

Concurrent chemo-radiotherapy in the treatment of early breast cancer: Current status

Nabil Ismaili

Medical Oncology, Oncology Center, University Hospital Mohammed VI, Cadi Ayyad University, Faculty of Medicine, Marrakech, Morocco

ABSTRACT

Concurrent chemo-radiotherapy (CCRT) in early breast cancer was investigated by few authors and remains controversial. This treatment is more commonly used for locally advanced breast cancer and showed high rate of complete pathological response. A search of articles published in English literature, between 1980 and November 2012, was conducted on Medline using the following terms: “breast cancer”, “chemotherapy”, “concurrent radiotherapy”, and “Trastuzumab”. We identified five phase I/II trials and three randomized phase three trials evaluating concurrent chemoradiotherapy in the adjuvant of breast cancer. In patients with early breast cancer having positive lymph nodes, phases III clinical trials showed that CCRT improved local control after conservative breast surgery. However, these randomized trials used non-standard regimen: Cyclophosphamide, methotrexate and fluorouracil (CMF) or fluorouracil, mitoxantrone and cyclophosphamide (FNC). In addition, in phases II clinical trials, concurrent use of taxanes and anthracycline with standard whole-breast irradiation showed high rate of toxicity: Pulmonary toxicity with taxane; and cardiac and skin toxicity with anthracycline. Consequently, CCRT is not be used in practice because of concerns of toxicity with the standard drugs (anthracyclines and taxanes) and radiation. Anthracyclines with partial breast irradiation (PBI) was feasible according to one phase I clinical trial, and should be investigated in randomized clinical trials. Concurrent Trastuzumab plus radiotherapy is safe and can be used in HER2-positive breast cancer; in this case, cardiac volume sparing and patient selections for internal mammary chain irradiation are highly recommended. The present paper aimed to review the current data evaluating the efficacy and safety of CCRT in early breast cancer.

Key words: Breast cancer, chemotherapy, concurrent radiotherapy, trastuzumab

INTRODUCTION

Over the recent years, breast cancer remains the most common cancer in women in the world.^[1] By contrast, the mortality rate has declined dramatically since the introduction of adjuvant systemic therapy and radiation therapy, which are now used extensively for their established benefit in local control (radiotherapy RT),^[2-8] survival without metastases (chemotherapy CT),^[9-11] and overall survival (OS) (CT and RT).^[12,13]

However, the optimal sequence of CT and RT remains controversial. During the last two decades, four sequences were investigated in early breast cancer:

1. Delivering all RT first,
2. A “sandwich” approach (one or more cycles of CT, then RT, then additional CT, without concurrent administration of CT and RT),
3. Concurrent administration of CT and RT, or
4. Delivering all CT first.

In current clinical practice, adjuvant CT is recommended after surgery in patients of high risk of recurrence and death. Post-operative radiotherapy is recommended after breast conservative therapy (BCT) in patient <70 years. Post-mastectomy radiotherapy is always recommended for patients with positive axillary nodes, and indicated for patients with T3–T4 tumors independent of the nodal status. The recommended sequence between the two treatments is chemotherapy followed by radiotherapy (European Society of Medical Oncology (ESMO) recommendations-2011).^[14]

Observational studies have suggested that delaying the initiation of CT increased the incidence of spared metastasis,^[13-16] and delaying the initiation of radiation therapy more than 6 months after breast cancer diagnosis might increase the risk of local-regional recurrence.^[17-19]

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Address for correspondence: Dr. Nabil Ismaili, Mohammed VI University Hospital, Marrakech, Morocco. E-mail: ismailinabil@yahoo.fr

Concurrent chemo-radiotherapy (CCRT) is not the standard treatment. It has the advantage of shortening the duration of therapy, allowing RT and CT to start temporally, and potentially improving local control via the radiation-sensitizing effects of CT.^[20-22] CCRT with cyclophosphamide, methotrexate and fluorouracil (CMF) is feasible without unacceptable toxicity.^[22,23] The concurrent use of taxanes and whole breast irradiation was investigated in few prospective clinical trials; it has the concern of pulmonary toxicity.^[24] Anthracycline regimens improve survival in the adjuvant setting.^[12] However, the concomitant use of anthracyclines produced high rate of high grade-skin toxicity, and more cardiac dysfunction, leading to conclude that this protocol cannot be used in practice.^[25-27] Trastuzumab was an effective part of adjuvant treatment for HER-2-positive BC.^[28-30] However, limited published data exist concerning concurrent adjuvant RT and T.

In this work, current literature is reviewed regarding the efficacy and toxicity of CCRT to provide additional insight into the problem of optimal integration of these two modalities in the management of early breast cancer, including treatment recommendations. A search of articles published in English literature, between 1980 and November 2012, was conducted on Medline using

the following terms: “breast cancer”, “chemotherapy”, “concurrent radiotherapy”, and “Trastuzumab”.

WHAT IS THE RATIONAL OF CCRT?

CCRT is the standard treatment in many solid tumors such as carcinoma of the cervix, head and neck carcinoma, nasopharyngeal carcinoma, esophageal cancer, and lung carcinoma.^[31-34]

CCRT was also investigated in locally advanced breast cancer (LABC) in neoadjuvant setting before surgery. It is aimed: (1) to shrink the tumor to facilitate surgery; (2) to avoid mastectomy, in the case of good clinical response. Preliminary studies (phases I/II) showed that CCRT demonstrated good efficacy, both in terms of pathologic complete response (pCR) (20-47%), and in allowing breast conservation (69% in one study), with acceptable tolerance. Chemoradiation toxicity was mainly dermatitis within the RT field [Table 1].^[35-39] Future studies should compare neoadjuvant CCRT to neoadjuvant chemotherapy in LABC.

In early breast cancer, there are three theoretical advantages of adjuvant CCRT:

- Delivering both treatments of CT and RT at same time

Table 1: Concurrent chemoradiotherapy in unresectable locally-advanced breast cancer

| Author | No. | Trial 1 phase | Treatment | Results | | | | | Acute toxicity from CCRT |
|-------------------------------------|--------------|---------------|---|------------|-----------|----------|----------|---------|---|
| | | | | ORR (%) | pCR (%) | LRFS (%) | EFS | OS | |
| Formenti 1997) ^[35] | 35 | II | Concurrent 5FU/RT/ postoperative AC | 71 | 20 | - | 58 (5y) | 74 (5y) | Grade 2 stomatitis (n=8), cellulitis (n=1), moist desquamation (n=9) |
| Formenti (2003) ^[36] | 44 | I/II | Concurrent paclitaxel 30 mg/m ² twice-weekly/ RT (45-46Gy)/ postoperative doxorubicin based CT | 91 | 34 | - | - | - | Grade 3 skin desquamation (7%), hypersensitivity (2%), and stomatitis (2%) |
| Kao (2004) ^[37] | 33 | I/II | Concurrent paclitaxel±vinorelbine/ RT (60-70Gy) | 93 (14/15) | 47 (7/15) | 83 (4y) | 33% (4y) | 56 (4y) | Moist desquamation (n=8) and grade 3-4 neutropenia (n=3) |
| Chakravarthy (2006) ^[38] | 38 | I/II | 3 cycles of paclitaxel 175 mg/m ² →concurrent twice-weekly paclitaxel/RT | 79 | 34 | - | - | - | Moist skin desquamation (n=1), fatigue (n=1), and liver function abnormalities (n=1). One patient suffered from a grade 4 skin reaction |
| Bollet (2006) ^[39] | 60 (Tm>3 cm) | II | Concurrent 5FU-vinorelbine/RT (50 Gy) | 64 | 27 | - | - | - | Grade 4 haematological=22%; grade 3 cardiovascular=5%; moist skin desquamation=14% |

LRFS: Loco-regional recurrence free survival, EFS: Event-free survival, OS: Overall survival, CCRT: Concurrent chemo-radiotherapy, RT: Radiotherapy, CT: Chemotherapy, FU: Fluorouracil, ORR: Objective response rate, pCR: Pathologic complete response, AC: Doxorubicin plus cyclophosphamide

- which shorten the duration of treatment;
- Delivering both treatments; chemotherapy and radiotherapy without any delay;
- Biological synergy effect that can increase the efficacy of the treatment.^[20-22]

RETROSPECTIVES AND PRELIMINARY STUDIES (PHASE I AND II STUDIES) EVALUATING CCRT IN EARLY BREAST CANCER

In the adjuvant setting, CCRT has been investigated using concurrent CMF, taxanes, or anthracyclines with radiation.

Concurrent chemo radiotherapy with cyclophosphamide, methotrexate and fluorouracil.

Three prospective pilot studies evaluated the efficacy and safety of CCRT using CMF CT.

In the first study, a German group prospectively included 45 patients treated with modified CMF (600 mg cyclophosphamide, 50 mg methotrexate and 750 mg 5-fluorouracil intravenously on day 1 of altogether nine 21-day cycles) and concurrent chest wall and regional nodal radiation (up to 40 Gy). No severe side effects were noted with CCRT. At 5 years, event-free survival (EFS) and OS were 61-74%, and 77-83%, respectively.^[40]

In the second trial, Dubey, *et al.*^[41] conducted a pilot study including 112 patients treated with CCRT regimen in which the whole breast RT dose was 39.6 Gy in 22 fractions, followed by a 16 Gy tumor bed boost in eight fractions. The most common acute toxicity observed was moist desquamation developed during or shortly after RT in 50% of patients, but only five patients required treatment breaks. Grade 4 neutropenia during RT occurred in 16 patients, but only one required hospitalization. One patient developed Grade 2 radiation pneumonitis. Ninety-three percent of patients received at least 85% of prescribed drug doses. Four local failures and 20 distant failures were observed. The authors concluded that CT-RT scheme had acceptable toxicity and outcome.

In the third study, Fiets, *et al.*^[26] compared the acute toxicity of RT only and RT administered concurrently with AC or CMF chemotherapy. CT and RT were administered at full dose. Patients treated with concurrent CT experienced higher incidences of skin toxicity, esophagitis, dyspnea, malaise, anorexia, nausea, and hospital admission. The inclusion of the nodal areas in the irradiation field enhanced the risk of acute toxicity, and more patients received an inadequate dose of CT.

We conclude that CCRT using CMF CT can be administered safely using an RT dose up to 40 Gy.

CCRT with taxanes

The feasibility of concurrent radiotherapy with taxane based chemotherapy regimens, which constitute a standard treatment used as adjuvant therapy, has been evaluated in early-stage breast cancer. Taxanes promote stabilization of microtubules, causing cell-cycle arrest at the G2/M junction, and serve as radiosensitizing agents.^[42] Combination therapy using taxanes and concurrent radiation has been evaluated in patients with aerodigestive tumors.

In a prospective study, 40 patients with operable Stage II or III breast cancer received protocol-based treatment with 4 cycles of AC CT followed by concurrent paclitaxel and radiation therapy. Paclitaxel was evaluated on 2 schedules, with treatment given either weekly for 12 weeks (60 mg/m²), or every 3 weeks for 4 cycles (135-175 mg/m²). The authors concluded that using a three-weekly paclitaxel dosing schedule may be possible, without dose-limiting toxicity. However, Grade 2 radiation pneumonitis not requiring steroid therapy was seen in 2 of 24 patients (8%) treated in such a fashion. Excessive radiation dermatitis was not observed with either paclitaxel schedule.^[43] We should note that CT dose used in the study was lower than standard that can cause a potential disadvantage in systemic control.

We conclude that randomized comparison of this approach with the sequential scheme is warranted.

CCRT with anthracyclines

Few prospective studies investigated CCRT using anthracycline regimen. Older trials showed that concomitant use of epirubicin or doxorubicin produced 30-44% rate of high-grade radiation dermatitis,^[25,26] and concurrent mediastinal irradiation with doxorubicin induced intense cardiac dysfunction.^[27] This was discouraging the use of anthracyclines and radiation concurrently. However, in a recent phase I trial, the authors showed that partial breast irradiation (PBI) with concurrent dose-dense doxorubicin and cyclophosphamide induced an acceptable hematologic and non-hematologic toxicity profile with the likelihood of RD \geq grade 2 is \leq 11%.^[44] These results were in favor of the use of CCRT based on anthracycline regimen.

Recently, a retrospective cohort study was conducted by our group to evaluate the efficacy and toxicity of two concurrent protocols administered either with anthracycline regimen or with CMF in adjuvant setting.^[45-47] At 74.5 months' median follow-up, the loco-regional recurrence-free survival (LRFS) at 5 years was significantly higher in

anthracycline group versus CMF group (98.7% vs. 95.3%; $P = 0.034$) with a trend toward significance for EFS in favor of anthracycline ($P = 0.057$).^[47] In addition, concomitant anthracycline was not associated with significant toxicity or factor inducing radiotherapy interruption. Moreover, no symptomatic cardiac events were recorded in concordance with a recent Italian study.^[48]

These results suggest the need of evaluation of CCRT using anthracycline and modern radiation techniques in randomized phase III clinical trial vs. the standard sequence.

RANDOMIZED PHASE III STUDIES

Three recent randomized phase III trials were conducted to compare the sequential protocol to the concomitant protocol [Table 2].^[49-51] In the first trial, 716 patients were treated by BCT and randomized into 2 groups (ARCOSEIN study).^[49] In the first group, the patients were treated by the FNC protocol (5-fluoro-uracil 500 mg/m², mitoxantrone 12 mg/m² and cyclophosphamide 500 mg/m²) with concomitant RT (50 Gy in 2-Gy \pm 10- to 20-Gy RT boost to the primary tumor bed). In the second group, the patients were treated by the FNC protocol followed by RT. Arcangely, *et al.*^[50] randomly assigned 206 patients (after quadrantectomy and axillary dissection) to concurrent or sequential treatments using CMF-based CT. In the third trial, Rouessé, *et al.*^[51] randomly assigned 638 patients with prior breast surgery and positive axillary dissection (from which 416 were BCT) to receive CCRT (FNC protocol) or CT (fluorouracil, epirubicin, and cyclophosphamide protocol) followed by RT. No differences in 5-years LRFS, disease-free survival, and OS were observed between the two treatment groups in the three trials. Nevertheless, in the ARCOSEIN study the authors identified a significant decrease in the risk of locoregional recurrence with CCRT for node-positive patients. Rouessé *et al.*^[40] showed that

concurrent treatment has a significantly better locoregional control in node-positive breast cancer after BCT.

In ARCOSEIN study, acute locoregional toxicities were moderate in both arms. Esophagitis was more frequent in the concurrent arm (115 v 89; $P = 0.04$). Nausea/vomiting was significantly higher in the sequential treatment arm, whereas anemia was significantly more frequent in the concurrent arm. Late toxicities; subcutaneous fibrosis, telangectasia, skin pigmentation, and breast atrophy, were significantly increased in the concurrent arm. One patient in each arm developed acute myelogenous leukemia in the first 18 months after treatment.

Rouessé, *et al.*^[51] reported more frequent febrile neutropenia, Grade 3-4 leukopenia, grade 2 skin toxicities, and more subclinical LVFE events at 1 year, in the concomitant arm.

The main limitation of the three European trials was the use of CMF protocol and FNC protocol which have a safer toxicity profile when radiation treatment was used without the use of anthracycline and taxane regimens. CMF and FNC are older CT regimen used in the past; however, more recently, anthracyclines and taxanes-containing regimens have become standard, and are demonstrated to have improved survival and local recurrence outcomes.

In conclusion, in randomized clinical trial, CCRT using CT treatments based on CMF or FNC has acceptable toxicity, but does not improve the outcome of patients with early breast cancer as compared with the sequential treatment.

CONCURRENT TRASTUZUMAB WITH RT

Approximately 15% to 25% of breast cancers (BCs) express

Table 2: Randomized phase III trials compared concurrent chemo-radiotherapy versus sequential chemo-radiotherapy

| Study name/ country/ author | Date of publication | No. | Study groups | Outcomes | Toxicity |
|--|---------------------|-----|--------------------|--|---|
| Arcosein France Toledano <i>et al.</i> ^[36] | 2007 | 716 | FNC+RT FNC→RT | *No differences in 5y survival and 5y DFS *Significant decrease in LRFS in favor of CCRT in node-positive breast cancer | More hematological and esophageal toxicities Moderate acute loco-regional toxicities were found in the concomitant arm |
| France Rouessé <i>et al.</i> ^[38] | 2006 | 638 | FNC+RT FEC60→RT | *No differences in 5y survival and 5y DFS *Better loco-regional control in node-positive breast cancer after BCT | More hematological toxicities More frequent grade 2 skin toxicities in the concomitant arm, and more subclinical LVFE events at 1 year |
| Italy Arcangely <i>et al.</i> ^[37] | 2006 | 206 | CMF+RT CMF→RT | *No differences in 5y survival and 5y DFS | No differences |

RT: Radiotherapy, FN: 5-fluorouracil – Mitoxantrone – Cyclophosphamide, CMF: Cyclophosphamide – Methotrexate-5-fluorouracil, DFS: Disease free survival, LRFS: Locoregional recurrence free survival, LVFE: Left ventricular fraction ejection, CCRT: Concurrent chemo-radiotherapy, BCT: Breast conservative therapy, FNC: Fluorouracil, Mitoxantrone and Cyclophosphamide, FEC: Fluorouracil, Epirubicin and Cyclophosphamide

Human Epidermal Growth Factor Receptor 2 (HER-2) amplification. Patients with HER-2-positive disease have greater risk for relapse and death. Trastuzumab (Herceptin [H]) is a recombinant, DNA-derived, monoclonal antibody that selectively binds to the extracellular domain of the HER-2 protein in BC cells. In adjuvant setting, randomized trials have shown the benefit of H in HER2-positive BC.^[28-30,52-54] However, limited published data exist concerning concurrent adjuvant RT and H [Table 3].^[55-57]

Preclinical data suggest a synergistic effect of H and ionizing radiation in experimental models. Authors showed in an *in vitro* model of HER2-positive BC cells a significant inhibition of DNA repair after concomitant radiation and H exposure compared with H or irradiation alone.^[58] The specific molecular pathways used by cells for suppression of DNA repair, which are triggered by ligand (or antireceptor antibody) interactions, remain unclear. However, several reports suggest p53-independent activation of cyclin-dependent kinase

Table 3: Randomized phases III trials investigating trastuzumab in adjuvant human epidermal growth factor receptor 2-positive breast cancer and the influence of the sequencing of trastuzumab and radiation

| Trials | Journal/ year | No | CT treatment | Sequencing of H and RT in the H arm | Outcomes | AE | |
|--|-------------------------|----------------------------------|---|--|--|---|---|
| NSABP-B31/ NCCTG N9831 ^[25] | NEJM 2005 | >3000 | NSABP-B31: 4AC→4 <i>P</i> versus 4AC→4 <i>P</i> +H weekly for 1 years (AC-PH-H) NCCTG N9831: 4AC 12 <i>P</i> weekly versus 4AC→12P weekly→H (excluded) versus 4AC PH weekly (AC-PH-H) | Concurrent H with RT | Statistically significant improvement in 4-year DFS (92.6%; <i>P</i> =0.00001) and OS (85.9%; <i>P</i> =0.0007) | Concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs (including CEs) | |
| BCIRG-06 ^[27] | NEJM 2011 | 3222 N+/N- High risk | 4AC→4 T (AC-T) AC-T+H (1 year) 6 TCH (1 year) | Concurrent H with RT | -Statistically significant improvement in 5 years DFS and OS in favor to CT+H; -No differences in efficacy were found between the 2 trastuzumab regimens | The rates of CHF and cardiac dysfunction were significantly higher in the group receiving AC-T plus trastuzumab than in the TCH group (<i>P</i> <0.001) | |
| HERA ^[44] | Lancet Oncol 2011 | >5000 N+/N- ≥T1c FE≥55% | CT/A CT/A→H (1 year) CT/A→H (2 years) | Sequential RT followed with 1 years or 2 years of H | Sequential RT followed with 1 year of H | Statistically significant improvement DFS and OS | Higher incidences of grade 3-4 and fatal adverse events (each in less than 1% of patients) were noted on 1-year trastuzumab versus observation group 3.8% in H arm and 1.5% in observation arm experienced a LVEF less than 45%; Symptomatic CHF were reported in 1 and 4 patients, respectively |
| PACS 04 ^[45] | JCO 2009 | 528 | *2 arms: 6 FEC 100±H 6 EC 75→6 D75±H | Sequential RT followed with 1 year of H | No difference in 4 years DFS and OS | Only one woman treated with H was diagnosed with a CHF | |
| FINHER ^[46] | JCO 2009 | 232 N+or high risk N- | 9 weeks of H+3 D or 3 Vinorelbine 3 FEC 60 | Sequential 9 weeks of H followed with RT | No statistically significant difference in 5 years DFS and OS | | |

CT: Chemotherapy, H: Trastuzumab, RT: Radiotherapy, AE: Adverse events, AC: Doxorubicin plus cyclophosphamide, P: Paclitaxel, T: Docetaxel, TCH: Docetaxel plus carboplatin plus trastuzumab, FEC: Fluorouracil plus epirubicin plus cyclophosphamide, DFS: Disease free survival, OS: Overall survival, TCH: Trastuzumab, HERA: Herceptin adjuvant, LVEF: Left ventricular ejection fraction, NSABP: The National Surgical Adjuvant Breast and Bowel Project, NCCTG: The North Central Cancer Treatment Group, NEJM: The New England Journal of Medicine, BC: Breast cancer, CE: Cardiac events, BCIRG: Breast Cancer International Research Group, CHF: Congestive heart failure, PACS: breast cancer adjuvant trial

inhibitor p21WAF1 following growth factor stimulation through direct activation by MAP kinase [Figure 1].^[58]

Trastuzumab was evaluated in adjuvant by using 2 different sequences:

1. In concomitant with RT:

In the NCCTG phase III N9831 trial which represent the largest study with the longest follow-up that systematically investigates potential RT and H interactions during adjuvant treatment, the authors confirms the beneficial effect of concurrent use of H and RT in DFS and OS, without significant differences among arms in incidence of acute skin reaction, pneumonitis, dyspnea, cough, dysphagia, or neutropenia. In addition, RT with H did not increase relative frequency of CE's regardless of treatment side (at a median follow-up of 3.7 years).^[55] In the BCIRG-006 phase III trial, Slamon, *et al.* randomly assigned 3222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 1 years of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 1 years of trastuzumab (TCH).

In H group, trastuzumab was delivered concurrently with RT. The estimated DFS and OS rates at 5 years were significantly higher in CT + H group. No significant differences in efficacy were found between the two trastuzumab regimens, whereas both were superior to AC-T. The rates of congestive heart failure and cardiac dysfunction were significantly higher in the group receiving AC-T plus H than in the TCH group ($P < 0.001$).^[30]

2. In sequence with RT:

The results of the Herceptin Adjuvant (HERA) showed that H improved the 5 years DFS.^[52] However, in the PACS 04 trial, there is no H improves neither DFS nor OS.^[53] The

final results of the Finnish Herceptin (FinHer) trial, when the RT was administered after the end of the H showed no improvement in DFS and OS.^[54] Only one patient developed CHF in the H arm. However, in this study the H was administered only for 9 weeks.

Acute toxicity of H and concurrent RT was analyzed In the French multicentric study including 146 patients. The authors showed 51% and 12% of Grade >2 dermatitis and esophagitis respectively. According to the Common Toxicity Criteria v3.0 scale and HERA (HERceptin Adjuvant) trial criteria, 10% and 6% of the patients had a grade ≥ 2 of left ventricular ejection fraction (LVEF) decrease after RT respectively. Consequently, the authors recommended the selection of patients who would derive benefit from the irradiation of internal mammary chain (IMC), such as patients who had more than three positive lymph nodes, and/or the use of IMRT and the gating to exclude the cardiac volume.^[57]

From preclinical and randomized studies, we conclude that concurrent use of Trastuzumab and radiotherapy in patient with early HER2-positive breast cancer was efficient and safe; cardiac volume sparing and patient selections for IMC irradiation are highly recommended. Cardiac toxicity should be assessed by measuring the LVEF before and after RT completion. Acute toxicity (grade ≥ 2) can be evaluated using the CTC v3.0 scale or the HERA trial criteria (decrease in the ejection fraction of ≥ 10 points from baseline to LVEF of <50% at any time).^[59]

CONCLUSIONS

CCRT is more commonly used in the management of locally advanced breast cancer in neoadjuvant setting in the case of failure of primary chemotherapy.

In early breast cancer, CCRT should not be used in routine clinical practice. It can be considered as a therapeutic option in the developed countries.

Concomitant use of Trastuzumab with RT using modern techniques was safe and can be considered in adjuvant setting; cardiac volume sparing and patient selections for IMC irradiation are highly recommended.

Adjuvant concurrent treatment with 3-weekly paclitaxel and radiation therapy is feasible and should be evaluated in randomized phase III trials; however caution is warranted in light of the apparent possibility of pulmonary injury. Further investigations are needed to evaluate the role of CCRT in the management of early breast cancer.

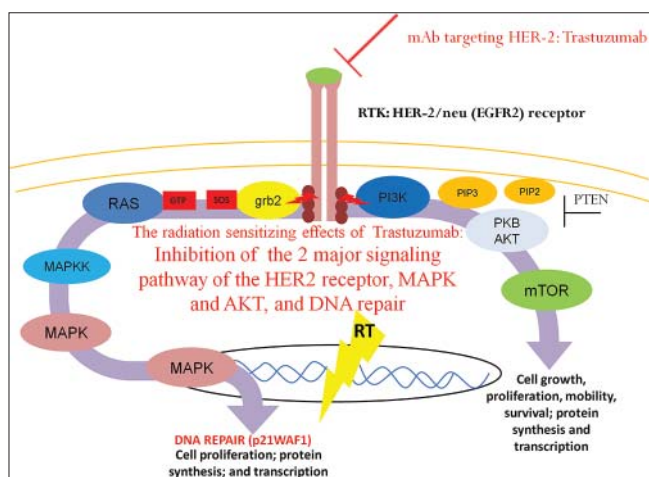


Figure 1: Mechanism of radio-sensitizing effect of trastuzumab in HER2-positive breast cancer cells^[58]

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