Recommendations for use of Chemotherapy

for the treatment of advanced breast cancer

JULY 2010 | Incorporates published evidence to December 2009

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY NATIONAL BREAST AND OVARIAN CANCER CENTRE (NBOCC)*

This document supplements guideline recommendation 25 on the use of *chemotherapy* for the management of *advanced breast cancer* contained in the National Breast Cancer Centre (NBCC)* *Clinical practice guidelines for the management of advanced breast cancer,* 2nd edition, 2001 (pages 9-10).[1]

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Purpose

This guideline includes statements and recommendations based on available, high-level evidence about the use of *chemotherapy* for the treatment of *advanced breast cancer*. The guideline provides health professionals with information designed to help them make management recommendations for improved patient outcomes. NBOCC* also develops information specifically for consumers about the diagnosis and treatment of advanced (secondary) breast cancer.

Endorsed by:

The Royal Australian and New Zealand College of Radiologists®
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Background

Advanced breast cancer includes locally advanced and *metastatic breast cancer*.[1] The goals of treatment in advanced breast cancer are to maximise length of life (overall survival) and quality of life.

There are a number of important components of clinical care for women with advanced breast cancer. These include using anti-cancer treatments to control disease-related symptoms and slow progression of disease, minimising treatment-related toxicity, and reducing the intrusion of the disease and treatment on a woman's life. Improvements in cancer treatment mean that some women will live for many years after a diagnosis of advanced breast cancer.

The standard *systemic treatments* for women with advanced breast cancer include chemotherapy, *targeted therapy* and *endocrine therapy*.[†]

Chemotherapy drugs used to treat advanced breast cancer include:

- alkylating agents, e.g. cyclophosphamide
- anthracyclines, e.g. doxorubicin, epirubicin
- antimetabolites, e.g. capecitabine, 5-fluorouracil, gemcitabine, methotrexate
- taxanes, e.g. docetaxel, *paclitaxel*, nab-paclitaxel
- vinorelbine.

Targeted therapies used to treat advanced breast cancer include:

- bevacizumab, lapatinib and trastuzumab.[‡]

The selection of specific chemotherapy drugs, combinations, doses, schedules and durations is based on:

- the pathological characteristics of the tumour, especially whether it expresses higher-than normal levels of the HER2 protein (HER2-positive tumours)
- the clinical characteristics of the tumour, especially its extent and growth rate
- the woman's past exposure and response to chemotherapy
- co-morbidities
- quality of life considerations including unwanted effects of chemotherapy
- the woman's preferences
- the woman's age
- practical considerations.

[†] For a summary of current evidence for endocrine therapy in advanced breast cancer, refer to NBOCC's* *Recommendations for use of endocrine therapy for the treatment of hormone receptor-positive advanced breast cancer.*[2]

[‡] For a summary of current evidence for trastuzumab in advanced breast cancer, refer to NBCC's* *Recommendations for use of trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer.*[3]

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Clinical practice recommendations

Please see statements of evidence on which the following recommendations are based.

Recommendations to individuals should be based on their circumstances, the absolute benefits and harms of treatment, and their personal preferences. These factors should be discussed with the woman.[8] Women receiving *chemotherapy* should be reviewed regularly and monitored for adverse events.

RECOMMENDATIONS	LEVEL OF EVIDENCE[9]	REFERENCE
In women with advanced breast cancer:		
There are several specific chemotherapy drugs and/or and combinations with similar efficacy in any given situation In general: - combination chemotherapy should be considered for women with little or no previous exposure to chemotherapy, widespread or rapidly progressing disease, and few or no co-morbidities - sequential single-agent chemotherapy should be considered for women with limited or indolent disease, previous exposure to chemotherapy,or significant co-morbidities	I II III	Cochrane[5] Sledge[10] Soto[11]
In women with visceral hormone receptor-positive disease that is extensive or rapidly progressing, initial chemotherapy should be considered in preference to initial endocrine therapy	I	Cochrane[5]
Duration of chemotherapy		
Tumour response should be assessed every 6-12 weeks (2-3 cycles) during chemotherapy	IV	
If disease control (stable disease or better) is confirmed and toxicity is tolerable, then chemotherapy should be continued for 18-24 weeks (6-8 cycles)	I	Gennari[12]
Extending chemotherapy beyond the standard duration (18-24 weeks; 6-8 cycles) is an option if toxicity is minimal and the goal is to delay progression Extending chemotherapy beyond the standard duration has little or no effect on overall survival	I	Gennari[12]
Taxanes		
Single-agent taxanes are an alternative to *anthracyclines* for first-line treatment for women with advanced breast cancer	I	Picart-Gebhart[13]
Combination chemotherapy that includes a taxane should be considered for women who have rapidly progressing or extensive visceral disease and limited previous exposure to chemotherapy	II	Sledge[10]
Paclitaxel The recommended dose and schedule for weekly paclitaxel is 80 mg/m2, with a one week break every 4-8 weeks according to toxicity and the woman's preferences	II II	CALGB 9840[14] CALGB 9342[15]

RECOMMENDATIONS	LEVEL OF EVIDENCE[9]	REFERENCE
The recommended dose for 3-weekly paclitaxel is 175 mg/m2 given over 3 hours		
Docetaxel The recommended dose and schedule for 3-weekly docetaxel is 75-100 mg/m^2	II	Harvey[16]
Albumin-bound paclitaxel Nanoparticle albumin-bound paclitaxel is an alternative to 3-weekly paclitaxel, but has not been compared with standard paclitaxel given weekly[a]	II	Gradishar[17] Guan[18]
Antimetabolites		
Capecitabine as first-line chemotherapy Single-agent capecitabine is an option for women for whom more intensive chemotherapy is not appropriate	II	Stockler[20]
Antimetabolites and taxanes		
Capecitabine and docetaxel The combination of capecitabine and docetaxel is an option for women with rapidly progressing or extensive visceral disease, good performance status and limited exposure to previous chemotherapy	II	O'Shaughnessy[21]
Gemcitabine and paclitaxel The combination of gemcitabine and paclitaxel is an option for women with rapidly progressing or extensive visceral disease, good performance status and limited exposure to previous chemotherapy[b]	II	Albain[22]
Targeted therapies		
Trastuzumab Recommendations for women with HER2-positive *advanced breast cancer* are detailed in NBCC's* guideline *Recommendations for use of trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer*[3]		
Bevacizumab with first- or second-line chemotherapy for metastatic breast cancer The routine addition of bevacizumab to chemotherapy is not recommended because the benefits do not outweigh the additional adverse effects[c]	II	ECOG E2100[23] AVADO[24] Miller[25]
Lapatinib after progression of disease on trastuzumab The combination of lapatinib and capecitabine is a good option for women with disease that has progressed afterchemotherapy with an anthracycline, a taxane and trastuzumab[d]	II	Geyer[26,27]

[a]A recent trial showed that first-line treatment with nab-paclitaxel significantly improved progression-free survival for women with *metastatic breast cancer* compared with 3-weekly docetaxel.[19]

[b] Preliminary results from a recent trial indicate that the addition of a PARP inhibitor to gemcitabine/carboplatin compared with gemcitabine/carboplatin alone shows potential benefit for progression-free survival and overall survival for women with triple negative metastatic breast cancer.[28]

[c] A recent trial showed that the addition of bevacizumab to first-line treatment with capecitabine/taxane/anthracycline significantly improved progression-free survival for women with HER2-negative metastatic breast cancer.[29]

[d] A recent trial showed that the combination of lapatinib and trastuzumab significantly improved progression-free survival compared with lapatinib alone for women with HER2-positive metastatic breast cancer.[30]

Statements of evidence

The following statements of evidence support the NBOCC* recommendations for use of chemotherapy for the treatment of *advanced breast cancer*.

STATEMENTS	LEVEL OF EVIDENCE[9]	REFERENCE
In women with advanced breast cancer:		
Combination *chemotherapy* increases response rates, time to progression, toxicity and overall survival, compared with single-agent chemotherapy, not including sequential use of the same drugs	I	Cochrane[5]
Combination chemotherapy increases response rates and toxicity, but not time to progression or overall survival, compared with sequential use of the same drugs as single agents	II	Sledge[10] Soto[11]
In women with hormone receptor-positive disease: • initial chemotherapy achieves similar overall survival to initial *endocrine therapy*, except in those with visceral disease that is extensive or rapidly progressing, where initial chemotherapy shows improved survival • endocrine therapy has fewer adverse effects than chemotherapy	I	Cochrane[5]
Dose		
Higher-than-standard doses of chemotherapy increase tumour response and toxicity, but not time to progression or overall survival, compared with standard doses	I	Cochrane[5]
Lower-than-standard doses of chemotherapy do not improve quality of life and survival, compared with standard doses	II	Tannock[37]
Duration		
Extending chemotherapy beyond the standard duration (18–24 weeks; 6-8 cycles) delays progression but has limited effect on overall survival	I	Gennari[12]
Shorter-than-standard durations (less than 18-24 weeks) of chemotherapy result in reduced overall survival and	II	Coates[36]

STATEMENTS	LEVEL OF EVIDENCE[9]	REFERENCE
quality of life		
Taxanes		
Single-agent taxanes give similar response rates and overall survival, but shorter time to progression compared with anthracyclines	I	Piccart-Gebhart[13]
Taxane-based combination chemotherapy increases response rates and time to progression, but not overall survival, compared with anthracyclines	II	Sledge[10]
Paclitaxel		
When compared with 3-weekly paclitaxel, use of weekly paclitaxel: • increases time to progression and overall survival • causes less myelosuppression, but more neuropathy • requires more clinic visits	II	CALGB 9840[14]
For 3-weekly paclitaxel: • increasing the dose beyond 175mg/m^2 increases toxicity, but not response rate, survival or quality of life	II	CALGB 9342[15]
Docetaxel		
For 3-weekly docetaxel: • increasing the dose from 75 mg/m^2 to 100 mg/m^2 increases response rates and toxicity, but not time to progression or overall survival • reducing the dose from 75 mg/m^2 to 60 mg/m^2 • decreases toxicity	II	Harvey[16]
Docetaxel versus paclitaxel		
3-weekly docetaxel and weekly paclitaxel both increase response rates, time to progression and overall survival, when compared with 3-weekly paclitaxel	II	Jones[34] CALGB 9840[14]
No randomised trials in advanced breast cancer have directly compared 3-weekly docetaxel with weekly paclitaxel		
When compared with paclitaxel, docetaxel causes: • more myelosuppression and gastro-intestinal toxicity • less neuropathy and allergic reactions	II	Jones[34]
Albumin-bound paclitaxel		
When compared with standard 3-weekly paclitaxel, nanoparticle albumin-bound paclitaxel: • increases response rate and time to progression, but not overall survival	II	Gradishar[17]
• causes more neuropathy, fatigue and gastrointestinal toxicity, but less neutropenia and allergic reactions	II	Guan[18]

STATEMENTS	LEVEL OF EVIDENCE[9]	REFERENCE
Nanoparticle albumin-bound paclitaxel has not been compared with standard paclitaxel given weekly		
Antimetabolites		
Capecitabine as first-line chemotherapy for metastatic breast cancer		
For women for whom more intensive chemotherapy is not appropriate, capecitabine improves overall survival and is better tolerated than oral cyclophosphamide, methotrexate and fluorouracil 5FU (CMF)	II	Stockler[20]
Antimetabolites and taxanes		
Capecitabine and docetaxel		
In women previously treated with an *anthracycline*, the combination of capecitabine and docetaxel, compared with single-agent 3-weekly docetaxel: • increases response rates, time to progression and overall surviva • increases toxicity	II	O'Shaughnessy[21]
Gemcitabine and paclitaxel		
In women previously treated with an anthracycline, the combination of gemcitabine and paclitaxel, compared with single-agent 3-weekly paclitaxel: • increases response rate, time to progression and overall survival • increases toxicity	II	Albain[22]
Targeted therapies		
Trastuzumab		
For women with HER2-positive advanced breast cancer, see NBCC's* guideline *Recommendations for use of trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer*[3]		
Bevacizumab with first-line chemotherapy for metastatic breast cancer		
When compared with weekly paclitaxel alone, the addition of bevacizumab: • improves response rates and time to progression, but not overall survival • causes more hypertension and proteinuria	II	ECOG E2100[23, 39, 40]
When compared with 3-weekly docetaxel alone, the addition of bevacizumab: • improves response rates and time to progression, but not overall survival • causes more febrile neutropenia	II	AVADO[24]
Bevacizumab with second- or third-line chemotherapy for metastatic breast cancer		
In women previously treated with an anthracycline and taxane, the addition of bevacizumab to capecitabine, compared with capecitabine alone: • improves response rates, but not time to progression or overall survival	II	Miller[25]

STATEMENTS	LEVEL OF EVIDENCE[9]	REFERENCE
• causes more hypertension, proteinuria and hand-foot syndrome		
Lapatinib after progression on trastuzumab		
When compared with capecitabine alone, the addition of lapatinib after progression on trastuzumab: • improves response rates and time to progression, but not overall survival • causes more diarrhoea, dyspepsia, liver dysfunction and rash	II	Geyer[26, 27]

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Summary of evidence

The statements and recommendations about the use of chemotherapy for women with *advanced breast cancer* are based on:

- a review of 63 randomised trials of chemotherapy in *metastatic breast cancer* published between 2000 and 2007[4]
- a Cochrane review investigating single-agent versus combination chemotherapy for metastatic breast cancer[5]
- a review of randomised trials comparing taxane-containing regimens for metastatic breast cancer[6]
- a review of randomised trials of adding targeted agents to a chemotherapy regimen for metastatic breast cancer.[7]

Additional relevant articles and two significant abstracts, published after the completion of these reviews up until December 2009, have also been considered.

No trials have directly compared chemotherapy with best supportive care in women with advanced breast cancer. Strong indirect evidence that chemotherapy improves survival and quality of life comes from older randomised trials of different doses and durations of chemotherapy,[1] and more recent trials comparing various chemotherapy regimens.

Chemotherapy improves overall survival and quality of life by reducing the tumour size, growth rate or both, in women with responsive tumours. However, chemotherapy can also cause adverse effects.[1]

Differences between the effect of various established chemotherapy drugs and regimens on overall survival are modest in women with advanced breast cancer. Treatment decisions should be based on consideration of the woman's specific circumstances, attitudes and preferences, as well as pertinent high-quality evidence from randomised trials.

Summary of trial or study results

The most commonly measured efficacy endpoints in *chemotherapy* trials are tumour response rate, progression-free survival and overall survival. Of these, the most critical is overall survival.

The evidence that chemotherapy improves overall survival in *advanced breast cancer* is indirect but compelling. However, significant benefits seen in overall survival for one chemotherapy regimen over another are relatively small in *clinical trials*. Superiority for these endpoints of one regimen over another will also influence treatment decisions, particularly where disease is rapidly progressing and a quick response is necessary.

Both quality of life and treatment toxicity are important factors to be considered. While toxicity is generally well-recorded in clinical trials, quality of life is less frequently measured and the reported analyses of quality of life data are often superficial.

Overall survival

A review[4] of 63 trials, including over 21,000 women, identified eight trials that reported a statistically significant overall survival benefit ranging from 3-7 months (see Table 1).

Table 1. *Chemotherapy* trials in *advanced breast cancer* with an overall survival benefit (p less than 0.05)

Trial	Arm A	Arm B	Number of patients (n)	OS Arm A (months)	OS Arm B (months)	p-value
Feher 2005[31]	Epirubicin	Gemcitabine	410	19.1	11.8	0.0004
O'Shaughnessy 2002[21]	Docetaxel/ capecitabine	Docetaxel	511	14.5	11.5	0.01
Jassem 2001[32]	Doxorubicin/ paclitaxel	FAC	267	23.3	18.3	0.01
Albain 2008[22]	Paclitaxel/ gemcitabine	Paclitaxel	529	18.5	15.8	0.02
Bontenbal 2005[33]	Docetaxel/ doxorubicin	FAC	216	22.6	16.2	0.02
Stockler 2007[20]	Intermittent or continuous capecitabine	CMF	325	22.0	18.0	0.02
Jones 2005[34]	Docetaxel	Paclitaxel	449	15.4	12.7	0.03
Icli 2005[35]	Oral etoposide/ cisplatin	Paclitaxel	201	14.0	9.5	0.04

Notes: OS = overall survival; FAC = 5-fluorouracil/doxorubicin/cyclophosphamide; CMF = cyclophosphamide/ methotrexate/5-fluorouracil

A Cochrane meta-analysis[5] found that combination chemotherapy improved tumour response rates, time to progression and overall survival, but was associated with higher rates of toxicity, compared with single-agent chemotherapy. However, very few such trials specifically compared a combination regimen with the sequential use of the component agents. In two trials[10,11] that did so, differences in time to progression (after both drugs) and overall survival were not seen, suggesting that the sequential use of single agents is safe and effective in the absence of rapidly progressive disease.

Older trials[36,37] have shown that lower-than-standard doses or very short durations of chemotherapy may be associated with reduced overall survival compared to standard doses. A Cochrane review[38] showed that very high dose chemotherapy did not improve overall survival and a 2008 meta-analysis[12] found that extending chemotherapy beyond the standard duration (18-24 weeks) had little effect on overall survival. Thus optimal overall survival is achieved when standard doses and durations of conventional drug regimens are used.

Progression-free survival and response rate

In trials published between 2000 and 2007, 22 trials[4] reported statistically significant differences in progression-free survival, and 19 trials[4] reported significant differences in response rate.Considered together, these trials[4] showed improved progression-free survival or response rates for combinations compared with single agents, *anthracyclines* compared with non-anthracycline regimens, and *taxanes* compared with non-taxane regimens.

Targeted therapies

How best to incorporate *targeted therapies* into *chemotherapy* regimens is the subject of ongoing trials. Trials[25-27, 39] testing the addition of lapatinib or bevacizumab have demonstrated some clinical benefits, but not differences in overall survival. A trial[26, 27] in women with HER2-positive breast cancer that had progressed after trastuzumab, showed that the addition of lapatinib to capecitabine improved response rate and time to progression, but not overall survival, compared with capecitabine alone.

Quality of life

Only a third of the 63 trials[4] identified in the 2000-2007 review mentioned formal quality of life measurements in the abstract. While toxicity is sometimes used as a surrogate for quality of life, two important older trials[36, 37] showed that toxicity and quality of life are not always closely linked. These trials[36, 37] showed that strategies to limit toxicity (by lowering either the dose or duration of chemotherapy) led to decreased quality of life.

Table 2. Common *chemotherapy* drugs and their side effects

Please see Statements of evidence for further evidence on adverse effects of chemotherapy drugs.

Class/agent	Characteristic side effects of common chemotherapy drugs
Alkylating agents[1] Cyclophosphamide	Bladder irritation, fatigue, hair loss, lowered blood counts, nausea/vomiting
Anthracyclines[1] Doxorubicin, epirubicin	Cardiac toxicity, fatigue, lowered blood counts, mouth ulcers, nausea/vomiting
Antimetabolites[1] Capecitabine	Diarrhoea, fatigue, hand-foot syndrome, nausea, stomatitis
Taxanes[1] Docetaxel, paclitaxel	Allergic reactions *paclitaxel*, fatigue, hair loss, lowered blood counts, muscle aches, neurological damage
Vinorelbine[1]	Fatigue, injection site pain, hair loss (moderate), lowered blood counts, neuropathy
Targeted therapies	

Class/agent	Characteristic side effects of common chemotherapy drugs
Bevacizumab[39]	Cerebrovascular ischemia, fatigue, headache, hypertension, infection, sensory neuropathy, proteinuria
Lapatinib[26]	Diarrhoea, dyspepsia, fatigue, hand-foot syndrome, nausea/vomiting, rash
Trastuzumab[3]	Anaemia, cardiac dysfunction, infection, leukopenia, neutropenia

Strengths and weaknesses of the evidence

The main strength of the evidence reviewed is the long history of well-conducted randomised trials testing different *chemotherapy* strategies in *advanced breast cancer*. A major limitation of the evidence is the paucity of data about the effects of different treatments on quality of life and symptom control.

Unanswered questions

Important unanswered questions about the use of *chemotherapy* in *advanced breast cancer* are outlined below:

- What is the optimal duration of chemotherapy, especially when combined with targeted therapy?
- How would clinical outcomes improve by individualising chemotherapy according to laboratory measures of tumour sensitivity?
- What is the significance of changes in tumour markers and genetic profiling for use of chemotherapy?
- What is the optimal duration of *targeted therapy* when combined with chemotherapy?
- What evidence is available from *clinical trials* for treatment of *metastatic breast cancer* beyond the first-line setting?
- What are the quality of life and symptom control issues associated with the use of chemotherapy?
- How could chemotherapy be used in association with *endocrine therapies* and supportive therapies?
- When disease progresses, when should *targeted therapies* be discontinued?

Ongoing and additional trials or studies

A number of ongoing trials are investigating the use of *chemotherapy* for the treatment of *advanced breast cancer*. Further detail about ongoing *clinical trials* can be obtained from the following websites: www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and www.controlled-trials.com

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Membership of NBOCC* Chemotherapy Working Group

This guideline was developed by a multidisciplinary working group convened by NBOCC*.

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* In July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

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The development of this guideline was overseen by a multidisciplinary working group convened by NBOCC*: Dr Karen Luxford (Facilitator), Dr David Blakey, Professor Phyllis Butow, Ms Helen Collyer (deceased), Ms Sally Crossing AM, Associate Professor Jane Dahlstrom, Dr Craig Murphy, Ms Janet Rice, Dr Catherine Shannon, Ms Ann Town (deceased), Professor Patsy Yates.

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Systematic Reviews

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External Review

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Pharmaceutical Benefits Scheme listings for drugs mentioned in this guideline for the treatment of advanced or *metastatic breast cancer* are available at www.pbs.gov.au

The Herceptin® Program

Trastuzumab is subsidised (via The Herceptin® Program funded by the Australian Government: www.medicareaustralia.gov.au) for the treatment of patients with HER2-positive metastatic breast cancer:

- in combination with *taxanes*, for patients who have not received *chemotherapy* for metastatic disease, or
- as monotherapy, for treatment of patients who have received one or more chemotherapy regimen(s) for metastatic disease.

Development process

Priority topic areas for NBOCC* guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary Working Group,

including consumers, is established for each topic identified and is involved in all aspects of guideline development. A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

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