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Systematic review of efficacy of dose-dense versus non-dose-dense chemotherapy in breast cancer, non-Hodgkin lymphoma, and non-small cell lung cancer

Gary H. Lyman [a,*], Richard L. Barron [b], Jaime L. Natoli [c], Ross M. Miller [c]

[a] *Division of Medical Oncology, Department of Medicine, Duke University School of Medicine and the Duke Comprehensive Cancer Center, Durham, NC, USA*
[b] *Amgen Inc., Thousand Oaks, CA, USA*
[c] *Cerner LifeSciences, Beverly Hills, CA, USA*

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Abstract

Randomized controlled trials (RCTs) have suggested a potential advantage of dose-dense chemotherapy in improving disease-free and overall survival in patients with certain malignancies. This systematic review summarizes the literature on the efficacy of dose-dense chemotherapy across various cancers (breast cancer, non-Hodgkin lymphoma [NHL], and non-small cell lung cancer) and chemotherapy regimens. Among the 17 trials identified, few reported statistically significant differences between dose-dense and standard chemotherapy, and most were small with limited statistical power. Statistically significant differences in overall survival favoring dose-dense schedules were apparent among large RCTs in potentially curative settings such as early-stage breast cancer and NHL. Clinical and treatment heterogeneity demonstrated the

* Corresponding author. Tel.: +1 919 681 1604; fax: +1 919 681 7488.
E-mail address: gary.lyman@duke.edu (G.H. Lyman).

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flexibility of the dose-dense paradigm but also precluded quantitative meta-analysis of results. Further study of dose-dense schedules based on large RCTs is needed to demonstrate the consistency and generalizability of these findings.

Keywords: Dose-dense chemotherapy; Breast cancer; Non-Hodgkin lymphoma; Non-small-cell lung cancer

1. Background

In most human cancers, tumor cell growth follows a Gompertzian curve, which is characterized by an initial rapid growth of cells followed by a decrease in doubling rate as tumor size increases [1]. The Norton-Simon hypothesis suggests that chemotherapy efficacy can be enhanced by decreasing the interval between treatment cycles [2,3]. By decreasing the interval between treatment cycles, an approach known as dose-dense chemotherapy, cytotoxic agents interrupt this rapid growth phase and limit growth of tumor cells [2,3]. However, the clinical application of dose-dense schedules is limited by adverse events associated with myelosuppression, most notably chemotherapy-induced neutropenia (CIN) [4]. The advent of granulocyte colony stimulating factors (G-CSF) has decreased the incidence of CIN and enabled the delivery of dose-dense schedules [5].

A number of randomized controlled trials (RCTs) have supported the potential advantage of dose-dense chemotherapy enabled by G-CSF support in improving disease-free survival (DFS) and overall survival (OS) in patients with responsive and potentially curable malignancies, such as early-stage breast cancer (ESBC) and non-Hodgkin lymphoma (NHL) [6–8]. CALGB 9741 [6] compared a dose-dense, every-two-week schedule of doxorubicin (Adriamycin), cyclophosphamide (Cytoxan), and paclitaxel (Taxol) to a conventional, every-three-week schedule of the same drugs in more than 2000 women with lymph node-positive ESBC. Utilizing a 2×2 factorial design, CALGB 9741 examined both concurrent (AC-T) and sequential (A-T-C) approaches. Patients randomized to the dose-dense schedule received the same total dose of chemotherapy in 33% less time compared to a conventional, every-three-week schedule. After three years of follow-up, patients receiving dose-dense chemotherapy schedules demonstrated improved DFS (risk ratio [RR] = 0.74, $p = 0.010$) and OS (RR = 0.69, $p = 0.013$) compared to patients randomized to standard treatments.

Favorable results for dose-dense chemotherapy also have been reported for RCTs in patients with NHL, while other trials including a mix of early-stage and advanced stage patients have provided mixed results [7,8]. A 2010 systematic review evaluated RCTs of patients with solid tumors or lymphoma who were randomized to chemotherapy with or without G-CSF support and that reported both occurrence of secondary malignancies and overall mortality [9]. The six eligible trials comparing dose-dense to standard treatment schedules did not demonstrate an increase in secondary cancers but did show a 16% (95% CI: 9–22%; $p < 0.001$) relative risk reduction for overall mortality at a median of nearly five years of follow-up in favor of the dose-dense schedule [9].

Nevertheless, it remains unclear as to whether dose-dense chemotherapy is universally applicable and beneficial across a variety of cancers and chemotherapy regimens. In an effort to summarize the existing literature on the efficacy of dose-dense chemotherapy, we conducted a systematic review of comparative clinical trials of dose-dense chemotherapy in breast cancer, NHL, and non-small-cell lung cancer (NSCLC), as they represent the most common disease settings for dose-dense regimens [9]. The focus of this review was on the impact of dose-dense regimens on clinical outcomes relating to overall survival, progression, and tumor response.

2. Methods

2.1. Search strategy and publication selection

A systematic review of clinical trials was undertaken including a search of Ovid-MEDLINE, CancerLit, EMBASE, and the Cochrane Library to identify English-language publications on dose-dense cancer chemotherapy published between January 1, 1995 and October 6, 2010. Since the nomenclature and terminology for dose-dense chemotherapy schedules are not standardized, a wide variety of terms related to dose-dense chemotherapy (e.g., *dense*, *accelerated*, *compressed*) were included in addition to search terms related to the specific cancers of interest. References provided in relevant clinical trials and review publications also were assessed for additional primary publications not captured by the search strategy.

In an effort to capture all relevant trials on dose-dense chemotherapy for the three cancers of interest, no restriction was placed on specific chemotherapeutic agents, drug classes, or regimens. Trials were included if they compared a dose-dense regimen to a standard regimen; trials did not have to have a primary or secondary objective of testing a dose-dense hypothesis. Dose-dense chemotherapy was defined as any regimen that decreased the interval between cycles while maintaining the same drugs and total dose per treatment as other regimen(s) in the trial. RCTs that reduced or increased the dose per treatment were excluded, even if the duration between intervals was shortened. No restrictions were made with regard to G-CSF use in any treatment arms (e.g., reactive administration, prophylaxis).

Both randomized and non-randomized trials in patients with breast cancer, NHL, or NSCLC were included. Trials were required to report one or more of the following outcomes: OS, progression-free survival (PFS), time to