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Treatment options for Indonesian triple negative breast cancer patients: a literature review of current state and potentials for future improvement

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ABSTRACT

Triple negative breast cancer (TNBC) is still associated with grave prognosis, especially compared to other breast cancer subtypes. Advances in medical science have improved our understanding on the biological nature and heterogeneity of TNBC, explaining the efficacy variability of existing chemotherapeutic drugs on TNBC patients. Complexity of TNBC has led to wide variation of TNBC treatment across the globe, resulting in unsatisfactory treatment outcome. This issue is further complicated by the absence of TNBC treatment guideline in many countries, including in Indonesia. This review discusses systemic treatment options for TNBC while taking account its molecular heterogeneity. Specific consideration is made for Indonesia, not only for current clinical practice, but also for future improvements. Immunotherapy, especially programmed cell death 1 (PD-1/PD-L1) inhibitor, has recently shown promising result in TNBC patients. It can be concluded that TNBC is heterogenous and treatment option should be tailored based on its molecular profile.

ABSTRAK

Kanker payudara tripel negatif (KPTN) masih berhubungan dengan kesintasan yang buruk, terutama jika dibandingkan dengan subtipe kanker payudara lainnya. Kemajuan teknologi telah meningkatkan pemahaman kita tentang sifat biologis dan heterogenitas KPTN yang merupakan dasar dari variabilitas respon pasien KPTN terhadap kemoterapi. Kompleksitas KPTN menyebabkan terjadinya perbedaan dan variasi dari pola pengobatan KPTN di seluruh dunia dan berdampak pada hasil pengobatan yang belum memuaskan. Hal ini diperburuk dengan tidak adanya panduan terapi KPTN di banyak negara, termasuk di Indonesia. Tinjauan ini membahas tentang pilihan terapi sistemik untuk pasien KPTN dengan mempertimbangkan heterogenitas molekuler pada subtipe ini. Perhatian khusus ditujukan pada Indonesia, baik untuk tatalaksana saat ini maupun untuk kemajuan di masa depan. Imunoterapi, *khususnya programmed cell death 1 (PD-1/PD-L1) inhibitor*, menunjukkan hasil yang menjanjikan pada pasien KPTN.Dapat disimpulkan bahwa KPTN bersifat heterogen dan pemilihan modalitas terapi sebaiknya disesuaikan dengan profil molekuler pasien.

Keywords:
triple negative;
breast cancer;
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treatment;
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INTRODUCTION

Triple negative breast cancer (TNBC) accounts for 10 – 20% of all breast cancers which roughly translates into 200.000 of new cases annually worldwide.[1,2] Epidemiological data of Indonesian showed that TNBC patients is very rare. According to reports from Widodo *et al.*[3] and Sitohang *et al.*,[4] TNBC accounts for 20-25% of all breast cancer cases in Dr. Sardjito General Hospital, Yogyakarta, Indonesia. TNBC is a very heterogeneous disease with wide variety of genetic expression and mutations. Collectively TNBC has the worst survival compared to other breast cancer subtypes. Existing treatment modalities still do not result in acceptable survival outcome.[5] Although both ESMO and ASCO (NCCN) have published treatment guidelinesfor TNBC,there is still no standard chemotherapy regimenfor TNBC, leading to wide variation of TNBC treatment across the globe.[6-8]

In Indonesia, TNBC patients are mainly treated surgically followed by adjuvant chemotherapy. Since currently there is no guideline for TNBC treatment in Indonesia, Indonesian health professionals have to adapt and implement multiple international guidelines into their daily practice, albeit with limited success. The lack of consensus on choosing chemotherapy regimen for TNBC patients in Indonesia further complicates this issue. The aimed of this review paper was to provide recommendation and suggestion for the development of Indonesian guideline on TNBC treatment as well as for other developing countries that donot have such guideline at the moment.

LITERATURE REVIEW

TNBCheterogeneity

TNBC is immunohistochemically defined as the lack of estrogen receptor (ER) and progesterone receptor (PR) expression accompanied with the lack of human epidermal growth FACTOR receptor2 (HER2) overexpression.[9] According to American society of clinical oncology/college of American pathologist (ASCO/CAP) guidelines, ER and PR expression have to be ≤ 1% for them to be considered as negative.[10] Classifying TNBC according to IHC is not enough as the heterogeneity of TNBC extend beyond ER, PR, and HER2 expression alone. Multiple attempts have been done to improve the classification of TNBC with the most widely discussed at the moment being classification by Perou *et al.*[11] (PAM50) and Lehmann *et al.*[12] (Vanderbilt).[12-16]

Perou *et al.*[11] provided the first insight on "intrinsic subtypes" of breast cancer based on gene expression profiling analysis. Perou *et al.*[11] came up with 4 intrinsic subtypes of breast cancer, namely luminal, HER2-enriched, basal-like and normal breast-like. Breast cancer subtypes according to Perou's classification was further added by research done by Sørlie *et al.*[12] which divided luminal subtypes into luminal A and B. Prat *et al.*[17] added Claudin Low subtype. Throughout the years, this classification has been intensively studied and has showed clinical and prognostic significance, albeit limited.[12-15] Prat *et al.*[14] later refined the 6 subtypes classification into 2 subtypes, basal-like and non-basal-like.

Lehmann *et al.*[18] initially classified TNBC into 6 subtypes (also known as TNBC type), namelybasal-like 1 and 2 (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem–like (MSL), and luminal androgen receptor (LAR). Further research then considered IM and MSL subtypes to had been defined by the high expression of genes from the tumor microenvironment and not from the actual tumor cells, leading to the omission of IM and MSL subtypes from the refined classification,

also known as TNBCtype-4.[14,16] Masuda *et al.*[19] investigated the clinical relevance of the original Vanderbilt classification (TNBCtype) in neoadjuvant setting with anthracycline and taxane chemotherapy. They found that BL1 subtype had the highest pathologic complete response (pCR) rate (52%) and BL2 and LAR had the lowest (0 and 10%, respectively).

Although Perou *et al,*[11] (later refined by Prat*et al.*[14]) and Lehmann *et al.*[16] came up with different classifications, both shared some overlapping entities. Both classifications came up with 3 basic subtypes, mesenchymal, basal-like, and LAR in Vanderbilt classification and Claudin-low, basal-like and luminal/ HER2E in PAM50 classification.[14] Apart from significant scientific contribution, neither of the two classifications can fully describe the heterogeneity of TNBC's biological characteristic which causes more researchers to try to find a better classification of TNBC. Burstein *et al.*[20] thought gene profiling alone might not be enough to classify TNBC and attempted to combine gene profiling with transcriptomic analysis according to mRNA to classify TNBC (Baylor classification). Burstein *et al,*[20] classified TNBC into 4 subtypes, namely: luminal-AR (LAR), mesenchymal (MES), basal-like immune-suppressed (BLIS), and basal-like immune-activated (BLIA). Out of the four subtypes, BLIS subtype has the best prognosis for both DFS and DSS while BLIA has the worst. According to Burstein *et al,*[20] Baylor classification does havesome similarities with both Vanderbilt and PAM50 classifications. The LAR subtype in Baylor classification is very similar with LAR subtype in Vanderbilt classification while both BLIS and BLIA subtypes from Baylor classification are entirely classified asbasal-like according to PAM50 classification.[20]

Current classifications of TNBC allow researchers to systematically analyze treatment effect on different TNBC subtypes. Although useful in clinical trials, more evidence is needed to establish the prognostic and therapeutic value of these classifications.

TNBC in Asian population

Race and ethnic group are known to influence characteristic and prognosis of TNBC.[21] Compared to America, India has higher prevalence of TNBC (>30% of all breast cancer) and is associated with younger age at diagnosis and worse prognosis.[22-25] Different pattern is observed in Chinese population. China has one of the lowest prevalence of TNBC among Asian countries (around 10.4-13.5% of all breast cancer) with significantly better survival compared to other population (5- and 10-year OS were as high as 79.92 and 82%, respectively).[26,27] Currently, there is no data of TNBC survival in Indonesian patients, although the incidence is around 20-25% of all breast cancer cases, relatively high compared to other countries.[3,4]

TNBC treatment modalities *Local control*

Surgery and radiotherapy in TNBC are principally similar with other breast cancer subtypes and will not be discussed in this paper.

Systemic therapy

Systemic chemotherapy, both as adjuvant and neoadjuvant therapy, is the main treatment of TNBC. All of the chemotherapy regimens used in breast cancer in general can be used in TNBC with anthracycline- and taxane-based chemotherapy being the more preferred option for both adjuvant and neoadjuvant settings.[28-30]

Platinum salt

Addition of platinum salt towards standard chemotherapy regimen had

been proven to improve survival in TNBC patients. CALGB 40603 trial showed that addition of carboplatin to standard regimen (paclitaxel 80 mg/m^2 once a week for 12 weeks, followed by doxorubicin plus cyclophosphamide once every 2 weeks for four cycles) significantly increased pCR breast (60% vs. 44%; p=0.0018) and pCR breast/axilla (54% vs. 41%; p=0.0029).[31] Follow-up analysis of CALGB 40603 trial reported that three-year overall EFS was 74.1% and OS 83.2%. Patients who achieved pCR breast had significantly better three-year EFS compared to those who did not (84.8% vs. 61.8%).[32] Although it should be noted that the addition of carboplatin or bevacizumab significantly increased chemotherapy-related toxicity which decreased the chance for patients to complete the standard chemotherapy regimen without skipped doses, dose modification, or early discontinuation.

Similar with CALGB 40603 trial, GeparSixto trial also showed that the addition of carboplatin to standard regimen (18 weeks of paclitaxel 80 mg/m^2 once a week and non-pegylated liposomal doxorubicin 20 mg/m^2 once a week) increased pCR rate in TNBC patients (53.2% vs. 58%; p=0.005) but not in HER2-positive breast cancer. Increased incidence of chemotherapy associated toxicity due to the addition of carboplatin also observed in GeparSixto trial.[33] Comparing 2 of the most commonly used platinum agents in treating metastatic TNBC patients, phase II TBCR009 trial found that cisplatin had abetter response rate compared to carboplatin (32.6% vs. 18.7%). The overall response rate for both agents combined was 25.6% and was particularly high in individuals with BRCA1/2 mutations compared to the ones without the mutation (54.5% vs. 19.7%).[34] Long term follow-up showed that stage II/III TNBC patients treated with paclitaxel (175 mg/m2, day1) plus carboplatin (area under the curve = 5, day2) resulted in significantly higher five-yearrecurrence-free survival (RFS) compared to patients treated with epirubicin (75mg/m2, day1) plus paclitaxel (175mg/m2, day2) (EP) (77.6% vs. 56.2%; p=0.014). Five-year OS were not significantly different between 2 treatment arms (83.3% vs. 70.7%; p=0.350). Patients who achieved pCR had significantly better five-year RFS (94.7% vs. 56.1%; p=0.043) and OS (100.0% vs. 67.2%; p=0.004).[35]

The effectiveness of platinum salt in treating TNBC is thought to be caused by formation of DNA-platinum adducts which leads to inter- and intra-strand cross-links. This cross-linking of DNA interferes with replication and transcription which results in the breaking of a double-stranded DNA strand and ultimately results in cell death.[36] Platinum is especially effective in TNBC with BRCA1 germline mutation because BRCA1 is a mediator of homologous recombination (HR) and mutation of BRCA1 leads to decreased DNA repair and DNA stability. Byrski *et al.*[37] observed 90% pCR rate in 10 patients with BRCA1 mutation (9 TNBC, 1 incomplete data) treated with cisplatin (75mg/m^2 every 3weeks for four cycles). Effectiveness of platinum in BRCA mutated patients is further elucidated in another study by Byrski *et al.*[37] In this study 102 BRCA1 mutation carriers were treated with different chemotherapy regimens and the highest pCR rate was achieved in patients treated with cisplatin (83%), followed by AC/FAC regimen (22%), AT regimen (8%), and CMF regimen (7%). Although positive results have been seen in BRCA1 mutated TNBC patients, BRCA1 mutation is found only in 23-57% of all TNBC cases.[38,39] Incidence of BRCA mutation seems to be varied according to race and country.[40] Nanda *et al.*[41] observed that BRCA mutations were highest among Ashkenazi Jewish families, followed by Caucasians and African Americans (69.0, 46.2, and 27.9% respectively). In Indonesia, studies have showed that BRCA mutations

occurred in 0-7.8% of all breast cancer patients,[42,43] which is similar with other Asian countries.[44,45] Furthermore, BRCA1 mutation represent only a fraction of basal-like subtype according to PAM50 or BL1 and BL2 according to Vanderbilt classification which means there is still a huge proportion of TNBC patients that requires different treatment approach.[14,18]

PARP inhibitor

Poly (ADP-ribose) polymerase (PARP) is important in facilitating base excision repair (BER).[46] As BER is essential in single-strand DNA breaks repair, inhibition of PARP may lead to accumulation of DNA single-strand breaks, which in the absence of double-strand homologous recombinant (HR) repair mechanism, causes "synthetic lethality".[47] In many breast cancer cases, including TNBC, double-strand HR repair defect is associated with BRCA1 mutation.[38,39,48] Since PARP is highly expressed in more than 80% of BRCA1 mutated TNBC patients, inhibition of PARP is thought to add benefit in treatment of TNBC.[49,50]

The positive impact of PARP inhibitor in the treatment of TNBC patients was shown in a phase II trial by O'Shaughnessy *et al*.[51] This study found that the addition of iniparib to gemcitabine and carboplatin improved the rate of clinical benefit from 34 to 56% (p=0.01) and the rate of overall response from 32 to 52% (p=0.02). The median progression-free survival (PFS) and overall survival (OS) were also prolonged with the addition of iniparib (3.6 vs. 5.9 months and 7.7 vs. 12.3 months respectively). However, the positive result from phase II trial did nottranslate very well in the phase III confirmation trial as the addition of iniparib to gemcitabine and carboplatin showed that improved OS (HR 0.65, 95%CI: 0.46-0.91) and PFS (HR 0.68; 95%CI: 0.50-0.92) only seen when the regimen was given as second-/third-line treatment.[52]

Other types of PARP inhibitor have been tested in clinical trials and showed positive result in treating TNBC. A report published from I-SPY 2 trial showed that addition of carboplatin and veliparib to standard chemotherapy regimen [12 cycles of weekly paclitaxel followed by doxorubicin/cyclophosphamide (AC) X 4] increased pCR rate of TNBC patients (51% vs. 26%) with 88% predicted probability of phase 3 success.[53] A phase III trial of 302 patients by Robson *et al.*[54] found that olaparib (PARP1 and PARP2 inhibitor) improves the outcome of metastatic breastcancer patients with *BRCA* mutation. Median progression-free survival was significantly longer in the olaparib group compared to the standard-therapy group (7.0 vs. 4.2 months; PFS: HR 0.58, 95%CI: 0.43-0.80). The response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group with sub analysis result showing significantly better response in TNBC patients compared to hormone-receptor positive patients/HR 0.43 (95%CI: 0.29-0.63) vs 0.82 (95%CI: 0.55-1.26).[54]

EGFR inhibitor

Epidermal growth factor receptor (EGFR),a member of ErbB family of receptor tyrosine kinasehas been showed to be important contributor oftumor cell proliferation, migration, and survival.[55-58] Research has showed that EGFR expression tend to be higher in TNBC patients when compared to non-TNBC patients, is more frequently seen in basal subtype and associated with worse prognosis.[14,18,59-61] However, reports on the frequency of EGFR overexpression in TNBC have been varied (13-89%), with lower frequency particularly observed in Korean patients (13-30%), suggesting EGFR overexpression might be influenced by race.[60,62,63] As EGFR is involved in various carcinogenesis processes and is highly expressed in TNBC, the addition

of EGFR inhibitor theoretically will add benefit in TNBC patients. Despite promising results in preclinical studies, results from clinical trials have been lackluster at best. Most trials reported that the addition of EGFR inhibitor didn't result in significant clinical response in advanced TNBC patients and was associated with increased incidence of chemotherapy-related side effects, especially hematological toxicities.[64-67] The only clinically significant result of EGFR inhibitor so far was reported by Carey *et al.*[68] with 6% response rate (RR) shown in the addition of cetuximab in metastatic TNBC treatment, while cetuximab plus carboplatin resulted in 16% RR after progression. Disappointing results from clinical trials makes it difficult to suggest the usage of EGFR inhibitor in TNBC treatment. However, because further research on this topic is ongoing, the role of EGFR inhibitor in management of TNBC patients has not been determined.

Androgen receptor inhibitor

Androgen receptor (AR) is expressed in all of breast cancer subtypes, including TNBC.[69-72] Researchhas shown that AR is expressed in 12-53% of all TNBC patients.[72-75] The wide frequency difference of AR expression between studies is partly explained by the absence of standardized method of determining AR positivity. AR negativity in TNBC is associated with younger age at diagnosis and worse prognosis in African American women. Classification of TNBC by Lehmann *et al.*[16] and Burstein *et al.*[20] grouped AR expressing TNBC as a separate entity (LAR subtype). This LAR subtype was observed to have lower rate of response towards neo-adjuvant chemotherapy, suggesting the need for different treatment approach towards this subtype.[19]

Due to the success of targeting estrogen and progesterone receptors in treating hormone positive breast cancer, research on the effectiveness of AR inhibitor in treating breast cancer, especially TNBC became more prevalent. As a proof of concept for the role of AR inhibitor in treating TNBC, Gucalp *et al.*[75] reported that bicalutamide showed 19% clinical benefit rate (CBR) when given to ER-PR- metastatic breast cancer patients. Similar with previous study, Bonnefoi *et al,*[76] reported that the addition of abiraterone acetate (AA) and prednisone resulted in 20% CBR and 6.7% objective response rate (ORR)in advanced AR+ TNBC patients.More recently, a phase II study by Traina *et al.*[77] reported that enzalutamide resulted in 33.3% of CBR when given to AR+ TNBC patients treated with 0-1 prior lines of therapy with fatigue as the only grade 3 or higher drug related toxicity.

PD-1/PD-L1inhibitor

Programmed death 1 receptor (PD-1) is an immune checkpoint receptor and when bound to its PD-L1 ligand, results in immunoinhibitory response which contributes to cancer cell survival and progression.[78-81] In cases of cancer that expresses PD-1/PD-L1, inhibition of PD-1/PD-L1 results in cancer cell death. Studies have shown that PD-1/PD-L1 expression in TNBC tend to be higher when compared to non-TNBC with estimated frequency of 20-58% in all of TNBC patients.[82-86]

High expression of PD-1/PD-L1 has been associated with high expression of TILs, including in TNBC.[87] Higher expression of TILs is associated with better survival in TNBC patients, suggesting the potential of PD-1/PD-L1 inhibitor as a candidate for TNBC treatment.[88]

Promising results have been seen in clinical studies of PD-1/PD-L1 inhibitor in TNBC treatment. A phase 1b KEYNOTE-012 study by Nanda *et al.*[83] reported that single agent pembrolizumab (10 mg/kg every 2 weeks) treatment in advanced TNBC patients resulted in 18.5% ORR accompanied by generally mild drug related toxicity, although 15.6% of the patients experienced grade ≥ 3 toxicity and one patient died due to treatment-related cause. In phase II study, Nanda *et al.*[89] reported that the addition of pembrolizumab increased the raw pCR rate by 52.1% (19.3 to 71.4%) and estimated pCR rate by > 40%, with predicted probability of success in phase III trial of 99.3%. Immune related toxicities were observed in 5 of 69 patients included in this study, which were hypophysitis (I patient) and adrenal insufficiency (4 patients).Given as first line therapy in metastatic TNBC patients, pembrolizumab (200 mg Q3W) monotherapy showed 23% ORR with manageable safety profile.[90]

Other trials have also showed similarly positive results of PD-1/PD-L1 inhibitor in advanced TNBC patients. A phase 1b KEYNOTE-173 study by Schmid *et al,*[84] reported overall ORR (CR+PR) before surgery of 80% (90% CI: 49-96) in A (single-dose pembrolizumab followed by 4 cycles of pembrolizumab Q3W + nab-paclitaxel (Np) weekly followed by 4 cycles of pembro + doxorubicin + cyclophosphamide Q3W)and 100% (90% CI, 74-100) in B (same as in A but with carboplatin Q3W added to pembro + Np). ypT0/Tis pCR rate was 70% (90% CI: 39-91) in A and 100% (90% CI: 74-100) in B; ypT0 ypN0 pCR rate was 50% (90% CI: 22-78) in A and 90% (90% CI: 61-100) in B; and yT0/Tis ypN0 pCR rate was 60% (90% CI, 30-85) in A and 90% (90% CI: 61-100) in B.A phase Ib trial by Adams *et al,*[91] showed that atezolizumab (800 mg Q2W; d1,15) and nab-paclitaxel (125 mg/m^2 Q1W; d1,8,15, q3 of 4 weeks) resulted in 42% confirmed ORR. PD-1/PD-L1 inhibitor is perhaps the most promising immunotherapy agent for TNBC that we have so far, although more evidence is still needed to support routine use of this agent for TNBC treatment.

Eribulin

Eribulin, a microtubule inhibitor, recently has shown positive results when given to TNBC patients. A phase III clinical trial assessing the effect of eribulin on pretreated metastatic breast cancer showed that the addition of eribulinmesylate 1.4 mg/m^2 significantly improved PFS (HR 0.77; 95% CI: 0.60-0.97; p=0.028) and OS (HR 0.72; 95% CI:0.57-0.90; p=0.005) in TNBC patients.[92] In another study, Manikhas *et al.*[93] observed that metastatic TNBC patients treated with erbulin resulted in 9.6% of clinical ORR and 46.1% stable disease with relatively well tolerated drug related toxicity. More recently, a phase Ib/II trial showed that eribulin in combination with pembrolizumab resulted in ORR of 29.2% (95% CI: 18.6-41.8) when given to metastatic TNBC patients (Eisai Co Ltd, 2017).[94]

TABLE 1. Summary of considerations in choosing treatment options

Treatment option	Consideration
Anthracyline + taxane chemotherapy	Generally, is the regimen of choice for initial treatment, both in neoadjuvant and adjuvant setting. [28-30]
Platinum salt	Generally sensitive for TNBC, is associated with the best outcome compared to other systemic chemotherapy regimen, especially in BRCA1(+). Can be used as 1st line agent.[31-35, 37]
PARP inhibitor	Improves survival when given in combination with platinum-based chemotherapy, possibly through "synthetic lethality." [51-54]
EGFR inhibitor	Theoretically will add benefit in TNBC patient. Phase II studies have shown small but significant clinical response. Currently evidence is still lacking to support routine use of this agent to treat TNBC.[64-68]
AR inhibitor	Androgen receptor is known to be expressed in some TNBC patients.[69-72] Phase II studies have shown moderate clinical response.[75-76] More evidence is required to understand its role in TNBC treatment.
PD-1/PDL-1 inhibitor	Promising agent for TNBC treatment. Multiple phase II studies have shown positive result in metastatic setting when used in combination with other chemotherapy agents.[89-90]
Eribulin	Moderate response is observed when given to metastatic patients. Although its role in improving survival, especially in early stage TNBC, is unknown.[92-94]

TP53 inhibitor

TP53, a tumor suppressor gene, is one of the most frequently found mutated gene in TNBC (64-82%) and is often associated with worse response to treatment and survival.[85,95-97] TP53 has been hypothesized as one of the most important driving forces in carcinogenesis of TNBC, suggesting its potential as a therapeutic target.[98] Preclinical studies have shown positive effect of TP53 inhibition in TNBC cell lines, albeit have not been validated by clinical trials.[99] Currently, two anti-TP53 drugs, APR-246 and COTI-2 are undergoing phase I clinical trials on other types of cancer that show high rate of TP53 mutation, showing tolerable toxicity, and promising efficacy.[100,101]

MiRNA inhibitor

Inhibition of miRNA has been discussed as an option to treat TNBC as it is known that certain types of miRNA are associated with the survival of TNBC patients. Meta-analysis by Lü *et al.*[102] showed that decreased expression of miR-155 and increased expression of miR-21 were predictive of reduced OS. Lü *et al.*[102] also found that elevated levels of miR-27a/b, miR-210, and miR-454 expression were associated with shorter OS, while the levels of miR-454 and miR-374a/b expression were associated with DFS. A study by Svoboda *et al,*[103] observed that miR-34b expression negatively correlated with DFS and OS in TNBC patients. Research on the therapeutic role of miRNA for TNBC is currently in preclinical phase. Li *et al.*[3] reported that miR-454 promoted and enhanced the proliferation, migration and invasion of TNBC cells. Overexpression of miR-454 inhibited TNBC cell death by ionizing radiation through the regulation of caspase 3/7 and Bcl-2 expression. Chen *et al.*[104] observed that miR-211-5p was significantly down regulated in TNBC and its expression level was associated with overall survival in TNBC. The expression of miR-211-5p suppressed TNBC cell proliferation, invasion, migration and metastasis *in vitro* and *in vivo*. Although there is no

targeted therapy aimed specifically at certain miRNA, recent reports have shown that the serum level of various miRNA is affected by chemotherapy and might be associated with patient survival, suggesting their involvement in healing process. There is substantial amount of miRNA which are potential targets for future TNBC therapy.[105-108] Unfortunately, we have not reached adequate understanding on the best way to target miRNA to treat TNBC, thus significant progress from preclinical studies is needed before we can move on to clinical trials.

PI3K/AKT/mTOR inhibitor

Phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) is one of the most important pathways in cell survival, proliferation, and metastasis of certain cancers.[109-111] During the creation of theirclassification, Lehmann *et al.*[18] observed that multiple components of PI3K/AKT/mTOR pathway were mutated in some TNBC patients, especially the ones classified into mesenchymal-like and mesenchymal stem-like subtypes. In recent years many discussions had taken place discussing whether inhibition of PI3K/AKT/mTOR pathway would lead to better survival in TNBC patients. Preclinical studies have shown that multiple agents targeting various points in PI3K/AKT/mTOR pathway have resulted in growth arrest of TNBC cell lines.[112-114] At the moment, there are numerous trials underway assessing PI3K/AKT/mTOR inhibitors in TNBC patients. Using metaplastic TNBC as a surrogate for mesenchymal TNBC, aphase I trial showed that the combination of liposomal doxorubicin, bevacizumab, and temsirolimus or everolimusresulted in 21% ORR (8% CR, 13% PR) and 19% stable disease for at least 6 months, for a clinical benefit rate of 40%. The presence of PI3K pathway aberration was associated with a significant improvement in ORR (31 vs. 0%; p=0.04) but not CBR (44 vs. 45%; p >0.99).[115] Although not yet proven to be efficacious as monotherapy, PI3K/ AKT/mTOR inhibitors might be useful as combination therapy in metastatic TNBC patients. Reports from ongoing phase II studies will improve our understanding on the best way to utilize these drugs in treating TNBC.

DISCUSSION

Studies from the past two decades have revealedthe complexity and heterogeneity of TNBC. Expression and mutation of various genes are known to have prognostic value and cause different response towards chemotherapy, explaining the disparity of survival between race and ethnic groupsin TNBC. This issue is especially problematic for a country such as Indonesia, which population is not only numerous (4th most numerous in the world), but also heterogenous (comprised of more than 730 ethnic groups). According to genetic pattern and anthropological analysis, Indonesian population has ancestral lineage stemming from China, India, and Africa, resulting in genetically unique and diverse population.[116] Potential solution for this problem is by implementation of targeted therapy which would allow for a more personalized medicine. Unfortunately, targeted therapy in Indonesia is still very expensive and not covered by Indonesian National Insurance, thus chemotherapy is still the more suitable approach at the moment.

TNBC is associated with higher sensitivity towards chemotherapy treatment compared to other subtypes, albeit is also associated with higher rate of recurrence and distant metastasis.[117-119] Liedtke *et al,*[120] observed that TNBC patients who received NAC treatment achieved higher rate of pCR when compared to non-TNBC patients

(22vs. 11%; p=0.034) but had decreased three-year progression-free survival rates (p=0.0001) and three-year overall survival (OS) rates (p=0.0001). However, similar survival is observed between non-TNBC patients and TNBC patients if pCR is achieved. The association between pCR status and improved survival was later confirmed by.[121] Cortazar *et al.*[121] performed meta-analysis and found that TNBC patients had the strongest association between pCR and event-free survival (EFS) (HR 0.39, 95%CI: 0.31-0.50) with the weakest association shown in HER2-positive, hormone positive subtype (HR 0.58, 95%CI: 0.42-0.82). Although all of the chemotherapy regimens used in treating breast cancer in general can be used in treating TNBC, platinum-based regimen is observed to be the best regimen for TNBC patients in Indonesia, especially for patients expressing BRCA mutation.

Targeted immunotherapy such as PD-1/PD-L1 inhibitor has proven to be useful in TNBC patients, both given as single agent, as well as in combination with chemotherapy. The effectiveness of PD-1/PD-L1 inhibitor has resulted in increased research interest in finding more immune checkpoints as potential target for therapy in TNBC, including CD73 andCDCP1.[122]

CONCLUSION

Heterogeneity of TNBC makes it impossible for the development of “one for all” treatment. Response towards existing treatment modalities has been diverse across all TNBC subtypes. Although, there isnot a single target molecule which is highly expressed in all of TNBC patients, targeted therapy, especially PD-1/PD-L1 inhibitor, has shown promising results but still require further validation through phase III and IV clinical trials.

Reports have shown that race and genetic profile are important risk factors and prognostic factors of TNBC. While research in Europe, East Asia and USA is numerous, TNBC research in Southeast Asia, especially in Indonesia is still far from adequate thus limiting our knowledge on how applicable research results from other countries to highly heterogeneous Indonesian patients. Before breakthrough in clinical research can be made, it is imperative for Indonesia to strengthen its epidemiological and molecular data. An ongoing collaboration between International Agency for Research on Cancer (IARC) and Dr. Sardjito General Hospital, Yogyakarta for the development of population-based cancer registry (PBCR) serves as an important stepping stone to reach that goal. It is also important for Indonesia to improve its efficiency on conducting clinical research. Instead of conducting multiple conventional trials assessing 1 treatment regimen at a time, implementation ofcentrally coordinated research through a platform similar to the one used in I-SPY 2 trial can substantially increase clinical research output as it allows for assessment of multiple treatment regimens at the same time.Further improvement on research efficiency can be doneby shifting from adjuvant to neoadjuvant chemotherapy as pCR has been proven by other studies as a predictor that can be done for long-term survival in TNBC.

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