Personalised Management for Breast Cancer – “One-Size-Fits-All” Approach is Over, But What Next?

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Introduction

With research and development, there have been increasing advances in the field of oncology, leading to better outcome of all cancer patients. Recommendation of systemic adjuvant therapy and choice of optimal agents for early-stage breast cancers remain a challenge.

Breast cancer has been the most common female cancer worldwide and is still the most common female cancer in Hong Kong with 1 in 21 cumulative life-time risk. It is indeed a major public health concern. The incidence of breast cancer is increasing.

Thanks to our scientists and dedicated oncologists who have made great successes in translational research, as breast cancer patients of all types and all stages are now living longer with much better quality of life, especially those with metastatic disease. While breast cancer patients are managed in a personalised manner in the context of the new evolving breast cancer molecular classification, the rapid development of all new cancer treatments has put a new challenge everyday for the physicians who are caring for cancer patients in terms of the high expectation of the patients and the general public and the relatively high costs of the new targeted therapy and prognostic tests. This requires the most optimal communication skills to discuss openly about different treatment options available with the patients. This article aims at giving an update of personalised management of breast cancer with particular references to adjuvant therapy and the challenges ahead with this new approach of practice.

Overview of Major Breakthroughs – Higher Hopes?

From Conventional Adjuvant Regimen to Newer Generations

Adjuvant therapy after definitive surgical resection of the breast tumour has been shown to increase the overall outcome of high-risk breast cancer patients, in terms of prevention of local recurrence and distant metastasis. For example, adjuvant radiotherapy is given according to the tumour risk to help prevent local recurrence while the benefits of adjuvant chemotherapy has become the standard of care for selected high-risk patients since the data published more than 30 years ago by Bonadonna. Since then, there have been many more international clinical trials showing further benefits with different chemotherapy regimens, such as the anthracycline-based chemotherapy was associated with further risk reduction when compared with the conventional cyclophosphamide, methotrexate and fluorouracil (CMF) regimen; followed by the added value of taxanes (T: paclitaxel, docetaxel) being included in many newer third generation regimens (ACx4 followed by Tx4) in the 1990s. The BCIRG 001 trial further showed 6 cycles of taxotere, anthracycline and cyclophosphamide (TAC) was superior to 6 cycles of fluorouracil, anthracycline and cyclophosphamide (FAC), but the TAC regimen was indeed associated with more significant myelosuppression including grade 4 neutropenia and even febrile neutropenia. The recent US Oncology Research Network trial has suggested superiority of replacing anthracycline (doxorubicin) with taxanes (taxotere) (i.e. TC replacing AC) . Up till now, there is indeed no recipe for adjuvant chemotherapy as individual assessment of all prognostic and predictive factors are all taken into account while open discussion with patients and the carers is of paramount importance before any final treatment decision could be made.

From Risk Assessment to Target Determinant

In the past, the final histopathology report of the definitive surgery for breast cancer has been crucial in terms of the decision on indication of adjuvant chemotherapy. Clinico-pathological features such as young age at presentation, pathological tumour size of more than 2 cm, high grade of tumour, presence of peritumoural vascular invasion, positive axillary lymph nodes, hormone-negative tumours and over-expression of receptor status have become important predictive factors of treatment response. With the added value of aromatase inhibitors in terms of adjuvant hormonal therapy for the post-menopausal hormone receptor positive breast cancer patients, the hormone receptors (oestrogen receptor and progesterone receptor) and the HER-2 receptor status have become important predictive factors of treatment response.

Therefore, there is a shift of paradigm of management and decision making on the most optimal adjuvant management for breast cancer patients, from the analysis of just the clinico-pathological features of the
breast tumour to the taking into account of predictive factors for treatment response and also potential prognostic indicators. This has further led to our better understanding of all the primary breast cancers in the context of different molecular subtypes. In the old days, systemic adjuvant therapy was indicated on the assumption of existing residual microscopic disease, with estimation of risk based entirely on extrapolation of data from previous clinical trials. It was further assumed that biological characteristics and treatment responsiveness are consistent between micrometastases and the primary tumour.

From “One-Size-Fits All” Approach to Tailored Made Management
Breast cancer is a heterogeneous disease. Molecular profiling identifies at least five breast cancer subtypes: luminal-A, luminal-B, HER2-enriched, basal-like and normal breast-like. An immunohistochemical profile based on the degree of expression of oestrogen receptor (ER), progesterone receptor (PgR), HER-2 and Ki-67 similarly identifies breast cancer subtypes which have diverse disease biology, behaviours, relapse risks and treatment responses. Though current evidence-based adjuvant treatment options include chemotherapy, endocrine therapy and anti-HER-2 targeted therapy, there is still an observational phenomenon where individuals at low risks who develop disease recurrence despite standard systemic treatment while some patients with high-risk disease remain relapse free for a long time without adjuvant intervention. On the other hand, promising novel agents that are being explored include therapies that target angiogenesis, DNA repair, apoptosis and immunity; but the evidence for the efficacy of these agents is lacking in the adjuvant setting. Therefore, the recommendation of the most appropriate adjuvant therapy for an individual diagnosed with early-stage breast cancer remains a difficult task. The more we know, the more we know how much we do not know. With the “one-size-fits all approach” being over in the management of breast cancer patients, there has been introduction of various decision making tools such as different multi-gene signatures to better tailor our management plan for individual patients.

Breast Cancer Assessment Tools
As decisions about adjuvant therapy must be made on an individual basis while there is no recipe for adjuvant therapy for breast cancer patients, there comes various prognostic and predictive assessment tools with the aim to assist breast oncologists to decide on the most appropriate treatment for each breast cancer patient, namely the computer-based model, Adjuvant! Online, international guidelines and consensus and other models using multi-gene signatures.

Adjuvant! Online
This is a validated computer-based model (https://www.adjuvantonline.com) which has been a popular breast cancer assessment tool among most breast oncologists giving an approximate risk evaluation in terms of 10-year breast cancer outcome based on selected prognostic features. This prognostic model was created using 10-year overall survival data from the Surveillance, Epidemiology, and End-Results (SEER) registry data for women aged between 36 and 69 years diagnosed with unilateral, unicentric, invasive breast adenocarcinoma between 1988 and 1992. However, this prognostic tool is limited as it does not incorporate important prognostic factors such as oestrogen receptor (ER), progesterone receptor (PgR), HER-2 receptor status or any proliferative markers such as Ki-67 level. The potential benefits of using third-line chemotherapy may sometimes be over-estimated, especially in those early-stage disease when available data are being extrapolated.

International Guidelines and Consensus
The St. Gallen Consensus which is one of the major international guidelines with regard to the most appropriate breast cancer adjuvant management with revision made every two-yearly at the St. Gallen Breast Cancer Conference during March every other year, has incorporated both risk assessment and therapy recommendation in its latest version in 2009. It has incorporated the standard cut-off levels for ER, PgR, HER-2 and Ki-67. The consensus recommends that tumours with ER staining ≥1% are classified as hormone receptor positive. The St Gallen Consensus recommends that patients with small primary tumours (pT1N0) with no vascular invasion may be spared chemotherapy. Patients with triple-negative (ER negative, PgR negative and HER-2 negative) tumours, have no systemic alternatives to chemotherapy. For patients with HER2-positive tumours, chemotherapy is indicated with anti-HER-2 targeted therapy with a total of 1-year adjuvant trastuzumab. For HER2-positive, small (<1 cm) node-negative tumours, the St Gallen Panel acknowledged emerging evidence of poor prognosis despite small tumour size. However, the lack of robust prospective evidence did not allow a definitive recommendation regarding anti-HER2 therapy in this cohort at this moment.

Multi-gene Signatures Assessment Tools
Over the last few years, significant effort has been made in identifying relevant molecular markers as prognostic and predictive factors to aid better decision making on adjuvant therapy for breast cancer patients. The innate capacity of a tumour to metastasise has prompted the use of multi-gene profiling for relapse risk estimation. A potential limitation of these mRNA-based signatures is the assumption that measurable mRNA will be translated to protein. However, most mRNA is not translated. Some markers, such as HER2, have evidence of a strong correlation between gene amplification and protein over-expression.

The 21-gene Oncotype DX® (Genomic Health Inc., Redwood City, CA) assay was developed to assign adjuvant chemotherapy in women with ER-positive, node-negative breast cancers who would receive adjuvant endocrine therapy. Sixteen cancer genes and five reference genes are used to calculate a Recurrence Score (RS) between 0 and 100, which correlates to a specific likelihood of recurrence within 10 years of diagnosis, defined as low (RS <18), intermediate (RS 18–31) or high (RS >31). As a prognostic tool for ER-positive, node-negative women, Oncotype DX® is superior to patient age, tumour size or tumour grade, and to a modified 5-year outcome version of Adjuvant! Online. However it remains to be seen whether
Oncotype DX® is more useful than combined assessment of ER, PgR, HER2 and Ki-67 at a high-quality laboratory. In another study, Microarray in Node-negative Disease may Avoid Chemotherapy Trial (MINDACT), the genomic profiling of a 70-gene signature (MammaPrint®) is studied and compared with the conventional clinical assessment to determine the indication of chemotherapy in women with node-negative breast cancers. So far, studies on the MammaPrint® 70-gene signature have shown that the multi-gene signatures correlate a good-risk signature with chemoresistance and a poor-risk signature with increased chemosensitivity, but they do not show that MammaPrint® is more clinically valuable than morphology and immunohistochemical (IHC) subtyping in predicting these responses.

What Next After All High Hopes – More Burden?

Matching Science with the Affordability
Our research and development has proven success as evidenced by the promising results of the clinical trials, leading to the many more options and avenues in the treatment for breast cancer patients. While the incidence of breast cancers is increasing and the number of breast cancer patients living with the disease is also increasing, the access to all the new regimens especially the targeted therapy and the assessment tools is not equal to all individuals. Currently, the use of adjuvant trastuzumab in the public sector is a self-financed item for patients in Hong Kong, so are some of the taxanes in the intermediate risk group. The cost of the Oncotype Dx is indeed a self-financed item if the patient and physician would like to ascertain the benefits of chemotherapy for the node-negative hormone receptor positive early breast cancer patients. The current cost of a total of 1 year adjuvant trastuzumab is about HK$ 200,000 while the cost of the Oncotype Dx test is about HK$ 20,000. The cost-effectiveness of the Oncotype Dx assay has been verified in the United States but not in individual countries and thus there is another challenge of whether the clinical data derived from these multi-gene signature assays could be translated into direct application in other non-US countries such as the Asian population like our Chinese population.

Open Discussion and Communication is of Paramount Importance
With the ever increasing number of new anti-cancer treatments and molecular assays, there comes the increasing high expectation from the patients and their families. While the issue of life and death, breaking bad news and dealing with complex psychosocial oncology of cancer patients is usually not thoroughly touched during our traditional medical training, not all oncologists or cancer physicians are well equipped with the proper communication skills in terms of discussing various costs and options of anti-cancer treatments with the breast cancer patients. This has been supported by the recent cross-sectional study looking at the perceived difficulties and stress from a cancer patient consultation among 134 Australian cancer specialists, all being members of the Clinical Oncological Society of Australia, and it has shown that to the doctors, the most stressful practice being discussing the high-cost drugs during the consultation”. There is indeed a growing challenge among the oncologists in discussing all the high-cost treatment options with the cancer patients”. Therefore, there is an unmet need to further better equip our cancer physicians and cancer carers with better communication skills so that they could provide relevant information with regard to the high-cost treatment and relevant tests to our cancer patients.

Conclusion
There has been ever increasing hopes for breast cancer patients with our better understanding of the breast cancer molecular biology, and the ever increasing avenues of different treatment options for different subtypes of patients. The “one-size-fits-all” approach is over and we have come to the new era of personalised medicine for our breast cancer patients. However, whether higher hopes mean greater burden in terms of the extra time and empathy to discuss various treatment options including the ever growing list of self-financed items with our patients, and whether we could translate all the clinical data from the western population to our own clinical practice, this requires the continuous effort of the multidisciplinary approach for breast cancer management, and further international multi-centre trials and investigation of biological and treatment heterogeneity within breast cancer subtypes, such as good prognosis subsets within triple-negative disease or benefit of anti-HER2 therapy in small, HER2-positive tumours, and within individuals are warranted to further advance our risk assessment. While we are planning to explore further clinical utility of promising assessment tools in future and biologically driven trials, we should also better equip our oncologists or oncologists-to-be with better communication skills which involves an appreciation of both art and science. There is no single recipe for adjuvant management of breast cancer patients, but there should always be an open discussion with the patient, the family and all other supporting parties before any treatment decision is made.

References
2. Hong Kong Cancer Registry, Hospital Authority, 2008.


