74.
24. Gluz O, Nitz U, Liedtke C, Christgen M, Grischke EM, Forstbauer H, et al. Comparison of Neoadjuvant Nab-Paclitaxel + Carboplatin vs Nab-Paclitaxel + Gemcitabine in Triple-Negative Breast Cancer: Randomized WSG-ADAPT-TN Trial Results. J Natl Cancer Inst. 2018;110(6):628–37.
25. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020;396(10257):1090–100.
26. Schmid P, Cortes J, Pusztai L, McArthur H, Kummel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020;382(9):810–21.
27. Bertucci F, Fekih M, Autret A, Petit T, Dalenc F, Levy C, et al. Bevacizumab plus neoadjuvant chemotherapy in patients with HER2-negative inflammatory breast cancer (BEVERLY-1): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2016;17(5):600–11.
28. Earl HM, Hiller L, Dunn JA, Blenkinsop C, Grybowicz L, Vallier AL, et al. Disease-free and overall survival at 3.5 years for neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin and cyclophosphamide, for women with HER2 negative early breast cancer: ARTemis Trial. Ann Oncol. 2017;28(8):1817–24.
29. Kim HR, Jung KH, Im SA, Im YH, Kang SY, Park KH, et al. Multicentre phase II trial of bevacizumab combined with docetaxel-carboplatin for the neoadjuvant treatment of triple-negative breast cancer (KCSG BR-0905). Ann Oncol. 2013;24(6):1485–90.

Figures

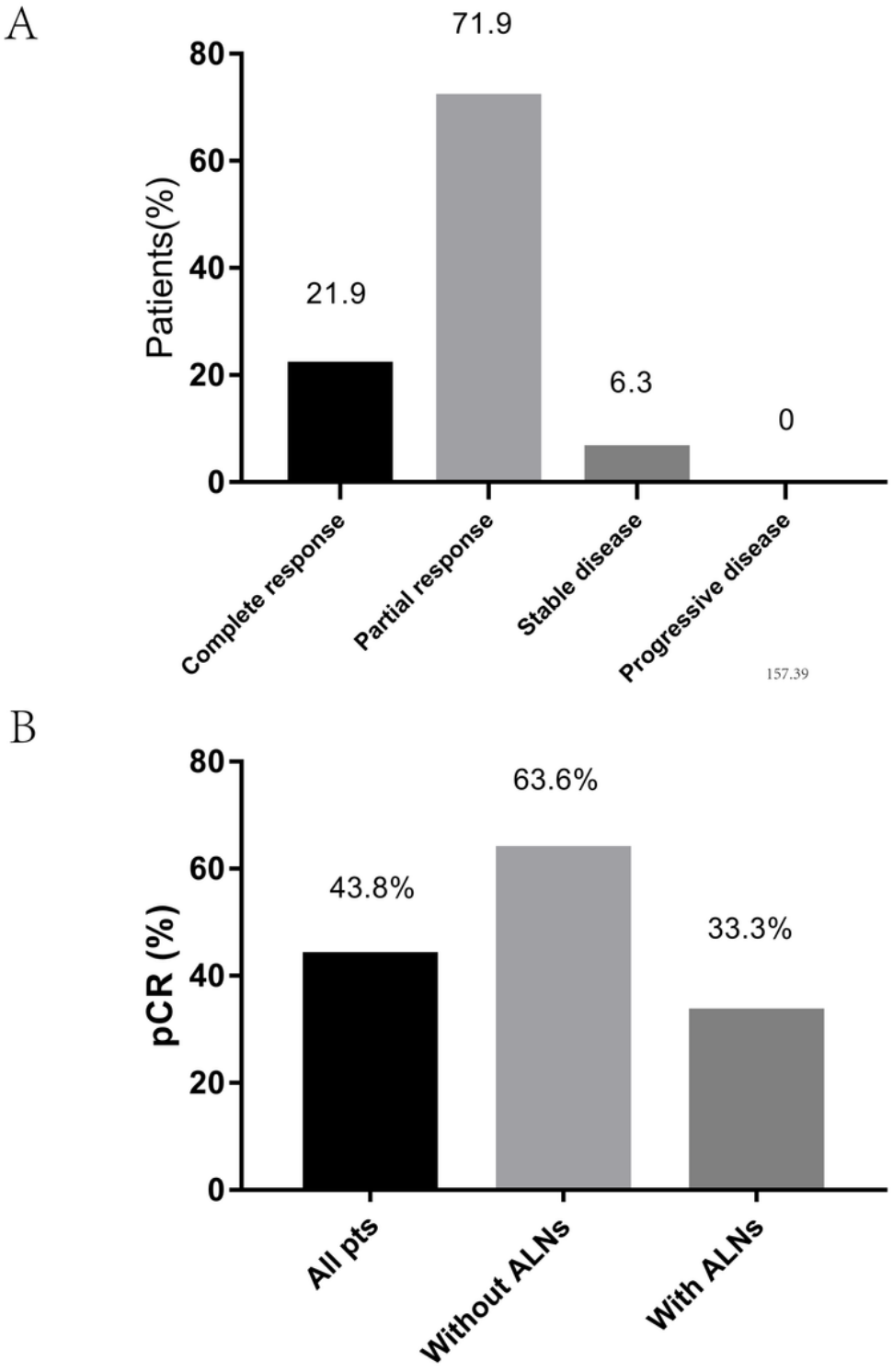

Figure 1

Efficacy of patients receive neoadjuvant treatment. (A). The rate of pCR in both breast and axillary lymph nodes. (B). Clinical responses in patients based on breast MRI and RECIST.

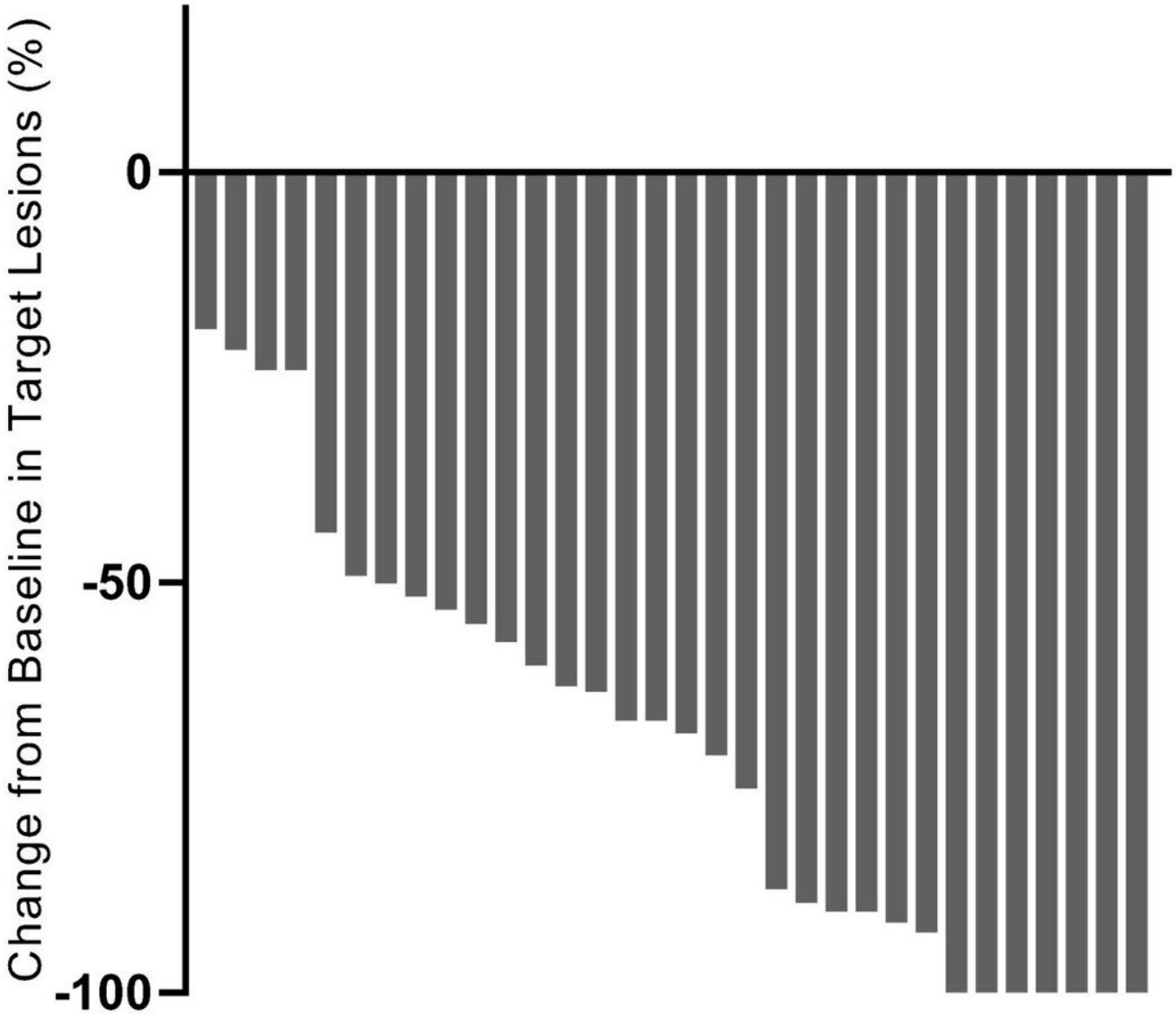

Figure 2

Shrinkage size of tumor after neoadjuvant apatinib.

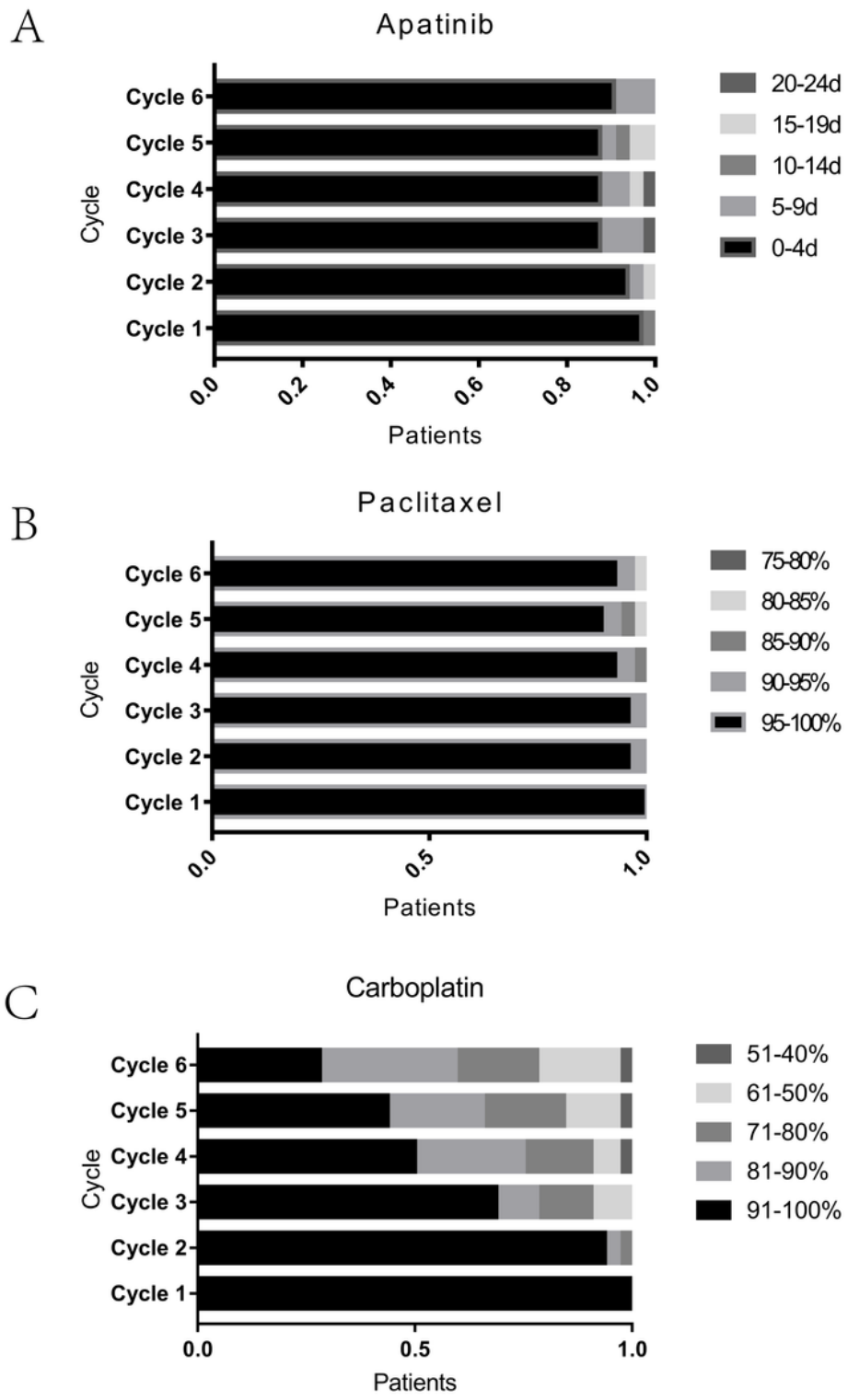

Figure 3

Dosage adjustment according to adverse events during the 6 cycles of therapy. (A)The number and the proportion of apatinib was delayed in patients. (B, C) The number and the proportion of dose reduction in nab- paclitaxel or carboplatin.