



Benefit of Platinum-based Chemotherapy in Metastatic Triple Negative Breast Cancer

Ency Eveline, * Andhika Rachman **

* Medical staff, MRCCC Siloam Hospitals,

** Hematology and Medical Oncology Division, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

ABSTRACT

Background: Management of triple-negative breast cancer (TNBC) is challenging because of a lack of targeted therapy, its aggressive behavior and its relatively poor prognosis. Various studies showed that these tumors are highly chemosensitive and in some cases are represented by complete pathological response (pCR), but the results remains unsatisfactory.¹ Recent experimental data strongly suggest that platinum-based chemotherapy (PBC) could improve the outcome of TNBC, but clinical data are still lacking.⁴ **Objective:** To evaluate the benefit of addition of platinum agents to metastatic TNBC therapy. **Method:** Several databases were searched. Comparative studies were identified using the following keywords: triple negative breast cancer, advanced, metastatic, metastases, platinum agents, cisplatin, and carboplatin. The search was not limited to controlled or randomized trials. The limitations used in searching the articles are human, english, and 5-year maximum of publication. Articles were reviewed by two authors and selected if they described advanced triple negative breast cancer, use of platinum agents, and outcome. **Results:** Seven studies were included. Median survival of metastatic TNBC patients treated with PBC was 10.4 to 32.8 months. There was a significant survival benefit compared to non-PBC treated patients with overall survival 7.5 to 21.5 months. However PBC did not show significant different benefit between TNBC and non-TNBC patients. **Conclusion:** PBC demonstrated not only higher response rate but also remarkable improvement in PFS and OS. It is still premature to draw a conclusion on survival advantage merely from phase II trials, but for this subtype, platinum agents had extra clinical benefit compared to other agents.

Keywords: Breast cancer, chemotherapy, platinum, triple-negative breast cancer

ABSTRAK

Latar Belakang: Topik manajemen *triple-negative breast cancer* (TNBC) masih merupakan sebuah tantangan karena ketidaktersediaan target terapi hormonal, sifatnya yang agresif dan prognosis yang lebih buruk. Beberapa studi menyimpulkan bahwa tumor ini sangat kemosensitif, sehingga pada beberapa kasus menghasilkan *complete pathological response* (pCR), tetapi makna klinisnya kurang berarti.¹ Meskipun data eksperimental secara kuat mendukung *platinum-based chemotherapy* (PBC) sebagai kemoterapi yang dapat memperbaiki *outcome* TNBC, namun belum ada data studi klinis.² **Tujuan:** Tujuan penulisan ini adalah untuk mengevaluasi manfaat penambahan agen platinum sebagai terapi pasien TNBC stadium lanjut. **Metode:** Beberapa *database* ditelusuri. Kata kunci yang digunakan antara lain *triple negative breast cancer*, *advanced*, *metastatic*, *metastases*, *platinum agents*, *cisplatin*, dan *carboplatin*. Pencarian tidak dibatasi hanya *controlled* atau *randomized trials* untuk meminimalkan hilangnya studi yang bermakna. Pencarian artikel dibatasi pada subjek manusia, bahasa Inggris, dan publikasi maksimal dalam 5 tahun terakhir. Artikel dianalisis oleh dua penulis dan diseleksi sesuai dengan TNBC stadium lanjut, penggunaan agen platinum, dan hasil terapi. **Hasil:** Median *survival* empat studi yang ditemukan berada dalam rentang 10,4 hingga 32,8 bulan. Terdapat manfaat cukup signifikan dari penambahan agen kemoterapi platinum sebagai terapi pasien TNBC stadium lanjut, dibandingkan regimen tanpa platinum yang berada dalam rentang 7,5 hingga 21,5 bulan. Akan tetapi, tidak ada perbedaan klinis mengenai penggunaan PBC antara pasien TNBC dan non-TNBC. **Simpulan:** PBC bukan hanya menghasilkan tingkat respons yang lebih tinggi, tetapi juga perbaikan PFS dan OS. Meskipun belum adekuat untuk menyimpulkan adanya perbaikan *survival* pasien TNBC, platinum lebih memberikan perbaikan klinis daripada agen kemoterapi lain. **Ency Eveline, Andhika Rachman. Manfaat Kemoterapi Berbasis-Platinum pada Kanker Payudara Triple Negative Metastatik.**

Kata kunci: Kanker payudara, kemoterapi, platinum, *triple-negative breast cancer*

BACKGROUND

Triple negative breast cancer (TNBC) is clinically defined as a type of tumor that

does not express estrogen receptor (ER), progesterone receptor (PR), and HER-2 (human epidermal growth factor receptor 2).³ TNBC

comprises of 12-20 percent of the overall breast cancer patients, African-American race being one of the risk factor. Most of these

Alamat korespondensi email: encyeveline3@gmail.com

ANALISIS



tumors are diagnosed at late stage (stage 4) with poor differentiation and histopathology classified as high grade. Treatment options of TNBC are also limited as there is no targeted therapy available, resulting in a poorer prognosis compared to other breast cancer subtype, with higher relapse rate.²

There is increasing evidence that some subtypes of TNBC share certain DNA repair defects characteristic to BRCA1 deficient breast cancer, which may confer sensitivity to platinum-derived compounds.³ The DNA of normal cells may be damaged and activate regulation by the DNA repair-associated protein, BRCA1. If BRCA1 mutations occur, the DNA repair function is not regulated. About 70% of breast cancer cases exhibit correlation between the BRCA1 gene immune group and TNBC.²

Platinum is a common second-line antitumor drug in breast cancer chemotherapy. It has been suggested that platinum may be an effective drug treatment for breast cancer with genetic mutations in the BRCA1 gene. Platinum drugs for TNBC may also have improved curative effects.² Platinum-based chemotherapy (PBC) includes cisplatin or carboplatin given as single-agent or in combination with other chemotherapy regimen.³

Table. Journal article search strategy

| Database | Search strategy | #found | #selected |
|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|
| Medline | Triple negative breast cancer AND metastatic OR metastases OR advanced AND cisplatin OR carboplatin OR platinum Filter: free full text available, publication date within 5 years, species humans | 28 | 5 |
| PMC | Triple negative breast cancer AND metastatic OR metastases OR advanced AND cisplatin OR carboplatin OR platinum | 444 | 4 |
| Cochrane | Triple negative breast cancer AND metastatic OR metastases OR advanced AND cisplatin OR carboplatin OR platinum | 46 | 0 |
| Oxford Journals Annals of Oncology | Triple negative breast cancer AND metastatic OR metastases OR advanced AND cisplatin OR carboplatin OR platinum | 94 | 5 |
| JCO | Triple negative breast cancer AND metastatic OR metastases OR advanced AND cisplatin OR carboplatin OR platinum | 15 | 2 |
| NEJM | Triple negative breast cancer AND metastatic OR metastases OR advanced AND cisplatin OR carboplatin OR platinum | 26 | 1 |

RESEARCH QUESTION

Does PBC improve the outcome of metastatic TNBC patients?

METHOD

Journal articles were searched using keywords that included population, indicator, comparator, and outcome. The keywords were: metastatic triple negative breast cancer' OR 'triple negative advanced breast cancer', indicator 'platinum-based chemotherapy', comparator 'non-platinum based chemotherapy' OR 'standard therapy', and outcome 'overall survival' OR 'pathological complete response' OR

'clinical benefit rate'. The search was limited to human subject, publications in English language within 5 years. Database search engines searched journal articles that included Medline, Pubmed Central (PMC), Cochrane, Oxford Journals Annals of Oncology, Journal of Clinical Oncology (JCO), and New England Journal Medicine (NEJM).

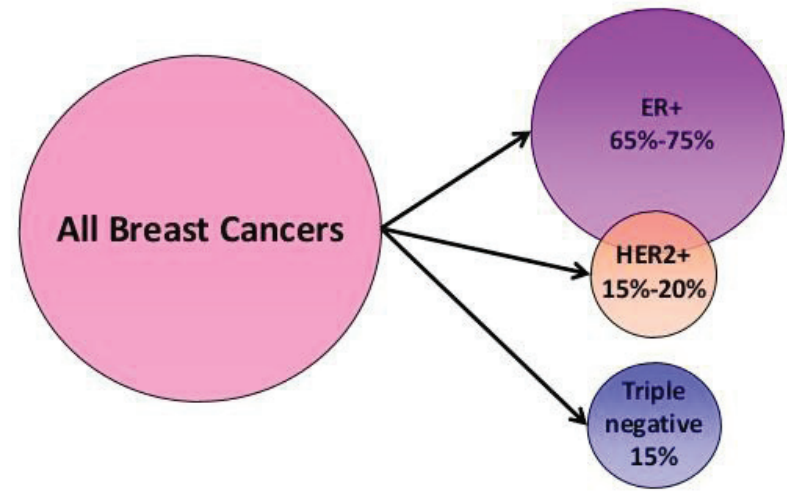
There were 28 related articles found in Medline, 444 articles in PMC, 46 articles in Cochrane, 94 articles in Oxford Journals Annals of Oncology, 15 articles in Journal of Clinical Oncology, and 26 articles in NEJM. Then the articles were selected with the inclusion criteria: metastatic triple negative breast cancer treated with platinum-based chemotherapy compared to non-platinum-based chemotherapy, and displayed their outcomes in the abstract. The selection yielded 17 articles to be analyzed.

From the 17 full-text journal articles, 7 articles were relevant to the topic. Critical appraisal was done to all 7 articles to judge the validity and applicability to answer the research question, which is the improvement of overall survival (OS) in advanced triple negative breast cancer population who received platinum-based chemotherapy.

RESULTS

From a total of seven obtained articles, four used retrospective cohort model, the remaining three used prospective cohort model. All seven studies were composed of prognostic studies which compared the addition of platinum agents and its benefit

Clinical Breast Cancer Subsets Defined by IHC



Picture. Clinical breast cancer subsets. (Sumber: Burstein, Goldhirsch. St Gallen. 2007.)

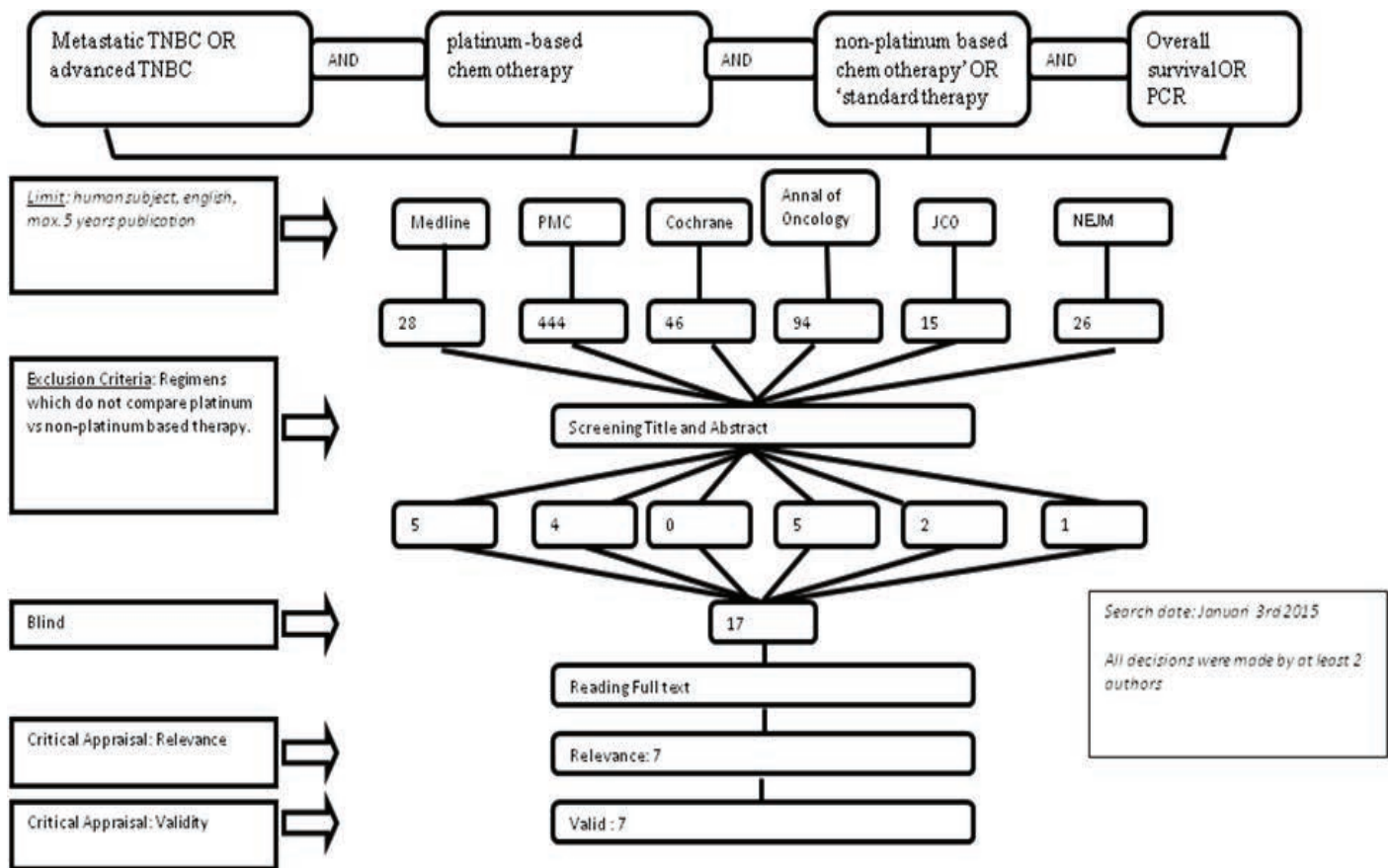


Diagram. Journal article search flow chart

to the survival of patients with metastatic TNBC. Platinum-based chemotherapy (PBC) includes chemotherapy regimens that use cisplatin or carboplatin as single agents or in combination with other chemotherapeutic drugs.³

A study by V.C. Garza, *et al*, showed OS improvement in patients that received PBC in comparison to standard therapy group (14.5 vs 10 months, $p=0.041$). The study produced interesting results that there was no significant difference of median treatment times between the two groups (2 vs 2 months, $p=0.9$) in first line group, but in the second and third line groups, results showed that the median treatment time was longer in the PBC group (4 vs 1 month, $p=0.004$; 4 vs 0.5 months, $p=0.004$ respectively).²

L. Staudacher, *et al*, compared PBC results in OS and PFS (Progression-Free Survival) of 11 and 5 months respectively in TNBC and non-TNBC patients. There was no significant

difference in OS, PFS, and response duration. The average response duration of TNBC patients was 8 months in comparison to 7 months in the non-TNBC group. OS of TNBC patients were lower than that of non-TNBC patients. In spite this, patients with TNBC showed higher/better OS results, 27 vs 8 months ($P<0.001$) with PFS of 10 vs 4 months ($P<0.001$).³

Fan Y, *et al*, divided patients into groups treated with Taxane – platinum (TP) or Taxane – capecitabine (TX) for 6 cycles every 3 weeks. The results of ORR 63% (3 CR, 14 PR) in the TP group and 15.4% (4 PR) in the TX group ($P=0.001$). The difference in CBR were higher in TP groups, but it was not statistically different (81.5% vs 61.5%, $P=0.135$).⁴ The study also compared the response to chemotherapy in various sites of metastases, higher response was found in the TP group compared to the TX group, irrespective of the site of metastases. Median PFS was 10.9 months in the TP group (95% CI 2.2-19.8 months) and 4.8 months in the

TX group (95% CI 3-6.7 months) [HR 0.29, 95% CI 0.14-0.57], $P<0.001$]. Median OS was also higher in the TP group (32.8 months vs 21.5 months) [HR 0.41 (0.18-0.92), $P=0.027$].⁴

Carey, *et al*, studied 102 patients with metastatic TNBC, 97 patients (95%) received prior chemotherapy either in the neoadjuvant setting or as metastatic treatment. From 86 patients that received neoadjuvant chemotherapy, 84 (98%) received anthracyclines, while 65 (76%) also received a taxane-based chemotherapy. This study compared the response of a cetuximab-carboplatin-based regimen to cetuximab only.⁵ With cetuximab as a single agent 2 out of 31 patients achieved PR (6%) and 1 patient achieved SD, with TTP 1.4 months, both of the patients were received it as second line therapy. Out of 71 patients that were given cetuximab – carboplatin, 1 patient achieved CR, 11 patients achieved PR, and 10 patients achieved SD for a significant amount of time. There was no correlation between outcome and line of chemotherapy.⁵

Table 2. Critical appraisal of articles based on centre of evidence medicine, University of Oxford⁶

| No. | Author | Study Design | Relevance | | | | Follow up | Missing data | | Level of Evidence | Blind | Adjustment for important prognostic factor | Validation in independent test |
|-----|---------------------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|--------------------------------|
| | | | mTNBC PBC | mTNBC non-PBC | mBC PBC | Outcome | | Drop out | Lost to follow up | | | | |
| 1. | C.V. Garza, <i>et al.</i> , 2014 | Retrospective cohort | n = 58 • Age at diagnosis = 45.5 • Visceral metastasis = 77.59% • Multiple metastasis site = 68.97% | n = 95 • Age at diagnosis = 51 • Visceral metastasis = 67.3% • Multiple metastasis site = 69.24% | | Median OS PBC = 14.5 months Median OS non-PBC = 10 months (p = 0.041) | Follow-up 120 months | 8 Due to side effect of PBC | ? | 2B | Yes (Age at diagnosis, location of metastases (visceral vs non-visceral), number of metastatic sites (single-multiple), line of chemotherapy) | Benefit of PBC vs Non-PBC in mTNBC | |
| 2. | L. Staudacher, <i>et al.</i> , 2011 | Retrospective cohort | N = 93 • Age at diagnosis = 48.4 • Visceral metastasis = 69% • History of first & second line chemotherapy = 53% | N = 50 • Age at diagnosis = 51.5 • Visceral metastasis = 41% • History of first & second line chemotherapy = 6% | | Median OS mTNBC+PBC = 27 months Median OS mBC+PBC = 8 months (P < 0.001) | Follow-up 44months | 0 (11 mTNBC regimens were switched from cisplatin to carboplatin, and 4 mBC were switched to carboplatin due to cisplatin side effects) | ? | 2B | Yes (Age at diagnosis, location of metastases (visceral vs non-visceral), number of metastatic sites (single-multiple), line of chemotherapy) | Usage of PBC in mTNBC patients vs mBC | |
| 3. | Fan Y, <i>et al.</i> , 2012 | Retrospective Cohort | n = 27 • Age at diagnosis = 48 • Visceral metastasis = 59.2% | n = 26 • Age at diagnosis = 49 • Visceral metastasis = 73% | | Median OS mTNBC+TP = 32.8 months Median OS mTNBC+TX = 21.5 months (P = 0.027) | Follow-up 24 months | 0 (docetaxel dose was reduced in 6 patients due to side effects) | ? | 2B | Yes (Age at diagnosis, no history of organ dysfunction, no history of usage of cisplatin and docetaxel) | Usage of PBC and non PBC in mTNBC patients | |
| 4. | Carey, <i>et al.</i> , 2012 | Prospective cohort | n = 71 • Age at diagnosis = 49 • Visceral metastasis = 58% | n = 31 • Age at diagnosis = 52 • Visceral metastasis = 58% | | Median OS mTNBC+Carboplatin/cetuximab = 10.4 months Median OS mTNBC+Cetuximab = 7.5 months | Follow-up 26 months | 7 26 patients were switched to cetuximab +carboplatin due to PD) | 6 | 2B | Yes (Age at diagnosis, location of metastases (visceral vs non-visceral), number of metastatic sites (single-multiple), line of chemotherapy) | Usage of PBC vs Non-PBC in mTNBC patients | |
| 5. | Zhang, <i>et al.</i> , 2014 | Prospective cohort | N = 64 • Age at diagnosis = 49 • Visceral metastasis = 62.5% | | | Median OS 19.1 months | Follow-up 42 months | 3 | ? | 2B | Yes (Age at diagnosis, history of organ dysfunction, location of metastases (visceral vs non-visceral), number of metastatic location (single-multiple), line of chemotherapy) | Single arm study PBC in mTNBC patients | |
| 6. | Ruoxi Hong, <i>et al.</i> , 2014 | Retrospective cohort | N = 34 • Age at diagnosis = 46 • >=2 lung metastases = 31% | N = 45 • Age at diagnosis = 48 • >=2 lung metastasis = 41% | | Median OS PBC 32 months Median OS PBC 21 months (P = 0.002) | Follow-up 67 months | 0 | ? | 2B | Yes (Age at diagnosis, menstruation status, histopathology result, number of lung metastases (<2 or >=2)) | Usage of PBC vs Non-PBC in mTNBC | |
| 7. | Hamilton, Erika, <i>et al.</i> , 2013 | Prospective cohort | N = 38 • Age at diagnosis = 50 • Visceral metastasis = 88% | | | CEBR 94% CR = 6patients (17.7%) PR = 23 patients (67.7%) SD = 3patients (8.8%) | Follow-up 50 months | 4 | ? | 2B | Yes (Age at diagnosis, location of metastases (visceral vs non-visceral), number of metastatic sites (single-multiple)) | Usage of PBC in mTNBC patients | |



Hong, *et al*, investigated the effectiveness of platinum agents for therapy of metastatic TNBC limited to the lungs. This study included 79 patients: 34 (43%) were given PBC and 45 (57%) received a non-PBC regimen; 50% had prior history of receiving anthracycline – taxane based therapy in the PBC group and 22% in the non-PBC group. The study found that the PFS in PBC group was 10 months (95% CI 6.6-13.4) and 5 months (95% CI 3.7-6.3 months) in the non-PBC group ($P=0.002$). Median OS also increased in the PBC group compared to the non-PBC group (32 vs. 21 months, $P=0.002$).⁸ Subgroup analysis of the PBC group revealed combination of platinum – taxane resulted in a longer PFS compared to other platinum based regimens (12 vs. 7 months, $P=0.009$). The platinum – taxane combination also showed a trend of improvement in OS (36 vs. 25 months, $P=0.112$).⁸

A single arm study by Zhang, *et al*, investigated the effectiveness of cisplatin and gemcitabine as the first line therapy in metastatic TNBC. This study included 64 patients: median PFS was 72 months (95% CI, 5.6-8.9 months) and median OS was 19.1 months (95% CI, 12.4-25.8 months). All patients underwent evaluation which resulted ORR of 62.5% (40 of 64 patients; 95% CI 50.3-74.7). The CBR rate was 78.1% (50 of 64 patients).⁷

Hamilton, *et al*, investigated the usage of nab paclitxel/bevacizumab/carboplatin as the first line therapy of metastatic TNBC. The single-arm study included 34 patients, the median PFS was 9.2 months (95% CI 7.8-25.1 months). PFS at 6 months was 88% (95% CI 75%-100%) and 64% (95% CI 43%-95%) at 9 months. The CBR was 94% (95% CI 80%-99%) which included 6 patients (17.7%) who reached CR, 23 with PR, 3 (8.8%) with SD and 2 (5.95%) with PD.⁹

DISCUSSION

TNBC is an aggressive subtype of breast cancer, more often found in younger population, demonstrates early recurrence (within the first 2 years), higher histological grade, higher visceral metastases, and increased mortality rates compared to hormone-positive breast cancer.¹⁰

Platinum-based therapy is a popular, but the effectiveness in metastasis has yet to be determined. Several studies used different variations of platinum-based therapy in metastatic TNBC, and the addition of platinum agents increased OS between 10.4-32.8 months.

The addition of targeted therapy in the form of PARP inhibitors such as iniparib and EGFR inhibitors like cetuximab and bevacizumab to chemotherapy in metastatic cases and for adjuvant therapy unfortunately did not improve outcome.³ So, the choice of therapy in metastatic TNBC is limited to chemotherapy. Adding to the complexity of the situation is the fact that treatment guidelines for metastatic TNBC have yet to be made, due to lack of results from phase three trials.

Therapeutic effect of platinum agents towards metastatic breast cancer has been evaluated due to the similarity between TNBC and BRCA-1 associated breast cancer. The usage of platinum agents is also popular in metastatic breast cancer resistant to anthracycline/taxane regimens, resulting in OR rates 26-50% and median OS 8-13 months.³ The interesting result found by Garza, *et al*, that a longer duration of therapy with PBC in second- and third-line chemotherapy compared to first-line, its also found in the research by O'Shaughnessy, *et al*, that OS and PFS were better in second- and third-line PBC treatment. The reason behind this result is still remain undiscovered.³

Several phase II and III trials comparing carboplatin versus docetaxel as the first line chemotherapy in advanced TNBC/BLBC are still going on. Staudacher, *et al*, showed no difference in outcome when PBC is given to patients with BRCA gene mutation compared to patients without BRCA gene mutation, but due to the small sample size (11 patients), no conclusion is drawn yet.⁴

Now the question is, "Is platinum agent specific to TNBC?" According to Fan, *et al*, docetaxel and capecitabine regimen is still one of the preferred choice in advanced breast cancer therapy. PBC is not only

associated with higher response rate but also results in higher PFS and OS when compared to TX. Although the benefit of cisplatin in increasing survival of metastatic TNBC patients cannot be drawn just based on phase II trials, the higher clinical benefit rate is apparent.⁵

According to Hurley, *et al*, cisplatin is more effective in locally advanced TNBC (stage II and III), compared to carboplatin in neoadjuvant setting, with higher pCR and survival in both PFS ($p=0.007$) and OS ($p=0.018$). Although Zhang, *et al*, showed that cisplatin/gemcitabine combination can be used as the first line in metastatic TNBC therapy, the question whether chemotherapy combination regimen cisplatin/gemcitabine or carboplatin/gemcitabine is more optimal in metastatic TNBC patients still need further research.⁷

CONCLUSION

Cytotoxic chemotherapy remains the mainstay treatment for TNBC because there are currently no specific targeted or biological agents available.⁷ The use of platinum-based chemotherapy (PBC) in the treatment of triple negative breast cancer (TNBC) has been a popular research topic since 10 years, ever since the discovery of similarity in some subtypes of TNBC with certain DNA repair defects characteristic of BRCA1 deficient breast cancer, which may confer sensitivity to platinum-derived compounds.^{3,7} The use of PBC has been associated with increased overall survival (OS) and progression free survival (PFS) in numerous studies.

It appeared that platinum-based combinations, but not single agents, were effective in patients with mTNBC. Preclinical data demonstrated cytotoxic synergy with the combination of cisplatin and gemcitabine (GP).⁷

The seven studies performed in metastatic setting have proven an increased OS and PFS in metastatic TNBC patients treated with PBC compared to non-PBC. However, conclusion should not be drawn merely from phase II trials.


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ANALISIS



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