



Evidence-based Series #1-12: Section 1

**The Role of Gemcitabine in the Management of
Metastatic Breast Cancer:
A Clinical Practice Guideline**

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**The full Evidence-based Series #1-12 is comprised of 3 sections
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Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review - Methods and Results

Question

- What is the role of gemcitabine, alone or in combination, as first-line chemotherapy in women with metastatic breast cancer?
- What is the role of gemcitabine, alone or in combination, as second-line or greater chemotherapy in women with metastatic breast cancer?

Target Population

Women with metastatic breast cancer.

Recommendations and Key Evidence

The combination of gemcitabine and docetaxel may be considered as an alternative to capecitabine and docetaxel for first- or second-line chemotherapy in patients where the toxicity of the capecitabine and docetaxel regimen is a concern.

- One randomized phase III study reported by Chan et al in abstract form (1,2) found no significant difference between the combination of gemcitabine (1000 mg/m² on days one and eight) and docetaxel (75 mg/m² on day one) every 21 days and the combination of capecitabine (1250 mg/m² twice a day for 14 days) and docetaxel (as above) every 21 days in terms of objective response rate (ORR), progression-free survival (PFS), duration of response, or time-to-progression (TTP). However, patients receiving gemcitabine plus docetaxel experienced significantly less hand-foot syndrome, diarrhea, and mucositis than those receiving capecitabine plus docetaxel.

Qualifying Statements

- The efficacy of capecitabine and docetaxel over docetaxel alone was demonstrated in a trial by O’Shaughnessy et al (3) but the clinical utility of this regimen has been hampered by significant toxicities, especially hand-foot syndrome and mucositis.

For patients with metastatic breast cancer who have received prior (neo)adjuvant anthracycline therapy, the combination of gemcitabine plus paclitaxel is superior compared to paclitaxel alone as first-line chemotherapy.

- A randomized controlled trial reported at the 2003 and 2004 American Society of Clinical Oncology (ASCO) meetings (4-9) compared the combination of gemcitabine (1250 mg/m² on days one and eight) and paclitaxel (175 mg/m² on day one) every 21 days to the same dosage and schedule of paclitaxel without gemcitabine in patients with metastatic breast cancer who had previously received adjuvant or neoadjuvant anthracycline chemotherapy. That trial found a significantly superior ORR (40.8% versus 22.1%, p<0.0001), median TTP (5.2 months versus 2.9 months, hazard ratio [HR] 0.650, 95% confidence interval [CI] 0.524 to 0.805), and overall survival (18.5 months versus 15.8 months, HR 0.775, 95% CI 0.627 to 0.959) in patients treated with the combination regimen.

Qualifying Statements

- Patients who received the combination regimen experienced a higher rate of neutropenia (48% versus 11%) over those treated with paclitaxel alone.
- The clinical relevance of this regimen in Ontario is questionable as docetaxel has been the standard taxane used in the metastatic setting.

Single-agent gemcitabine is NOT recommended for women with metastatic breast cancer who are being considered for first-line single-agent anthracycline chemotherapy.

The combination of gemcitabine, epirubicin, and paclitaxel (GET) is NOT recommended as first-line chemotherapy for women with metastatic breast cancer who are being considered for anthracycline-based combination chemotherapy.

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- One randomized phase III study reported by Feher et al in (10) compared epirubicin (35 mg/m² on days one, eight, and 15) with gemcitabine (1200 mg/m² on days one, eight, and 15) every 28 days in postmenopausal patients aged 60 or older. No significant differences were found between the treatment arms in terms of time to response and duration of response. Epirubicin was significantly better than gemcitabine in terms of ORR (40.3% versus 16.4%, p<0.0001), TTP (6.1 months versus 3.4 months, p=0.0001), and overall survival (19.1 months versus 11.8 months, p=0.004).
- A randomized controlled trial reported by Zielinski et al (11) compared the combination of gemcitabine (1000 mg/m² on days one and four), epirubicin (90 mg/m² on day one), and paclitaxel (175 mg/m² on day one), with the combination of 5-fluorouracil (500 mg/m²), epirubicin (90 mg/m²), and cyclophosphamide (500 mg/m²), all on day one. Both combinations used a 21-day cycle. Patients were required to have had one prior non-anthracycline adjuvant chemotherapy. That trial found no significant differences in terms of ORR, TTP, or overall survival and found significantly higher haematological toxicities, polyneuropathy, and mucositis in the gemcitabine-containing arm.

Qualifying Statements

- Doxorubicin given as a single agent or in combination is currently approved and funded for women with metastatic breast cancer in Ontario. Epirubicin-based combinations are not funded for women with metastatic breast cancer in Ontario

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