

# Triple Negative Breast Cancer Treatment: Use of Platinum and Platinum Analogs

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## ABSTRACT

Triple negative breast cancer (TNBC) is characterized by a high sensitivity to antiproliferative drugs and a high pathological complete remission rate after neoadjuvant therapy. In patients showing complete remission, the probability of developing metastatic disease would seem to be reduced. Nonetheless, this cancer has a high percentage of relapse. Anthracyclines, taxanes and platinum compounds are the most effective drugs for the treatment of TNBC. There is substantial evidence to support the efficacy of platinum-based chemotherapy, probably attributable to the mechanism of action of such drugs, which react with the DNA repair system. PARP inhibitors would also seem to be very interesting. Despite promising results, TNBC remains a disease with a poor prognosis due to the lack of targeted therapy. The discovery of new targets and new agents is thus a high priority issue for this type of breast cancer. In this respect, lipoplatin has been identified as a potentially interesting treatment option to evaluate in both neoadjuvant and advanced settings.

**Keywords:** Breast Cancer; Triple Negative; Treatment; Platinum; Platinum Analogs

## 1. Introduction

Breast cancer is the most common malignancy and leading cause of cancer death in women, both worldwide and in many developed countries, including Italy.

It is a heterogeneous disease whose prognosis is related mainly to stage and biological characterization, which defines a variety of conditions ranging from a low risk of relapse and indolent clinical course to a high relapse risk and rapid clinical progression, despite aggressive therapies [1]. Routine pathological reports, in addition to defining tumor stage and grade, include an assessment of proliferation index (Ki-67/MIB-1 immunostaining), expression of estrogen (ER) and progesterone receptors (PR), and HER-2/neu status (evaluated through protein immunostaining or the study of gene amplification). Whilst these biological features have some prognostic value, they are principally considered as predictors of response to different treatments, especially targeted therapies. Breast cancer can be classified into three large subgroups: hormone receptor-positive, HER-2-positive (which is also hormone-receptor positive in less than half of cases), and the so-called “triple negative” (TN) tumors, where ER and PR are negative and there is no amplification or overexpression of HER-2 [2].

Studies of gene expression profiling have confirmed the existence of breast cancer subtypes, leading to a more accurate definition: luminal tumors are typically ER-positive but with different expression of ER-related genes and proliferative genes; HER-2 positive tumors are characterized by the overexpression and/or amplification of HER-2 and other genes; the normal breast-like subtype and basal-like subtype are usually TN at immunostaining studies [3]. This classification has biological and clinical relevance, defining how tumor growth is driven by different pathways, as best exemplified by the luminal and HER2/neu subtypes, and with different prognoses. TN tumors merit special attention because they have a poor prognosis and also because no targeted therapy has been approved as yet for clinical use [4]. TN tumors defined by immunostaining differ somewhat from the basal-like subtype defined by gene profiling, but the latter subtype is the most frequent and most important form of triple negative breast cancer (TNBC) [5]. The most important features of TN/basal-like tumors include a strong expression of basal cytokeratins CK5/6 and CK17 (high molecular weight cytokeratins, found in the basal layer of stratified epithelia), expression of proliferation related genes, high tumor grade, frequent p53 mutations and p63 gene amplification, low expression of BRCA1, frequent expression of EGFR, KIT, vimentin, p-

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cadherin, fascin, caveolins 1 and 2, alpha-B-crystallin, and genes involved in matrix remodeling and angiogenesis.

Using univariate analysis, we can define the differences between the two main histological subgroups. In Bertucci and co-workers 2008 study on TNBC, the median age of patients with basal tumors (50 years) was lower than that of patients with other TN types (57 years). Basal tumors exhibited a higher pathological grade: 88% were grade III versus only 51% in non basal tumors. The pathological tumor size (pT) was higher in basal tumors: 60% pT2 - pT3 versus 46% in the other group. No correlation was found with pathological axillary lymph node status (pN). There were more medullary breast cancers within the basal tumors, and more lobular breast cancers within the non basal tumors. Five-year metastasis-free survival was 65% in the basal group and 75% in the other group, while 5-year overall survival (OS) was 68% and 78%, respectively. Pathological complete response (pCR) after primary chemotherapy was observed in 59% of basal tumors versus 27% in the other group [6].

TNBC represents a heterogeneous group of tumors that include 70% of basal tumors and 30% of the non basal kind. TN basal tumors are characterized by ER, PR and HER-2 negativity, and EGFR and cytokeratin 5/6 and 17 positivity. In contrast, TN non basal tumors are characterized by ER, PR and HER-2 negativity and EGFR and cytokeratin 5/6 and 17 negativity. Nevertheless, it is impossible to distinguish between basal and non basal subtypes in the results obtained from the clinical treatment of TN tumors in neoadjuvant, adjuvant and metastatic settings because they are not considered separately in either clinical practice or in the majority of published papers.

## 2. Treatment of TNBC

TNBC is characterized by a high sensitivity to antiproliferative drugs. Although an elevated percentage of pCR is observed in the neoadjuvant setting and a high remission rate in metastatic disease, this breast cancer subtype shows a high percentage of relapse. Numerous drugs have been evaluated for the treatment of this tumor, the most efficacious being anthracyclines, taxanes (paclitaxel and docetaxel) and platinum compounds. Among the new drugs, PARP-inhibitors would seem to be of particular interest. However, because of the biological heterogeneity within TNBC, many patients show an excellent outcome while others obtain much poorer results, despite the administration of systemic treatments considered effective.

### 2.1. The Experience in Neoadjuvant Settings

In the neoadjuvant treatment of TNBC, the paradox of high sensitivity to anthracyclines and a high percentage of relapse in this poor prognostic subgroup is attributable

to the elevated recurrence rate in patients who have residual disease at the time of surgery. Those who achieve pCR in basal-like, HER-2 positive and ER negative tumors would seem to show a higher rate of survival, in contrast to patients who do not achieve pCR and appear more likely to experience early relapse and early death. One of the most important studies published to date is by Carey and coworkers who examined the response rate to neoadjuvant anthracycline-based chemotherapy in 34 TN patients, reporting 85% clinical response (complete or partial), more than the value reached in luminal subtypes [7]. pCR to chemotherapy was significantly better among basal-like subtypes (27%) than among other subtypes (7%). Furthermore, the percentage of patients with minimal residual disease after chemotherapy was higher in basal-like (58%) than in luminal A subtypes (21%). Despite sensitivity of basal like-TNBC in Carey's study, his group still showed very poor prognosis, for the high relapse rates observed among those who do not achieve pCR.

In another study by Liedtke and coworkers, response to neoadjuvant chemotherapy and survival was compared in TNBC and non-TNBC patients [8]. 1118 patients at M.D. Anderson Cancer Center received neoadjuvant chemotherapy for stage I-III breast cancer from 1985 to 2004. Although patients with TNBC (23%) had higher pCR rates than those with non-TNBC (22% versus 11%), they showed poorer 3-year progression-free (PFS) and overall survival ( $p < 0.0001$  and  $p < 0.0001$ , respectively). Recurrence and death rates were higher for the TNBC group, but only in the first three years. When pCR was achieved, patients with TNBC or non-TNBC showed similar survival while those with residual disease had a poorer outcome, especially if they had the TNBC subtype, confirming previous observations in larger groups of patients.

### 2.2. The Experience in Adjuvant Settings

Numerous studies have reported on the adjuvant treatment of TNBC basal-like and non basal-like TNBC, the majority concerning retrospective experiences analyzing breast cancer treatments in different subsets. Although locoregional and distant relapse in TNBC occur mainly during the first three years of follow up after the end of therapy, we found few reports on long-term follow up that made a distinction between TN and other kinds of breast cancers. In Voduc and coworkers's report of 4033 patients followed up for almost ten years after breast-conserving surgery and given post-operative radiotherapy and hormone or antiproliferative treatment, regional relapse-free survival (RRFS) was 86% for basal-like breast cancer and 92% for non basal-like TNBC, while the percentage of RRFS of luminal A breast cancer was 97% [1]. The observation that TNBCs are especially sensitive to

antiblastic drugs has been made by numerous authors. The Cancer and Leukemia Group B reported a benefit from the addition of a taxane to the adjuvant treatment of ER, PR and HER-2 negative tumors, whereas no benefit was observed in patients with ER positive tumors [9]. Furthermore, the Breast Cancer Intergroup, in their review of 6644 node-positive breast cancer patients, reported more important results in those with ER- negative tumor given chemotherapy [9]. Patients with a high proliferative index and ER/PR negativity showed very impressive results at ten years with CMF chemotherapy. More recently, Colleoni and his collaborators published a paper on the use of classic CMF in TN node-negative breast cancer patients [10]. They found that CMF chemotherapy produced a stronger effect in patients with TNBC than in those who did not receive the schedule or whose tumors showed ER positivity.

New approaches to adjuvant therapy are guided by results from preclinical models, molecular profiling, and findings from trials on metastatic disease. Numerous adjuvant clinical trials are currently ongoing to evaluate the role of ixabepilone, platinum agents and VEGF in this clinical setting [11]. The PACS 08 adjuvant trial [12], built on data from PACS 01 [13,14], is a phase III study of TNBC patients randomized to receive three cycles of FEC followed by three cycles of docetaxel or ixabepilone every three weeks. The phase III adjuvant TITAN trial is evaluating four cycles of standard doxorubicin plus cyclophosphamide followed by four cycles of ixabepilone or twelve cycles of weekly paclitaxel [15]. The phase III BEATRICE study is assessing numerous chemotherapy agents with or without bevacizumab at a dosage of 5 mg/Kg weekly for patients with TNBC [16]. Findings are expected in the next year.

In conclusion, TN tumors are currently most effectively treated with conventional adjuvant or neoadjuvant therapies (anthracyclines and taxanes). Although significant results have been achieved, TN patients show lower disease-free survival than those with non TN tumors.

### 2.3. The Experience in a Metastatic Setting

Results on the treatment of TNBC in a metastatic setting do not differ from those described in neoadjuvant and adjuvant situations. These tumors only respond to chemotherapy, and although a substantial percentage of complete response (CR) can be achieved, relapse and non clinical response remain high. Whilst anthracyclines and taxanes have proven the most effective drugs in this setting, cisplatin also shows very promising results [17]. Among the new products, PARP-inhibitors are considered to be potentially important drugs. Indeed some reports suggest that TNBC expresses high levels of poly-merase 1 (PARP-1), a DNA repair enzyme which is the molecular target of PARP inhibitors. In a randomized

phase II study in patients with metastatic TN disease, the PARP inhibitor BSI-201 significantly improved objective response rates (48% vs 16%,  $p = 0.002$ ), PFS (6.9 vs 3.3 months,  $p < 0.0001$ ) and median OS (9.2 vs 5.7 months,  $p = 0.0005$ ) when added to carboplatin and gemcitabine [11]. However, despite such encouraging findings, prognosis in TNBC patients with advanced disease (apart from those with accurately verified CR), remains very poor.

### 2.4. Platinum and Lipoplatinum Experience

Although cisplatin is one of the oldest and more effective anticancer drugs, its use may be limited by adverse events, mainly nephrotoxicity and neurotoxicity.

A number of studies evaluating platinum agents in patients with metastatic TNBC have been carried out. A retrospective study by Uhm and coworkers comparing outcome in patients with TNBC with that of patients with other BC subtypes, all treated with a taxane-platinum regimen, did not highlight a difference in response rates between these two groups [18]. A similar experience from the UK showed that patients with advanced TNBC treated with platinum-based chemotherapy had ORRs similar to those with non-TN tumors [17].

Favorable results have also been obtained with cisplatin in a metastatic setting. A single institution phase II study on weekly cisplatin and metronomic cyclophosphamide reported that such a regimen appeared to be safe and effective, with an ORR of 63% and median time to progression of 13 months in contrast to 33% and 7 months, respectively, in patients not treated with cisplatin [19,20]. The association of carboplatin with paclitaxel [21] or irinotecan [22] in pretreated metastatic patients with TN tumours has also shown good response rates (57% and 30%, respectively). A study conducted at the Royal Marsden Institute also supported the hypothesis that patients with TN tumors have a significantly longer PFS compared with that of other histological subtypes, with a trend towards an improved OS when treated with platinum.

Very few studies have been conducted on lipoplatinum in advanced TNBC. Only recently Farhat and coworkers reported the results of their phase II trial of lipoplatin and vinorelbine combination in patients with HER-2 negative metastatic breast cancer who had not received prior treatment in an advanced setting [23]. A 53.1% ORR was reported (CR in 3 patients, 9.4%) and 37.5% patients showed stable disease. The majority of adverse events were mild or moderate. For this reason lipoplatin would seem to be an attractive treatment option for these patients.

Lipoplatin is a novel liposomal formulation of cisplatin, designed to increase safety and tolerability by decreasing toxicity and nephrotoxicity. It decreases the

exposure of organs to cisplatin, whilst effectively delivering the drug to the tumor. The formulation comprises cisplatin and liposomes based on 1,2 dipalmitoyl-sn-glycero-3-phospho-rac-1-glycerol (sodium salt) (DPPG, mw 745), soy phosphatidyl choline (SPC-3, mw 790), cholesterol (CHOL, mw 386.66) and methoxy-polyethylene glycol-distearoyl phosphatidyl-etha-nolamine lipid conjugate (mMPEG2000-DSPE, mw 2807). At steady state, particles have a weight ratio of 8.9% cisplatin to 91.1% lipids (0.9:9.1). The total lipid to cisplatin ratio in lipoplatin is 10 mg lipid/mg cisplatin. The cholesterol content of lipoplatin is 11.6% of the total lipids. It is calculated that 1.3 mg of cholesterol is injected per mg of cisplatin [24]. There are numerous indications that point towards the potential usefulness of lipoplatin as treatment of TNBC. Consequently, our group is currently planning a new trial on patients with TNBC who have become resistant to anthracyclines and taxanes, offering lipoplatin as second-line treatment following progression after first-line therapy.

### 3. Conclusion

TNBC is a very serious illness and conventional treatments only obtain partial control of the disease, and normally for a short period of time. The search for new treatments is urgently needed and lipoplatin could be potentially useful in advanced disease and could also represent a new possible treatment in the future in neoadjuvant and adjuvant settings.

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