Article published online: 2020-12-22

Original Article

Practical consensus recommendations regarding the management of HER2 neu positive early breast cancer

A. Bahl, R. Singh[1], J. Wadhwa[2], S. Gupta[3], M. Ahmed[4], P. N. Uppal[5], Purvish M. Parikh[6], S. Aggarwal[7]

Abstract

Over-expression of HER2 is generally considered to be a negative prognostic feature because it accompanies an increase in breast cancer mortality. However, the development of agents that specifically target HER2 has improved the management of patients with these tumours. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations with regards to the use of these agents and the management of HER2 neu early breast cancer for the benefit of community oncologists.

Key words: Adjuvant trastuzumab, double agent, TCH regimen, tumor size

Introduction

The incidence of Her2 positivity in Indian population is between 26% and 50%.[1-3] A number of studies have established that HER2 over-expression is a poor prognostic factor in patients with early breast cancer.[4-9] The development of trastuzumab, a humanized monoclonal antibody against the extracellular domain of HER2 and other targeted therapies has led to a marked improvement in the outcome of patients with early breast cancer whose tumours over-express the HER2 receptor.[10-13] However, trastuzumab is an expensive treatment that is beyond the reach of the majority of patients in developing countries.[14,15] This manuscript was prepared to help community oncologists better manage HER2 neu positive early breast cancer and provide guidelines regarding the use of trastuzumab and other agents.

Expert oncologists from all over India met to discuss and reach a consensus statement to provide community oncologists practical guidelines on the management of HER2 neu early breast cancer. The discussion was based on published evidence and practical experience in real life management of such patients. The expert group discussions were moderated by Dr Ankur Bahl and Dr Randeep Singh. The core expert group consisted of Dr Jyoti Wadhwa, Dr Ashutosh Gupta and Dr Mushtaq Ahmed. Members of the panel were also allowed to share their personal experiences and make comments. This manuscript is the outcome of the expert group discussion and consensus arrived at in 2017.

Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared. The experts discussed a case of a 40 year old premenopausal lady diagnosed with infiltrating duct carcinoma in left breast. She underwent modified radical mastectomy. Histopathology results were - T1N0M0, ER-80%, PR-80% and HER2 neu-3+. Based on this case, a series of questions were put up for poll upon which the expert group discussed and aimed to reach a consensus. Each question had multiple choice options from which participants were to select the one most appropriate for their clinical practice setting. The expert group then formed the practical consensus recommendations for the community oncologists.

Trastuzumab Treatment and the Size of Tumour

Trastuzumab is not used routinely for early-stage, HER2-positive breast cancers that are 0.5 cm or smaller. The polled oncologists concurred with this notion as 65.5% were not in support of recommending trastuzumab treatment to patients with tumour size of 0.5 cm [Table 1]. This is because the risk of recurrence of these types of breast cancers is relatively low. A study at Kaiser Permanente Northern California between 2000 and 2006 was carried out to observe the recurrence rate in mostly untreated patients with T1a and T1b tumours.[16] After a median 6 years of follow up, out of 237 HER2-positive cases, 15 invasive recurrences were observed. Out of these invasive recurrences, only 4 were in patients with T1a tumour. Out of the 7 distant recurrences that were observed, only 1 was in a patient with T1a tumour. The 5-year distant relapse–free rate was 89.5% for T1b and 99.1% for T1a tumours. Only 1 patient out of 101 with a T1a tumour not treated with chemotherapy experienced a distant recurrence. The experts discussed whether a risk for distant recurrence approaching 1% is worth a year of treatment for the patients with a 0.5 cm tumour. The expert consensus was that adjuvant Trastuzumab is not recommended in patients with tumour size less than or equal to 0.5 cm.

As to the question whether they would recommend trastuzumab treatment in patients with a tumour size between 0.5 cm and 1 cm, majority of the polled oncologists gave an affirmative response as indicated in Table 2. The experts were divided in their opinion regarding this matter. For node-positive disease and node-negative cancers greater in size than 1 cm, chemotherapy and trastuzumab is generally recommended, but oncologists today vary in their practice for treating tumours

Access this article online

Quick Response Code:

Website: www.sajc.org

DOI: 10.4103/sajc.sajc_111_18

Deparment of Medical Oncology, Max Hospital, [3]Department of Medical Oncology, Sarvodaya Hospital, [5]Department of Surgical Oncology, Jaipur Golden Hospital, [7]Department of Medical Oncology, Sir Ganga Ram Hospital, New Delhi, [1]Department of Medical Oncology, Artemis Hospital, [2]Department of Medical Oncology, Medanta Hospital, Gurugram, [4]Departmentt of Radiation Oncology, Jolly Grant Himalayan Institute, Dehradoon, [6]Department of Oncology, Shalby Cancer and Research Institute, Mumbai, Maharashtra, India

Correspondence to: Dr. Randeep Singh, E-mail: drrandeep@yahoo.co.in

How to cite this article: Bahl A, Singh R, Wadhwa J, Gupta S, Ahmed M, Uppal PN, *et al*. Practical consensus recommendations regarding the management of HER2 neu positive early breast cancer. South Asian J Cancer 2018;7:102-5.

with size between 0.5 cm and 1 cm.[17] Still, there is evidence that sub-centimetre HER2-positive tumours carry a higher risk of recurrence than their HER2-negative counterparts.[18,19] Also, as stated by Fehrenbacher *et al*.,[16] T1b tumours have a higher risk of recurrence than their T1a counterparts. A meta-analysis by Zhou *et al*.[20] concluded that adjuvant trastuzumab might bring significant survival benefit to HER2-positive patients with pT1a-bN0M0 breast cancer. Some other studies have also suggested that adjuvant trastuzumab-based therapy may improve outcomes for T1 tumours that are HER2-positive.[21-23] The expert panel discussed about a Cochrane meta-analysis[24] which suggests that trastuzumab significantly improves OS and DFS in HER2-positive women with early and locally advanced breast cancer, although it also significantly increases the risk of congestive heart failure. The experts opined that the risk to benefit ratio in patients at lower risk (small tumour) must be carefully evaluated. The panel concluded that for node-negative tumours with size between 0.5 and 1.0 cm, adjuvant trastuzumab treatment can be considered based on age and co-morbidities.

Treatment for Patients with T1c Tumours

According to the NCCN guidelines, all HER2 positive patients with tumour size more than 1 cm should be offered chemotherapy with trastuzumab.[25] The question arises as to what treatment should be accompanied with trastuzumab. When posed with this question, 41.7% of the polled oncologists were in support of recommending a treatment plan of weekly taxol for 12 weeks and trastuzumab. Another 41.7% of the polled oncologists voted in support of TCH treatment and the remaining 16.6% voted for 4ACTH treatment [Table 3]. The BCIRG 006 trial[26] has indicated that the addition of 1 year of adjuvant trastuzumab to chemotherapy significantly improves disease-free and overall survival among women with HER2-positive breast cancer. The risk-benefit ratio favoured the non-anthracycline TCH regimen over AC-TH, given its similar efficacy, fewer acute toxic effects, and lower risks of cardio-toxicity and leukemia. The expert panel was also of the opinion that it is best to avoid anthracycline based treatment regimens citing their cardiotoxicity.[27-29] Now, the recently concluded Adjuvant Paclitaxel and Trastuzumab (APT) study of 406 women with HER2-positive, node-negative tumours lesser than 3 cm in size demonstrated that lower-intensity chemotherapy and trastuzumab is associated with fewer side effects.[30] Patients received postoperative weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of treatment with trastuzumab alone. At a median follow-up of 4 years, the 3-year rate of survival free from invasive disease was 98.7%. Twelve patients relapsed, 2 due to distant metastatic breast cancer. Two patients had symptomatic congestive heart failure. Another study by Hayes *et al*.[31] has also indicated paclitaxel to be beneficial to HER2-positive patients with node positive tumours. The expert panel consensus was that in patients with tumour size between 1 cm and 2 cm, weekly paclitaxel along with trastuzumab should be offered whereas in patients with tumour size more than 2 cm, either paclitaxel with trastuzumab or TCH should be offered based on individual preference.

Combination of Trastuzumab with other Anti-Her2 Agents

Trastuzumab was the first anti-HER2 agent that was developed. Since then, some other anti-HER2 drugs like pertuzumab and lapatinib have also been developed. All these anti-HER2 agents target HER2 in a different way. So, the question regarding the use of these agents in a combination is a valid one, but when asked, the majority of the polled oncologists were not in support of adding any other anti-HER2 agent to trastuzumab [Table 4]. The experts discussed about some ongoing trials on the matter. The main highlight of the discussion was the ALTTO trial[32] which compared the effect of trastuzumab plus lapatinib with only trastuzumab treatment in adjuvant setting for HER2-positive patients. A total of 8,381 patients were enrolled in the study between 2007 and 2011. The study concluded that adjuvant treatment that includes lapatinib with trastuzumab did not significantly improve disease free survival compared with trastuzumab alone. Along with this, it was also seen that the lapatinib containing arm suffered from higher toxicity. The benefit of adding lapatinib is not yet clear as there have been conflicting results from different studies.[33,34] Regarding pertuzumab data, the experts were of the opinion that it is not yet mature enough for reaching a consensus over its use in combination with trastuzumab. The expert panel recommended that it is best to wait for further data before the financial burden of the patients is increased. The panel concluded that as of now, there is no recommendation for adding another anti-HER2 agent to trastuzumab in the adjuvant setting.

Need for Anthracyclines in Node Positive HER2 Disease

To the question that if they choose to give trastuzumab to patients with HER2 and node positive tumour, would they always combine it with anthracycline, the polled oncologists

Table 1: Question 1 - Would you recommend trastuzumab for patients with 0.5 cm tumour?

Options	Yes	No
Percentage of polled oncologists	65.5	34.5

Expert group consensus: Adjuvant trastuzumab is not recommended in patients with tumour size ≤0.5 cm, unless there are other high risk factors

Table 2: Question 2 - Would you recommend trastuzumab for patients with tumour size between 0.5 and 1 cm?

Options	Yes	No
Percentage of polled oncologists	70	30

Expert group consensus: For patients with tumoursize between 0.5 and 1.0 cm, adjuvant trastuzumab treatment can be recommended based on other risk benefit factors

Table 3: Question 3 - What protocol would you recommend if the tumour size is 2 cm?

Options	Weekly taxol ×12 and TCH	TCH	4AC→TH
Percenatge of polled oncologists	41.7	41.7	16.6

Expert group consensus: Weekly paclitaxel along with trastuzumab should be offered to patients with tumour size between 1 and 2 cm. Either paclitaxel with trastuzumab or TCH should be considered for patients with tumour size >2 cm

Table 4: Question 4 - Would you add another anti-human epidermal growth factor receptor 2 agent to trastuzumab?

Options	Yes	No
Percentage of polled oncologists	23.1	76.9

Expert group consensus: There is no recommendation for adding another anti-HER2 agent to trastuzumab in the adjuvant setting. HER2=Human epidermal growth factor receptor 2

Table 5: Question 5 - Would you always combine trastuzumab with anthracycline for the treatment of node positive patients?

Options	Yes	No
Percentage of polled oncologists	0.0	100

Expert group consensus: In HER 2 positive patients with positive lymph nodes, TCH regimen should be first chemotherapy option. Anthracyclines may be considered in higher risk patients. HER2=Human epidermal growth factor receptor 2

unanimously gave negative answer as indicated in Table 5. The anthracyclines are among the most effective anticancer treatments ever developed.[35-37] Their main adverse effect is cardiotoxicity, which considerably limits their usefulness.[27-29] Use of anthracyclines has also been shown to be significantly associated with cycle 1 severe or febrile neutropenia.[38] The BCIRG 006 trial[26] has already shown that non-anthracycline regimens have similar efficacy and lower risks of toxic adverse effects in node positive as well as high risk node negative early breast cancer patients. A study has also shown a non-anthracycline regimen to provide better DFS and OS than the anthracycline regimen.[39,40] TCH regimen has now been backed up by the BETH trial[41] which showed that TCH has a much better safety profile than anthracycline/trastuzumab combinations and also equally effective in HER2 positive, node positive patients. Even as new non-anthracycline treatment regimens are being developed to replace those with anthracyclines, the efficacy and benefits of anthracyclines cannot be overlooked.[42] Anthracyclines have been extensively tested in clinical trials spanning several decades[43-46] and have been shown to be one of the most effective group of agents for the treatment of breast cancer. Considering all the evidence at hand, the expert panel concluded that in HER2 positive patients with positive lymph nodes, TCH regimen should be offered over anthracyclines. The panel added that anthracyclines may be used in higher risk patients in whom the tumour has spread to numerous regional lymph nodes (N3).

Take Home Message

1. Adjuvant trastuzumab is not recommended in patients with tumour size less than or equal to 0.5 cm, unless there are other high risk factors
2. For patients with tumour size between 0.5 and 1.0 cm, adjuvant trastuzumab treatment can be recommended based on other risk benefit factors
3. Weekly paclitaxel along with trastuzumab should be offered to patients with tumour size between 1 cm and 2 cm. Either paclitaxel with trastuzumab or TCH for patients with tumour size more than 2 cm
4. There is no recommendation for adding another anti-HER2 agent to trastuzumab in the adjuvant setting
5. In Her 2 positive patients with positive lymph nodes, TCH regimen should be first chemotherapy option. Anthracyclines may be considered in higher risk patients

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Vaidyanathan K, Kumar P, Reddy CO, Deshmane V, Somasundaram K, Mukherjee G, *et al.* ErbB-2 expression and its association with other biological parameters of breast cancer among Indian women. Indian J Cancer 2010;47:8-15.
2. Nikhra P, Patel S, Taviad D, Chaudhary S. Study of ER (Estrogen Receptor), PR (Progesterone Receptor) and HER-2/NEU (Human Epidermal Growth Factor Receptor) expression by immunohistochemistry in breast carcinoma. Int J Biomed Adv Res 2014;5:275-8.
3. Zubeda S, Kaipa PR, Shaik NA, Mohiuddin MK, Vaidya S, Pavani B, *et al.* Her-2/neu status: A neglected marker of prognostication and management of breast cancer patients in India. Asian Pac J Cancer Prev 2013;14:2231-5.
4. Dykins R, Corbett IP, Henry JA, Wright C, Yuan J, Hennessy C, *et al.* Long-term survival in breast cancer related to overexpression of the c-erbB-2 oncoprotein: An immunohistochemical study using monoclonal antibody NCL-CB11. J Pathol 1991;163:105-10.
5. Andrulis IL, Bull SB, Blackstein ME, Sutherland D, Mak C, Sidlofsky S, *et al.* Neu/erbB-2 amplification identifies a poor-prognosis group of women with node-negative breast cancer. Toronto Breast Cancer Study Group. J Clin Oncol 1998;16:1340-9.
6. Hartmann LC, Ingle JN, Wold LE, Farr GH Jr., Grill JP, Su JQ, *et al.* Prognostic value of c-erbB2 overexpression in axillary lymph node positive breast cancer. Results from a randomized adjuvant treatment protocol. Cancer 1994;74:2956-63.
7. Press MF, Pike MC, Chazin VR, Hung G, Udove JA, Markowicz M, *et al.* Her-2/neu expression in node-negative breast cancer: Direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease. Cancer Res 1993;53:4960-70.
8. Seshadri R, Firgaira FA, Horsfall DJ, McCaul K, Setlur V, Kitchen P, *et al.* Clinical significance of HER-2/neu oncogene amplification in primary breast cancer. The South Australian Breast Cancer Study Group. J Clin Oncol 1993;11:1936-42.
9. Têtu B, Brisson J. Prognostic significance of HER-2/neu oncoprotein expression in node-positive breast cancer. The influence of the pattern of immunostaining and adjuvant therapy. Cancer 1994;73:2359-65.
10. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr. Davidson NE, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.
11. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72.
12. Slamon D, Eiermann W, Robert N. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. Breast Cancer Res Treat 2005;94 Suppl 1:S5a.
13. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809-20.
14. Ghosh J, Gupta S, Desai S, Shet T, Radhakrishnan S, Suryavanshi P, *et al.* Estrogen, progesterone and HER2 receptor expression in breast tumors of patients, and their usage of HER2-targeted therapy, in a tertiary care centre in India. Indian J Cancer 2011;48:391-6.
15. Adusumilli P, Konatam ML, Gundeti S, Bala S, Maddali LS. Treatment challenges and survival analysis of human epidermal growth factor receptor 2-positive breast cancer in real world. Indian J Med Paediatr Oncol 2017;38:22-7.
16. Fehrenbacher L, Capra AM, Quesenberry CP Jr., Fulton R, Shiraz P, Habel LA, *et al.* Distant invasive breast cancer recurrence risk in human epidermal growth factor receptor 2-positive T1a and T1b node-negative localized breast cancer diagnosed from 2000 to 2006: A cohort from an integrated health care delivery system. J Clin Oncol 2014;32:2151-8.
17. Rocque G, Onitilo A, Engel J, Pettke E, Boshoven A, Kim K, *et al.* Adjuvant therapy for HER2+breast cancer: Practice, perception, and toxicity. Breast Cancer Res Treat 2012;131:713-21.
18. Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, *et al.* High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 2009;27:5700-6.
19. Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N, *et al.* Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 2009;27:5693-9.
20. Zhou Q, Yin W, Du Y, Lu J. For or against adjuvant trastuzumab for pT1a-bN0M0 breast cancer patients with HER2-positive tumors: A meta-analysis of published literatures. PLoS One 2014;9:e83646.
21. Rodrigues MJ, Wassermann J, Albiges L, Brain E, Delaloge S, Stevens D, *et al.* Trastuzumab treatment in t1ab, node-negative, human epidermal growth factor receptor 2-overexpressing breast carcinomas. J Clin Oncol

2010;28:e541-2.
22. McArthur HL, Patil S. Benefits of Trastuzumab-Based Therapy for Women with Small, Node-Negative, HER2-Positive Breast Cancer. San Francisco, CA: ASCO Breast Cancer Symposium; 2009.
23. van Ramshorst MS, van der Heiden-van der Loo M, Dackus GM, Linn SC, Sonke GS. The effect of trastuzumab-based chemotherapy in small node-negative HER2-positive breast cancer. Breast Cancer Res Treat 2016;158:361-71.
24. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, *et al*. Efficacy and safety of trastuzumab in early breast cancer. Cochrane Rev 2012.
25. National Comprehensive Cancer Network. Available from: http://www.nccn.org. [Last accessed on 2017 Nov 21].
26. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, *et al.* Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-83.
27. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials. Cancer 2003;97:2869-79.
28. Valcovici M, Andrica F, Serban C, Dragan S. Cardiotoxicity of anthracycline therapy: Current perspectives. Arch Med Sci 2016;12:428-35.
29. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM, *et al.* Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther 2017;31:63-75.
30. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, *et al.* Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372:134-41.
31. Hayes DF, Thor AD, Dressler LG, Weaver D, Edgerton S, Cowan D, *et al.* HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 2007;357:1496-506.
32. Piccart-Gebhart M, Holmes E, Baselga J, de Azambuja E, Dueck AC, Viale G, *et al.* Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: Results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. J Clin Oncol 2016;34:1034-42.
33. Dang C, Lin N, Moy B, Come S, Sugarman S, Morris P, *et al.* Dose-dense doxorubicin and cyclophosphamide followed by weekly paclitaxel with trastuzumab and lapatinib in HER2/neu-overexpressed/amplified breast cancer is not feasible because of excessive diarrhea. J Clin Oncol 2010;28:2982-8.
34. Moreno-Aspitia A, Dueck AC, Ghanem-Cañete I, Patel T, Dakhil S, Johnson D, *et al.* RC0639: Phase II study of paclitaxel, trastuzumab, and lapatinib as adjuvant therapy for early stage HER2-positive breast cancer. Breast Cancer Res Treat 2013;138:427-35.
35. Weiss RB. The anthracyclines: Will we ever find a better doxorubicin? Semin Oncol 1992;19:670-86.
36. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: Molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev 2004;56:185-229.
37. Peng X, Chen B, Lim CC, Sawyer DB. The cardiotoxicology of anthracycline chemotherapeutics: Translating molecular mechanism into preventative medicine. Mol Interv 2005;5:163-71.
38. Lyman GH, Kuderer NM, Crawford J, Wolff DA, Culakova E, Poniewierski MS, *et al.* Predicting individual risk of neutropenic complications in patients receiving cancer chemotherapy. Cancer 2011;117:1917-27.
39. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, *et al.* Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006;24:5381-7.
40. Tuma R. Anthracycline therapy may be avoidable in early breast cancer, new studies suggest. J Natl Cancer Inst 2008;100:459-61.
41. Slamon DL, Swain SM, Buyse M. Primary results from BETH, a phase 3 controlled study of adjuvant chemotherapy and trastuzumab±bevacizumab in patients with HER2-positive, node-positive, or high-risk node-negative breast cancer. San Antonio Breast Cancer Symposium; 2013.
42. Savage L, Andrea Widener A. Anthracyclines improve survival in HER2-positive breast cancer patients. J Natl Cancer Inst 2008;100:1.
43. Muss HB, Thor AD, Berry DA, Kute T, Liu ET, Koerner F, *et al.* C-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 1994;330:1260-6.
44. Gennari A, Sormani MP, Pronzato P, Puntoni M, Colozza M, Pfeffer U, *et al.* HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: A pooled analysis of randomized trials. J Natl Cancer Inst 2008;100:14-20.
45. Dhesy-Thind B, Pritchard KI, Messersmith H, O'Malley F, Elavathil L, Trudeau M, *et al.* HER2/neu in systemic therapy for women with breast cancer: A systematic review. Breast Cancer Res Treat 2008;109:209-29.
46. Pritchard KI, Messersmith H, Elavathil L, Trudeau M, O'Malley F, Dhesy-Thind B, *et al.* HER-2 and topoisomerase II as predictors of response to chemotherapy. J Clin Oncol 2008;26:736-44.