Clinical Oncology (2009) **21:** 532—535
doi:10.1016/j.clon.2009.04.005

Overview

Radiochemotherapy in the Treatment of Breast Cancer

N. S. Bese

Department of Radiation Oncology, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey

ABSTRACT:
Radiotherapy and chemotherapy have established roles in the multidisciplinary management of early breast cancer. The optimal integration of these treatment modalities is controversial. The most common approach is to deliver each treatment modality sequentially. For patients with close surgical margins or with other risk factors for local recurrences, initiation of adjuvant treatment with radiotherapy is recommended. A sandwich regimen is not the preferred schedule because of a decreased dose density for anthracyline- and taxane-based regimens. However, it can be an option for patients receiving adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF). Concomitant radio- and chemotherapy remain in principle an attractive treatment schedule to provide an additive interaction of tumour control and shortening the duration of the overall treatment of time. However, it should be avoided due to the potential risk of augmented cardiac and skin toxicity for anthracyclines. Recent studies revealed an increased locoregional control and a slight toxicity when radiotherapy was given concurrently with cyclophosphamide, mitoxantrone and fluorouracil (CNF). On the other hand, CNF is no longer considered as standard adjuvant chemotherapy in breast cancer because of reports of secondary acute myeloid leukaemias. Bese, N. S. (2009). *Clinical Oncology* 21, 532—535

Key words: Adjuvant treatment, breast cancer, chemotherapy, concomitant, concurrent, radiotherapy, sandwich, sequential

Statement of Search Strategies Used and Sources of Information

The present review was based on a systematic literature search of Medline (Pub Med by the National Library of Medicine, National Institutes of Health, Bethesda, Maryland, USA), last accessed 15 February 2009. The key words used were: radiotherapy, chemotherapy, breast cancer, adjuvant treatment, concomitant, concurrent, sequential, sandwich.

Introduction

Radiotherapy plays an essential role in the multimodal treatment of breast cancer. It has a major effect on local control, and effective and safe radiotherapy can improve overall survival rates for patients with early stage disease [1—3]. The use of chemotherapy improves disease-free and overall survival in women with early breast cancer [4] and in addition its role on local control has been established [5,6]. The optimal sequence of these two treatment modalities has yet to be defined. For adjuvant treatment, radiotherapy and chemotherapy can be delivered: (a) sequentially (chemotherapy followed by radiotherapy or vice versa); (b) as a sandwich regimen (radiotherapy is delivered after a few courses of chemotherapy and chemotherapy courses are continued afterwards); (c) radiotherapy and chemotherapy can be delivered concomitantly after the breast cancer surgery.

In this overview, current literature is reviewed regarding the efficacy and toxicity for different administration schedules to provide additional insight into the problem of optimal integration of these two modalities in the treatment of early breast cancer, including recommendations for countries with limited resources.

Sequential Administration of Radiotherapy and Chemotherapy in the Treatment of Early Breast Cancer

A major debate has existed whether radiotherapy or chemotherapy should be given first. In patients treated with breast-conserving surgery, there is a concern that delaying the initiation of radiotherapy to permit delivery of chemotherapy might lead to an increased risk of local recurrences. This concern is enhanced by the pooled analyses of 10 retrospective studies in which the local recurrence rate was 16% for patients who were treated initially with chemotherapy and 6% for patients who were treated initially with radiotherapy [7]. Additionally, the local recurrence rate seemed to be doubled if radiotherapy started more than 8 weeks after surgery. Most of these data are subject to criticism due to their retrospective nature.

The sole prospective randomised trial designed to evaluate the sequencing of chemotherapy (four courses of doxorubicin, cyclophosphamide, methotrexate, fluorouracil, prednisone) and radiotherapy after breast-conserving

0936-6555/09/210532+04 $36.00/0

surgery revealed that there were more local recurrences in the arm of patients who received chemotherapy first and more distant metastases in the arm of patients who received radiotherapy first as sites of first failure [8]. However, the updated report at 10 years showed no significant differences in patterns of first failure, event-free survival and overall survival rates [9]. A subset analyses showed a high rate of local recurrence in patients with close margins who were treated initially with chemotherapy. The limitations of the study were a small sample size to detect small but clinically important differences, inclusion of patients with positive or unknown margins, which does not reflect the current standards of breast-conserving surgery, and inadequate treatment of receptor-positive patients with tamoxifen, which has been shown to have an effect on local control [10].

More recently, the local control of patients due to additional delays in the initiation of radiotherapy with the addition of taxane-based chemotherapy regimens was addressed by the retrospective analyses of the prospective randomised trial of Cancer and Leukemia Group B (CALGB) 9344 [5]. In this study, among the patients treated with breast-conserving surgery, 125 women who were treated with doxorubicin and cyclophosphamide followed directly by radiotherapy and 144 patients who received doxorubicin and cyclophosphamide and paclitaxel and then radiotherapy were compared. Patients in this randomised trial presumably had negative surgical margins. Despite the further delay in the initiation of radiotherapy, the addition of paclitaxel was associated with a significantly decreased rate of locoregional recurrences at 5 years. Moreover, the addition of paclitaxel did not alter the delivery of radiotherapy, did not increase radiotherapy interruptions or the overall treatment time. This study indicates that more effective systemic therapy is more successful at decreasing the local tumour burden as well as eliminating systemic micrometastases effectively. On the basis of this study [5], it can be concluded that radiotherapy can be delivered after the completion of taxane-based chemotherapy. However, for patients with close surgical margins or with other risk factors for local recurrences, the initiation of radiotherapy should not be delayed.

Sandwich Regimens in the Treatment of Early Breast Cancer

In this treatment schedule, chemotherapy is interrupted with the administration of radiotherapy between the chemotherapy courses. As supported by preclinical trials, during the longer chemotherapy breaks, regrowth of surviving tumour cells can happen. Therefore, in the setting of adjuvant chemotherapy for early breast cancer, such growth can be limited if the time interval between schedules is kept as short as possible, which is the rationale for the dose-dense concept [11]. The International Breast Cancer Study Group's randomised trial showed that reintroduction of cyclophosphamide, methotrexate and fluorouracil (CMF) after a 3 month interval has an additional benefit [12,13], which may support the idea that a sandwich regimen can be applied with the CMF regimen. In addition, a British Columbia study revealed that the addition of postmastectomy radiotherapy delivered between CMF courses significantly increased disease-free and overall survival rates when compared with a group of patients who received only nine cycles of CMF consequently [14]. In contrast to the CMF regimen, the importance of dose density and a positive effect of the delivery of anthracyclines without longer intervals has been shown [15]. Consequently, radiotherapy insertion between anthracycline-based chemotherapy courses is not recommended. In current practice, taxanes are also given without longer intervals to maintain dose density and dose intensity for the adjuvant chemotherapy of early breast cancer [5].

Concomitant Radiochemotherapy in the Treatment of Early Breast Cancer

The concomitant administration of radiotherapy and chemotherapy would eliminate the need to delay the initiation of one modality until the end of the other and it reduces the overall duration of treatment. Furthermore, concomitant administration of radio- and chemotherapy could provide an additive interaction of tumour control. On the other hand, this concomitant treatment could be expected to have negative consequences in terms of side-effects and quality of life during treatment.

In the randomised study by Arcangeli *et al*. [16], concomitant administration of CMF and radiotherapy was found to have acceptable toxicity, without any difference in 5 year breast recurrence-free, metastasis-free, disease-free and overall survival rates when compared with the sequential administration of CMF and radiotherapy. No difference in dose intensity of radio- and chemotherapy was observed. A favourable outcome with concomitant radiotherapy and CMF was shown by Bellon *et al*. [17], in a single-arm prospective study. However, in this study, the total radiotherapy dose was reduced. Although some retrospective studies have confirmed the feasibility and safety of concomitant CMF and radiotherapy [18,19], others have revealed increased toxicity [20,21].

Concomitant administration of anthracyclines (e.g. doxorubicin, epirubicin) is associated with an increased risk of serious skin toxicity and should be avoided due to the potential risk of augmented cardiac toxicity [22,23]. On the other hand, in phase II trials, anthracenediones (mitoxantrone), which have more favourable toxicity profiles regarding cardiotoxicity and alopecia when compared with anthracyclines, have been shown to be tolerable when used concomitantly with radiotherapy [24,25]. In a multicentre randomised Arcosein trial [26], improved local control in axillary lymph node metastatic patients was obtained with concomitant cyclophosphamide, mitoxantrone and fluorouracil (CNF) and radiotherapy, when compared with the group who received sequential CNF and radiotherapy [26,27]. However, concomitant CNF and radiotherapy was associated with slightly more early (oesophagitis and