台灣乳房醫學會
TAIWAN BREAST CANCER SOCIETY

2020 TRIPLE-NEGATIVE BREAST CANCER CONSENSUS

主編 台灣乳房醫學會

PREFACE

乳癌一直是台灣婦女癌症中的頭號殺手，據衛福部統計，近年每年新增超過 12,000 名乳癌患者，其中 12–15% 為三陰性乳癌，這類型乳癌具有高度的基因變異性，有較高的機會面臨化療後復發困境；所幸隨著醫療的進步，在三陰性乳癌的治療上近年已有了重大的突破，讓存活率大幅提升。

學會為秉持加強乳癌疾病之醫療、教學及研究之宗旨精神，特參照國際準則及國內臨床狀況，制定全國性的治療共識，依證據強度設定建議等級，給予乳癌領域相關醫師遵循參考。推動一系列乳癌治療共識、制定標準臨床處置流程，臨床醫師願意遵守，治療中能收集到高品質的台灣實證（Real world data），應用分析，甚而能當作藥物給付的重要參考依據，一直是本人任內亟待達成的目標。此次針對三陰性乳癌共識先於 2019 年 6 月成立了共識會議工作小組，由盧彥伸及饒坤銘帶領沈士哲、林季宏、林柏翰、郭文宏、許志怡、張源清、黃其晟、趙大中、劉峻宇、戴明燊等諸位醫師（依姓氏筆畫排列、職稱省略概以醫師稱謂）進行共識會議籌備，擬定三陰性乳癌治療重要議題，本人衷心感謝工作小組的辛勞付出。本會於 2019 年 11 月 24 日，假台北榮總致德樓正式舉辦「2019 TNBC Leading Opinion Symposium」，與全國專家學者們共同討論，會後彙整專家建議，經台灣乳房醫學會第八屆理監事審議通過。鑑往知來，醫學與時俱進，共同促進醫學之進步發展為吾人終生努力職志，誠摯期待各界先進能不吝指教、提供新知，共同為台灣乳癌治療盡最大努力，讓國人乳癌防治止於至善。

台灣乳房醫學會 理事長
曾令民 于 2020 年 4 月

特別感謝以下專家（依姓氏筆畫排列、職稱省略概以醫師稱謂）

于承平、王明暘、王惠暢、王甄、沈士哲、杜世興、李國鼎、林季宏、林柏翰、洪志強、俞志誠、侯明鋒、洪朝明、郭文宏、馬旭、陳守棟、陳芳銘、陳訓徹、陳達人、許志怡、張金堅、許居誠、張振祥、許桓銘、莊捷翰、張獻崑、張源清、張耀仁、曾令民、黃其晟、黃俊升、葉大成、葉顯堂、趙大中、趙祖怡、廖國秀、鄭翠芬、劉自嘉、劉良智、蔡宜芳、蔡青樺、劉建良、劉美瑾、劉峻宇、盧彥伸、沈陳石銘、戴明燊、鍾為邦、饒坤銘、歐陽賦等諸位醫師。

AGENDA

TOPIC	SPEAKER	MODERATOR
Opening	台灣乳房醫學會 曾令民理事長	
Welcome Remarks	台北榮民總醫院外科部 馬旭部主任	
TNBC Overview	長庚醫院乳房外科 沈士哲醫師	長庚醫院乳房外科 陳訓徹教授
Overview of TNBC Pathological Diagnosis	台北榮總病理檢驗部 許志怡主任	台北馬偕醫院 劉建良院長
Molecular Characteristics of TNBC	台北榮總輸血醫學科 劉峻宇主任	彰化基督教醫院 陳達人教授
BREAK		
Genetic Testing in Breast Cancer and TNBC	台大醫院基因醫學部 林柏翰醫師	台北慈濟醫院 張耀仁副院長
Panel Discussion	台北長庚一般外科 沈士哲醫師 台北榮總病理檢驗部 許志怡主任 台北榮總輸血醫學科 劉峻宇主任 台大醫院基因醫學部 林柏翰醫師 羅東博愛醫院 葉顯堂副院長 和信醫院腫瘤內科 劉美瑾主任 高醫大附設醫院乳房外科 歐陽賦醫師 台北榮總乳房醫學中心 黃其晟醫師 長庚醫院腫瘤科 張獻崑醫師 衛生福利部雙和醫院 趙祖怡教授	中國醫藥大學 附設醫院 王惠暢顧問 臺北醫學大學 臺北癌症中心 杜世興副院長
LUNCH		
Current Therapies for Early TNBC	台大醫院外科部 郭文宏醫師	三軍總醫院 俞志誠教授
Current Therapies for Metastatic TNBC	馬偕醫院乳房外科 張源清醫師	新光醫院 鄭翠芬主任
BREAK		
Immunotherapy for TNBC: Rationale, Results, and Ongoing Trials	三軍總醫院腫瘤科 戴明燊主任	員林基督教醫院 陳守棟協同院長
Clinical Application of DDR Targeting Agents for TNBC	台大醫院腫瘤醫學部 林季宏醫師	臺北醫學大學附設醫院 沈陳石銘教授
Panel Discussion	台大醫院外科部 郭文宏醫師 馬偕醫院乳房外科 張源清醫師 三軍總醫院腫瘤科 戴明燊主任 台大醫院腫瘤醫學部 林季宏醫師 台北榮總乳房醫學中心 趙大中醫師 台北榮總乳房醫學中心 蔡宜芳醫師 中國醫大附設醫院乳房外科 劉良智主任 成大醫院血液腫瘤科 鍾為邦醫師 台南新樓醫院乳房外科 張振祥主任 義大癌治療醫院 饒坤銘副院長	台大醫院外科部 黃俊升部主任 台灣乳房醫學會 曾令民理事長
Update Current TNBC Consensus in Taiwan	台灣乳房醫學會 陳芳銘秘書長	高醫大附設醫院 侯明鋒院長
Closing	台大醫院外科部 張金堅教授	

CONTENTS

LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATION

Strength	Recommendation
A	Strong recommendation for use
B	Moderate recommendation for use
C	Marginal recommendation for use
D	Recommendation against use
N/A	Inconclusive

Quality of Evidence	Recommendation
I	Evidence from at least 1 properly designed randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

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TNBC OVERVIEW

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. TNBC account for 13~15% in all invasive breast cancer, the ratio is similar between age groups.	II		[1]
2. In HER2 negative breast cancer, ER 1~10% tumors take up 5.6% ~ 8% of cases.			[4]
3. Low ER/PR expression (1-9%), HER2-negative breast cancer behaves more like triple negative breast cancer (TNBC).	II	B	[2] [4] [6]
4. In comparison to tumor with higher ER/PR expression, low ER/PR and HER2 negative breast cancer is associated with worse prognosis.	II	B	[3] [4]
5. For low ER/PR expression, HER2-negative breast cancer, hormonal therapy is also beneficial. Threshold for chemotherapy in this group of patient should be individualized and approaching to TNBC.	II	B	[3] [5] [6]

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OVERVIEW OF TNBC PATHOLOGICAL DIAGNOSIS

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. The good-prognosis subtypes of triple-negative breast cancers are low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, adenoid cystic carcinoma, secretory carcinoma, and medullary carcinoma.	II	B	[1]
2. ETV6-NTRK3 translocation-associated secretory carcinoma can be targeted by Trk inhibitors.	II	B	[2]
3. Most of the metaplastic carcinomas have a worse prognosis, except low-grade adenosquamous carcinoma and fibromatosis-like metaplastic carcinoma.	II	B	[3]
4. Mixed subtype breast cancer is defined by a tumor with 10%–90% of special subtype of the cancer. The prognosis of mixed subtypes TNBC is inconclusive (not significantly different from IDC).	III	C	[4]
5. Ki67 is a predictive and prognostic marker of triple-negative breast cancer. But cut-off value is inconclusive.	II	B	[5]
6. Androgen receptor is positive in 24% of triple-negative breast cancers. It associated with lower tumor grade, lower risk of disease recurrence. But, the assays and definition of positivity differ among studies.	III	C	[6]
7. Discordance of ER (median 14%), PR (21%), HER2 (10%) occurred in recurrent and metastatic breast cancers. Re-biopsy is recommended and may have an impact on patient outcomes and management.	II	B	[7]
8. Tumor-infiltrating lymphocytes (TILs) are a prognostic marker. High TILs are associated with better outcome and better response to neoadjuvant therapy in triple-negative breast carcinomas.	II	B	[8]

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MOLECULAR CHARACTERISTICS OF TNBC

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Currently NO single molecular subtyping method such as Lehmann's TNBC-4, PAM50, or Burstein's Immune subtyping should be routinely used to guide treatment for TNBC.	III	A	[1-6]
2. AR inhibitors are still under investigation and awaits phase III clinical trials in TNBC. TBCS recognizes that there is NO approved AR inhibitor yet in TNBC therapy.	II	A	[7]
3. The development of drugs targeting the PI3K/AKT/mTOR pathway for the treatment of TNBC is an evolving field that should take into account the efficacies and toxicities of new agents in addition to their interactions with different cancer pathways. TBCS recognizes that there is NO approved PI3K/AKT inhibitors in TNBC therapy.	II	A	[8]
4. For patients eligible for clinical trials, PI3K/Akt/PTEN testing can be considered	III	B	[8]

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GENETIC TESTING IN BREAST CANCER AND TNBC

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. In the setting of hereditary breast cancer genetic counseling and prevention, genetic testings can be suggested for all TNBC patients (either EBC or MBC) age ≤60 years; the genes to be tested included those recommended by the NCCN guideline (i.e. ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11, TP53, NBN, NF1, PALB2, RAD51C, RAD51D)	II	B	[1] [2]
2. In the setting of therapeutic consideration, such as treatment for metastatic TNBC and/or when treatment choice includes a PARP inhibitor, germline BRCA status should be tested.	I	A	[3] [4]
3. After genetic testing, if the patient has BRCA or other variants of hereditary cancer genes, it is suggestion that the patient and his/her family be referred to genetic counseling and follow the NCCN guideline for cancer screening and prevention.	II	B	[1] [2]

References

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CURRENT THERAPIES FOR EARLY TNBC

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Not all TNBC patients are required for dose-dense adjuvant chemotherapy. The use of dose-dense should be considered, particularly in highly proliferative tumours.	II	C	[1]
2. In the neoadjuvant setting, there is high- to low-certainty evidence of equivalent outcomes for the sequence in which taxanes are delivered. In the adjuvant setting, none of the studies reported on overall survival or disease-free survival. In most institutions, standard practice would be to deliver anthracycline followed by taxane, and currently available data do not support a change in this practice.	II	C	[2]
3. The correlation between pathologic response and long-term outcome is strongest for TNBC. Neoadjuvant chemotherapy allows the modification or addition of adjuvant regimens among TNBC patients with residual disease. For patients with more than T2 disease, neoadjuvant approach should be considered.	II	B	[3] [4] [5]
4. Recommend adjuvant capecitabine(at a dose of 1250 mg per square meter of body-surface area, twice per day, on days 1 to 14) every 3 weeks up to 8 courses in patients with TNBC and residual invasive disease following standard neoadjuvant/adjuvant treatment with taxane and anthracyclin-based chemotherapy. The dose of capecitabine may be adjusted according to patients' clinical complications.	I	B	[5]
5. In TNBC patients, platinum-based neoadjuvant chemotherapy is associated with significantly increased pCR rates at the cost of worse hematological toxicities. Platinum-based neoadjuvant chemotherapy may be considered an option in TNBC patients.	II	B	[6]

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CURRENT THERAPIES FOR METASTATIC TNBC

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Both combination and sequential single-agent chemotherapy (CT) are reasonable options. We recommend combination therapies including combined CT, CT with immunotherapy in PD-L1 + group or CT with bevacizumab as the preferred choice for mTNBC. Sequential single-agent CT should be reserved for patients not requiring rapid symptom and/or disease control.	I	A	[1]
2. Paclitaxel and platinum (prefer carboplatin over cisplatin), as combination agents, would usually be considered as first-line CT (treatment naïve or > 12 months since adjuvant taxane) for mTNBC.	I	B	[1]
3. In the absence of medical contraindications or patient concerns, anthracycline or taxane-based regimens are recommended. Other options such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.	II	A	[2]
4. In patients pretreated with an anthracycline and a taxane, single-agent eribulin is the preferred choice.	I	A	[3]
5. In mTNBC patients carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared with docetaxel, and is , therefore, an important treatment option particularly for BRCA-associated advanced TNBC.	I	A	[4]

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
6. Metronomic CT is a reasonable treatment option for unfit TNBC patients and those not requiring rapid tumor response. Preferred options include CM(low-dose oral cyclophosphamide and methotrexate), capecitabine and/ or vinorelbine.	I	B	[5]
7. In patients with mTNBC who achieved disease control with an initial CT, we recommend maintenance CT.	I	A	[6]
8. Metronomic CT is a reasonable treatment option for maintenance therapy in patients following regimens with tumor response but developing unacceptable toxicity.	III	B	[7]
9. Optimal combination and sequence of bevacizumab and CT can be considered as an option in selected cases who desperate for a response particularly for brain metastases.	II	B	[8]
10. For patients with cancer experiencing CT-induced peripheral neuropathy (CIPN), clinicians may offer duloxetine. There are no established agents recommended for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents.	II	A	[9]

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IMMUNOTHERAPY FOR TNBC: RATIONALE, RESULTS, AND ONGOING TRIALS

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Anti-PDL1 (Atezolizumab) is active in the 1st line treatment of PDL1+ advanced or metastatic TNBC.	I	A	[1]
2. PDL1 (SP142) is the major biomarker for immunotherapy in advanced or metastatic TNBC.	I	A	[1]
3. Other biomarkers, TILs, mutation burden, CD8+ cells, MSI, gBRCA mutation, need further validation.	N/A	N/A	[2]
4. Best chemotherapy partner for immunotherapy combination to be explored.	N/A	N/A	

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CLINICAL APPLICATION OF DDR TARGETING AGENTS FOR TNBC

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. PARP inhibitor, either olaparib or talazoparib, is indicated for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated , HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting.	I	B	[1] [2]
2. For gBRCAm/PD-L1- MBC, PARP inhibitor is preferred. Atezolizumab benefit is not significant in this population.	I	B	[3]
3. For gBRCAm/PD-L1+ MBC, the choice between PARPi or atezolizumab/chemotherapy as the first line treatment has not been answered. For de Novo stage IV, atezolizumab/chemotherapy is preferred because this population is not eligible for OlympiA and EMBRACA trials.	III	N/A	[1] [2] [4]
4. A small phase II study showed that two patients with gPALB2 responded to PARPi.	II	C	[5]
5. The efficacy of PARPi for advanced BC with somatic BRCA1/2m is currently being investigated in a phase II single arm trial (NCT03344965)	III	N/A	[6]
6. Some studies showed high HRD predicted response of neoadjuvant platinum, but it did not predict platinum efficacy in MBC (TNT trial). Its role in predicting PARPi has not been well studied.	II	D	[7]

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