ELSEVIER

Critical Reviews in Oncology/Hematology 93 (2015) 203–210

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

A review of relative dose intensity and survival in patients with metastatic solid tumors

Laura J. Havrilesky[a,b], Maureen Reiner[c], Phuong Khanh Morrow[d], Holly Watson[d], Jeffrey Crawford[b,e,*]

[a] *Division of Gynecology Oncology, Duke University Medical Center, Durham, NC, USA*
[b] *Duke Cancer Institute, Durham, NC, USA*
[c] *Global Biostatistical Science, Amgen Inc., Thousand Oaks, CA, USA*
[d] *Hematology/Oncology, Amgen Inc., Thousand Oaks, CA, USA*
[e] *Division of Medical Oncology, Duke University Medical Center, Durham, NC, USA*

Accepted 1 October 2014

Contents

Abstract

Studies have shown that in the curative setting patients with cancer receiving chemotherapy at higher relative dose intensity (RDI) had better clinical outcomes than those receiving treatment at lower RDI. However, the impact of RDI in advanced/metastatic disease remains unclear. A review of the literature was performed to evaluate the relationship between RDI and survival in patients with metastatic lung, breast, or ovarian cancer receiving chemotherapy. Few studies attempted to specifically associate RDI with survival in a systematic way. Findings from studies that analyzed overall survival with a prespecified RDI threshold support the emerging perception that maintaining an RDI $\geq$ 85% has a favorable impact on survival. Nonetheless, these studies were limited by their retrospective nature. More studies are needed to further evaluate the impact of maintaining planned chemotherapy dose intensity on outcomes in metastatic solid tumors.

Keywords: Relative dose intensity; Survival; Outcomes; Metastatic disease; Lung cancer; Breast cancer; Ovarian cancer

* Corresponding author at: Duke Cancer Institute and Duke University Medical Center, Division of Medical Oncology; DUMC 3476, Durham, NC 27710, USA. Tel.: +1 919 681 9509; fax: +1 919 681 9599.
E-mail addresses: jeffrey.a.crawford@duke.edu, crawf006@mc.duke.edu (J. Crawford).

http://dx.doi.org/10.1016/j.critrevonc.2014.10.006
1040-8428/

1. Introduction

Relative dose intensity (RDI) is the ratio of the delivered dose intensity of chemotherapy to the standard (referenced) dose intensity. The variation in approaches used to estimate RDI has led to difficulty in the standardization of RDI evaluation across clinical trials and studies. Specifically, previous studies have calculated RDI for either selected agents, by averaging the RDI of individual agents within a regimen [1], or for all agents within a regimen [2], by estimating actual dose intensity relative to a reference (often the mean dose intensity throughout the treatment duration or the dose intensity of the first cycle [2,3]). Prior to the year 2000, most published findings of RDI were conducted in the adjuvant or early disease setting where the intent of treatment was cure and where the duration of chemotherapy regimens was fixed [4–10]. In these early studies, the RDI calculation was more straightforward in regard to the planned/standard dose intensity. Even then, however, there was often a lack of clarity regarding RDI calculation.

The Hryniuk model is the oldest, simplest, and most widely used method for RDI calculation [11]. Based on the Hryniuk model, delivered dose intensity is calculated as the total dose delivered divided by the total time to complete chemotherapy[1] [11]. RDI is calculated as the percentage of the delivered dose intensity divided by the standard dose intensity[2] [11].

Maintaining full chemotherapy dose intensity has been shown to improve clinical outcomes in various cancers, particularly in the curative setting. In patients with early-stage breast cancer, an RDI $\geq$ 85% was associated with longer disease-free survival and overall survival [3]. In patients with diffuse large B-cell lymphoma, an average RDI > 90% was associated with longer overall survival [12]. The ability to calculate RDI in the adjuvant setting is facilitated by the standardization of regimen dosing and duration. This can also be the case for diseases such as ovarian cancer, which although at diagnosis may be advanced or metastatic, is rendered appropriate for adjuvant medical treatment following optimal surgical debulking. In other cancers in the metastatic or recurrent setting, regimen duration may not be standardized but rather impacted primarily by disease response/progression and toxicity (often unrelated to neutropenia), making RDI calculation and evaluation across studies more difficult.

In order to clarify the existing evidence regarding the relationship between RDI and clinical outcomes, we performed a review of the literature with an emphasis on the association of RDI with survival outcomes in patients with advanced, metastatic, or recurrent lung, breast, or ovarian cancer who received chemotherapy. PubMed was searched for peer-reviewed English articles published between January 1, 2000 and April 30, 2013. The search terms included dose intensity, relative dose intensity, advanced, metastatic, recurrent, lung cancer, breast cancer, and ovarian cancer. The full list of search terms is presented in the Supplemental material. Selected studies reported both survival and RDI or dose intensity. Articles on radiotherapy, stem cell transplantation, and targeted therapy were excluded. Conference abstracts, review articles, editorials, letters, guidelines, addresses, case reports, comments, lectures, introductory journal articles, government publications, consensus development conference statements, news, and newspaper articles were also excluded.

[1] Delivered dose intensity (mg/m^2/unit time) = total dose delivered/total time to complete therapy.

[2] RDI (%) = (delivered dose intensity/standard dose intensity) × 100.

2. Studies identified in the literature review

Eighty-nine studies were identified (Fig. 1). As summarized in Table 1, 39 studies were on lung cancer, 37 were on breast cancer, and 13 were on ovarian cancer. The majority of studies (n = 59) were phase 1–3 clinical trials and evaluated therapies in the first-line setting (n = 49). Thirty studies did not identify a clinical trial phase in their study design and included cooperative group, observational, retrospective, prospective, and/or exploratory studies. Of the 89 studies reviewed, 26 estimated dose intensity, and 12 reported both RDI and overall survival. Fewer studies (n = 5) analyzed the association between RDI and overall survival by using a preplanned threshold for RDI or dose intensity.

2.1. Lung cancer

Six studies reported RDI and overall survival in metastatic lung cancer: five in non-small cell lung cancer (NSCLC) and one in small cell lung cancer [13–18]. Of these six studies, two analyzed overall survival by RDI (Table 2) [13,18]. In a retrospective NSCLC study, Brunetto et al. evaluated overall survival in 169 patients who received platinum-doublet chemotherapy using a prespecified RDI threshold of 90% and found that RDI across regimens was not associated with overall survival (platinum, P = 0.4; vinorelbine, P = 0.3; gemcitabine, P = 0.6) [13]. Conversely, in another retrospective NSCLC study, Luciani et al. examined overall survival in 107 elderly patients ($\geq$70 years) using a prespecified RDI threshold of 80% and found that patients receiving chemotherapy at a higher RDI had improved survival (P < 0.0001) [18].

The remaining four of the six lung cancer studies evaluated survival by either comparing different doses (e.g., "high" vs "low" dose) [15,17], different dosing schedules [14], or different agents [16]. These four studies did not directly investigate the effect of RDI on overall survival.

2.2. Breast cancer

Two studies reported RDI and overall survival in metastatic breast cancer (Table 3), and both analyzed overall survival by RDI or dose intensity [19,20]. In a small retrospective study, Battelli et al. evaluated survival in 41 patients