Over the past decade mortality of early breast cancer has significantly decreased due to earlier detection, and more effective and more frequent use of (neo-)adjuvant systemic treatment, i.e., chemotherapy, HER2 targeted therapy and endocrine therapy. With current third generation chemotherapy schedules, with the addition of taxanes to anthracyclines and cyclophosphamide, overall survival has clearly improved. However, anthracycline/taxane combination chemotherapy is associated with an increased risk of myelotoxicity and febrile neutropenia (FN). Acknowledging the fact that FN may cause life-threatening infections, it was (inter)nationally agreed to offer primary G-CSF prophylaxis to patients at risk of FN (a risk of at least 20% per patient) in order to reduce the risk of FN. Actually, an increased risk of FN is the case when docetaxel is combined with anthracyclines or trastuzumab, or when given to patients ≥65 years of age as monotherapy. As a result (neo-)adjuvant chemotherapy or chemo-immunotherapy in breast cancer comes with considerable additional costs because of prophylactic treatments, also at a macro economic level because of the high incidence of breast cancer. In a time of rapidly increasing overall cancer care costs, considering ways to reduce costs without jeopardizing the quality of care becomes more and more important.

In Chapter one, a general introduction and outline of the thesis is presented. As, our research group had shown before, that FN incidence was generally the highest during the first two chemotherapy cycles, irrespective of tumor and chemotherapy type, with a rapid decline thereafter, we hypothesized that the benefit of G-CSF prophylaxis may largely disappear during later chemotherapy cycles. In this thesis we focussed on breast cancer patients treated with chemotherapy schedules with increased risk of FN. The aims of the studies presented were to investigate the effectiveness of primary G-CSF prophylaxis during the first two chemotherapy cycles only compared to primary G-CSF prophylaxis throughout all chemotherapy cycles; to assess the cost-effectiveness between the two treatment strategies; to describe the economic impact when quality-adjusted life-years (QALYs) and secondary G-CSF prophylaxis were incorporated in a model-based economic evaluation; to report the hematologic toxicity and to determine if there was a protective effect of prior chemotherapy or of prior G-CSF on the next cycle blood cell counts; and, to investigate whether concurrent or sequential use of docetaxel after doxorubicin/cyclophosphamide provides the best outcome in early stages and locally advanced breast cancer.

In Chapter 2, we report the main results of the ‘Two-to-Six’ study, in which the effectiveness of primary G-CSF prophylaxis during the first two chemotherapy cycles only (experimental arm, G-CSF 1-2 arm) was compared to primary G-CSF prophylaxis throughout all chemotherapy cycles (standard arm, G-CSF 1-6 arm) in patients at risk of FN. In this nationwide study, we included breast cancer patients with an indication
for 3-weekly chemotherapy in the adjuvant, neo-adjuvant or advanced setting and more than 20% risk of FN. G-CSF (pegfilgrastim) was administered 24-30 hours after chemotherapy in a 6 mg fixed dose. Primary endpoint was the percentage of patients who developed FN in both treatment arms. The incidence of FN was 36% (30 out of 83 patients) in the experimental arm as compared to 10% (8 out of 84 patients) in the standard treatment arm (relative risk 0.26 (95% CI, 0.13 to 0.54), with a peak incidence of 24% in the third cycle, i.e. the first cycle without G-CSF prophylaxis. Therefore, we conclude that primary G-CSF prophylaxis during all chemotherapy cycles is of clinical relevance.

To determine the cost-effectiveness of primary G-CSF prophylaxis in breast cancer patients at risk (>20%) of FN, an economic analysis based on patient data derived from the ‘Two-to-Six’ study is described in Chapter 3. Primary outcome was cost-effectiveness expressed as costs per patient with episodes of FN prevented. The analysis was carried out using a health care perspective. The mean total costs were €20,658 (95% CI €20,049 to €21,247) in the G-CSF 1-6 arm and €17,168 (95% CI €16,239 to €18,029) in the G-CSF 1-2 arm per patient. Costs of G-CSF and of chemotherapy determined 80% of the total costs. FN-related costs were higher in the G-CSF 1-2 arm, mainly dominated by hospitalization costs. The incremental cost-effectiveness ratio for G-CSF 1-6 cycles compared with G-CSF 1-2 cycles arm was €13,112 per patient with episode of FN prevented. We conclude that continued G-CSF is more effective, but more costly. Whether continued G-CSF prophylaxis is considered cost-effective depends on the willingness to pay per patient with episodes of FN prevented.

The threshold of the willingness to pay (WTP) per patient with FN episode prevented is not well established. However, for quality-adjusted life-years (QALYs) informal WTP values exist. We therefore developed a probabilistic decision-analytic Markov cohort model, described in Chapter 4, to compare the cost-effectiveness of primary G-CSF prophylaxis during the first two chemotherapy cycles only (without or with secondary prophylaxis) with primary G-CSF prophylaxis throughout all six chemotherapy cycles in breast cancer patients who had an increased risk (>20%) of FN. The QALYs ranged from 0.213 to 0.215 for all three strategies, whereas the costs were €17,014, €18,842 and €22,778 respectively. G-CSF prophylaxis limited to the first two chemotherapy cycles without secondary G-CSF prophylaxis is the most cost-effective strategy.

In Chapter 5 we evaluated the hematologic toxicity for both treatment arms. A possible protection against FN during later chemotherapy cycles could be due to intrinsic hematopoietic growth factor production as a result of chemotherapy-induced myelosuppression. On the other hand continued use of G-CSF prophylaxis may be less effective because of the lower baseline risk of FN in later chemotherapy cycles, as was
suggested from prior studies. The primary objective therefore was to analyze, whether there is indeed a protective effect of prior chemotherapy or of prior G-CSF on the next cycle blood cell counts. We investigated nadir blood cell counts over cycles 1 to 6 for patients in G-CSF 1-6 arm and over cycles 3 to 6 for patients in G-CSF 1-2 arm. We excluded patients with FN and patients with G-CSF or chemotherapy treatment modifications. In the G-CSF 1-6 arm, the median white blood cell count (WBC) slowly decreased from 10.8x10^9/l in cycle 1 to 7.5x10^9/l in cycle 6 and absolute neutrophil count (ANC) nadir decreased from 7.1x10^9/l to 5.5x10^9/l. The median WBC nadir in G-CSF 1-2 arm decreased from 1.2x10^9/l in cycle 3 to 0.9x10^9/l in cycle 6 and ANC nadir showed a grade 4 neutropenia of 0.1x10^9/l in cycle 3 through 6. We conclude that there is no protective effect of prior G-CSF or prior chemotherapy use on nadir blood counts in subsequent cycles, substantially confirming the results of the main trial.

Neoadjuvant chemotherapy is currently more applied; not only in locally advanced or borderline resectable disease but also in less advanced disease stages. The advantage of neoadjuvant therapy is the possibility of down-staging the primary tumor and the axilla, and therefore facilitates breast conserving therapy and/or obviates the need of completion axillary treatment. In Chapter 6 we investigated whether concurrent versus sequential use of docetaxel with or after doxorubicin/cyclophosphamide (TAC or AC-T, respectively) improves breast cancer outcome. For TAC chemotherapy primary G-CSF prophylaxis was recommended. AC-T resulted in a pCR in 21% and TAC in 16% of patients (odds ratio pCR was 1.44; 95%CI 0.67-3.10). In the AC-T arm without primary G-CSF prophylaxis the FN incidence was 23%, compared to 9% in the TAC arm with primary G-CSF prophylaxis. We conclude that both regimens are equally effective in achieving pCR, although this was reached at a lower cumulative dose per chemotherapy agent for patients treated with AC-T compared to those treated with TAC chemotherapy.