



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*

The Faculty of Radiation Oncology



The Royal Australasian
College of Surgeons

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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 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 <i>anthracyclines</i> 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
<i>Paclitaxel</i> The recommended dose and schedule for weekly paclitaxel is 80 mg/m ² , with a one week break every 4-8 weeks according to toxicity and the woman's preferences The recommended dose for 3-weekly paclitaxel is 175 mg/m ² given over 3 hours	II II	CALGB 9840 ¹⁴ CALGB 9342 ¹⁵
<i>Docetaxel</i> The recommended dose and schedule for 3-weekly docetaxel is 75-100 mg/m ²	II	Harvey ¹⁶
<i>Albumin-bound paclitaxel</i>	II	Gradishar ¹⁷ Guan ¹⁸



RECOMMENDATIONS	LEVEL OF EVIDENCE ⁹	REFERENCE
Nanoparticle albumin-bound paclitaxel is an alternative to 3-weekly paclitaxel, but has not been compared with standard paclitaxel given weekly ^a		
Antimetabolites		
<i>Capecitabine as first-line chemotherapy</i> Single-agent capecitabine is an option for women for whom more intensive chemotherapy is not appropriate	II	Stockler ²⁰
Antimetabolites and taxanes		
<i>Capecitabine and docetaxel</i> 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
<i>Gemcitabine and paclitaxel</i> 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		
<i>Trastuzumab</i> Recommendations for women with HER2-positive <i>advanced breast cancer</i> are detailed in NBCC's* guideline <i>Recommendations for use of trastuzumab (Herceptin[®]) for the treatment of HER2-positive breast cancer</i> ³		
<i>Bevacizumab with first- or second-line chemotherapy for metastatic breast cancer</i> 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
<i>Lapatinib after progression of disease on trastuzumab</i> The combination of lapatinib and capecitabine is a good option for women with disease that has progressed after chemotherapy 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 <i>chemotherapy</i> 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:		
<ul style="list-style-type: none"> 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 quality of life	II	Coates ³⁶
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
<i>Paclitaxel</i>		
When compared with 3-weekly paclitaxel, use of weekly paclitaxel: <ul style="list-style-type: none"> increases time to progression and overall survival 	II	CALGB 9840 ¹⁴



STATEMENTS	LEVEL OF EVIDENCE ⁹	REFERENCE
<ul style="list-style-type: none"> causes less myelosuppression, but more neuropathy requires more clinic visits 		
For 3-weekly paclitaxel: <ul style="list-style-type: none"> increasing the dose beyond 175mg/m² increases toxicity, but not response rate, survival or quality of life 	II	CALGB 9342 ¹⁵
<i>Docetaxel</i>		
For 3-weekly docetaxel: <ul style="list-style-type: none"> increasing the dose from 75 mg/m² to 100 mg/m² increases response rates and toxicity, but not time to progression or overall survival reducing the dose from 75 mg/m² to 60 mg/m² decreases toxicity 	II	Harvey ¹⁶
<i>Docetaxel versus paclitaxel</i>		
3-weekly docetaxel and weekly paclitaxel both increase response rates, time to progression and overall survival, when compared with 3-weekly paclitaxel No randomised trials in advanced breast cancer have directly compared 3-weekly docetaxel with weekly paclitaxel	II	Jones ³⁴ CALGB 9840 ¹⁴
When compared with paclitaxel, docetaxel causes: <ul style="list-style-type: none"> more myelosuppression and gastro-intestinal toxicity less neuropathy and allergic reactions 	II	Jones ³⁴
<i>Albumin-bound paclitaxel</i>		
When compared with standard 3-weekly paclitaxel, nanoparticle albumin-bound paclitaxel: <ul style="list-style-type: none"> increases response rate and time to progression, but not overall survival causes more neuropathy, fatigue and gastrointestinal toxicity, but less neutropenia and allergic reactions Nanoparticle albumin-bound paclitaxel has not been compared with standard paclitaxel given weekly	II II	Gradishar ¹⁷ Guan ¹⁸
Antimetabolites		
<i>Capecitabine as first-line chemotherapy for metastatic breast cancer</i>		
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		
<i>Capecitabine and docetaxel</i>		



STATEMENTS	LEVEL OF EVIDENCE ⁹	REFERENCE
<p>In women previously treated with an <i>anthracycline</i>, the combination of capecitabine and docetaxel, compared with single-agent 3-weekly docetaxel:</p> <ul style="list-style-type: none"> • increases response rates, time to progression and overall survival • increases toxicity 	II	O'Shaughnessy ²¹
<i>Gemcitabine and paclitaxel</i>		
<p>In women previously treated with an anthracycline, the combination of gemcitabine and paclitaxel, compared with single-agent 3-weekly paclitaxel:</p> <ul style="list-style-type: none"> • increases response rate, time to progression and overall survival • increases toxicity 	II	Albain ²²
Targeted therapies		
<i>Trastuzumab</i>		
For women with HER2-positive advanced breast cancer, see NBCC's* guideline <i>Recommendations for use of trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer</i> ³		
<i>Bevacizumab with first-line chemotherapy for metastatic breast cancer</i>		
<p>When compared with weekly paclitaxel alone, the addition of bevacizumab:</p> <ul style="list-style-type: none"> • improves response rates and time to progression, but not overall survival • causes more hypertension and proteinuria 	II	ECOG E2100 ^{23, 39, 40}
<p>When compared with 3-weekly docetaxel alone, the addition of bevacizumab:</p> <ul style="list-style-type: none"> • improves response rates and time to progression, but not overall survival • causes more febrile neutropenia 	II	AVADO ²⁴
<i>Bevacizumab with second- or third-line chemotherapy for metastatic breast cancer</i>		
<p>In women previously treated with an anthracycline and taxane, the addition of bevacizumab to capecitabine, compared with capecitabine alone:</p> <ul style="list-style-type: none"> • improves response rates, but not time to progression or overall survival • causes more hypertension, proteinuria and hand-foot syndrome 	II	Miller ²⁵
<i>Lapatinib after progression on trastuzumab</i>		
<p>When compared with capecitabine alone, the addition of lapatinib after progression on trastuzumab:</p> <ul style="list-style-type: none"> • 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 2007⁴
- a Cochrane review investigating single-agent versus combination chemotherapy for metastatic breast cancer⁵
- a review of randomised trials comparing taxane-containing regimens for metastatic breast cancer⁶
- 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 review⁴ 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-analysis⁵ 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 review³⁸ showed that very high dose chemotherapy did not improve overall survival and a 2008 meta-analysis¹² 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 trials⁴ reported statistically significant differences in progression-free survival, and 19 trials⁴ reported significant differences in response rate. Considered together, these trials⁴ 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 trials⁴ 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 <i>paclitaxel</i> , 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	
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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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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