Is Higher Efficacy Always at the Price of More Side Effects during Chemotherapy?

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Key Words

Breast cancer · Chemotherapy: dose-dense, tailored · Efficacy · Toxicity · Dose intensification ·

Summary

Breast cancer remains the most prevalent cancer diagnosed in women worldwide. The number of effective treatments for breast cancer is on the rise, however, the benefit from specific treatments to individual patients and the adverse events experienced vary considerably. Efficacy and safety of anticancer therapies may depend on tumor, treatment, and host characteristics. Advances in the adjuvant chemotherapy of operable breast cancer have come from the introduction of effective agents and the application of the principles of combination chemotherapy. Attempts to advance these principles by substantial escalation of drug dosage have proven unsuccessful with a potentially higher rate of side effects. Another concept to increase efficacy is dose density, the administration of drugs with shortened intertreatment interval, and sequential therapy. The dose-dense concept improved clinical outcome significantly and was not accompanied by an increase in toxicity.

Schlüsselwörter

Mammakarzinom · Chemotherapie: dosisdichte, individuell angepasste · Wirksamkeit · Nebenwirkungen · Dosisintensivierung

Zusammenfassung

Das Mammakarzinom ist nach wie vor das häufigste Karzinom der Frau weltweit. Die Zahl der wirksamen Therapien steigt, jedoch ist der Gewinn von einzelnen Therapien und deren Nebenwirkungen für die individuelle Patientin sehr unterschiedlich. Wirksamkeit und Nebenwirkungen der Chemotherapie hängen von Charakteristika des Tumors, aber auch von Eigenheiten der Therapie und der Patientin ab. Fortschritte in der adjuvanten Chemotherapie des primär operablen Mammakarzinoms wurden durch die Einführung neuer Substanzen und durch die Verabreichung einer Kombinationschemotherapie erzielt. Versuche, diese Fortschritte durch Dosisescalation zu verbessern, erwiesen sich als erfolglos mit beträchtlicher Zunahme der Nebenwirkungen. Ein anderer Weg, die Effektivität zu erhöhen, ist das Dose-dense-Prinzip, in dem die Intervalle zwischen den Chemotherapien verkürzt werden, und die sequentielle Verabreichung der Zytostatika. Das Dose-dense-Prinzip erwies sich der konventionellen Verabreichung signifikant überlegen, ohne Zunahme der Nebenwirkungen.

Introduction

Breast cancer is the most common malignancy in women in industrialized countries, and the leading cause of death among women aged 40–79 years [1]. Adjuvant combination chemo-

therapy reduces the risk of relapse and death for patients with operable primary breast cancer. In an attempt to improve these results, various manipulations of dose and schedule of administration have been tested.

Dose Intensity

The response to conventional doses of chemotherapy to treat breast cancer is dose-related. Dose intensification has generated great research interest over the last decades. The term dose-intensity was formulated as body size-adjusted dose divided by time [2]. Part of the appeal of dose intensity has been the experimental observation that efficacy can be increased for some agents by increasing the dose [3]. But clinical results did not match this prediction. Dose escalation of doxorubicin in the Henderson trial [4] did not suggest an advantage for doses of more than 60 mg/m². However, this was not true for epirubicin. The French adjuvant study group [5] has demonstrated an absolute 5-year survival gain of 12% for patients receiving epirubicin at 100 mg/m², compared with 50 mg/m² in the FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimen. The benefit of a higher epirubicin dose has also been demonstrated in another randomized epirubicin-containing adjuvant study by Piccart et al. [6]. For cyclophosphamide, intensifying dose levels over 2,400 mg/m² did not substantially improve outcome in reports of the NSABP B-22 and NSABP B-25 trials [7]. Moreover, the results from these studies indicate that higher doses of cyclophosphamide may increase the risk of secondary leukemia. The dose intensification for paclitaxel is less studied and was complicated by the duration of infusion. There seems to be an advantage for 175 mg/m² when administered over 3 h, and even higher doses may offer a small additional benefit [8]. The standard dose and administration of docetaxel is 100 mg/m² as a 1-h infusion every third week. The dose-limiting toxicity is myelosuppression which is dose- but not schedule-dependent. The French study PACS 01, comparing 3 cycles of F₅₀₀E₁₀₀C₅₀₀ followed by 3 courses of docetaxel 100 mg/m² revealed an overall survival gain compared with 6 courses of F₅₀₀E₁₀₀C₅₀₀ [9].

The concept of dose intensification in breast cancer was developed at the Dana-Faber Cancer Institute by Dr. Emil Frei [10] who was the first to demonstrate that the cell kill effected by multiple alkylating agents had a step-dose-response correlation. Because most of the toxicity of these agents was to the bone marrow, one could administer these lethal doses only with autologous stem cell transplant, but at a considerable risk of treatment-related mortality [11]. Although several randomized studies suggested a reduction in recurrence risk among subsets of breast cancer patients, there has been no convincing evidence of a survival benefit of high-dose chemotherapy [12–16]. A randomized trial of Southwest Oncology Group 9623 compared intensive dose-dense with high-dose adjuvant chemotherapy for high-risk operable breast cancer, with no evidence that transplantation was superior to dose-dense dose-escalated therapy. Transplantation was associated with increased toxicity and possible inferior outcome, although the hazard ratios were not significantly different from the dose-dense regimen [17].

Dose-Dense

To overcome resistance, combination chemotherapy using several drugs simultaneously at full dosages or, where possible, in rapid alternation, was predicted to be superior and was clinically studied [18]. The lack of success with alternating therapy in breast cancer suggests that the underlying assumptions may be incorrect [19]. Human solid tumors do not grow exponentially, but in a Gompertzian pattern [20]. Tumor regrowth after subcurative therapy is rapid after each cycle of treatment, so eradication of disease is difficult even when all of the cells are sensitive to the drugs used. An alternative model to eradicate these cells is the dose-dense model. Dose-dense treatments increase dose intensity not by increasing the dose, as with dose escalation, but by decreasing the time. Although dose intensity may be increased by dose escalation or by increasing dose density or by both, an advantage of dose density is that it should work even when the dose relationship for the agents being used is not rising steeply in the feasible dose range. Sequential therapy is by definition more dose-dense than alternative regimens. Hudis et al. [21] reported a promising 4-year disease-free survival rate of 78% and an acceptable toxicity profile in women with high-risk node-positive breast cancer, who were treated in an adjuvant phase II study with both sequential dose-dense and dose-escalated paclitaxel, doxorubicin, and cyclophosphamide. The following Intergroup trial C9741 was a randomized adjuvant trial in women with node-positive breast cancer. The 2 × 2 factorial design compared single sequential-agent doxorubicin, paclitaxel, and cyclophosphamide to concurrent doxorubicin and cyclophosphamide followed by paclitaxel, delivered either every 2 weeks, dose-dense, with growth factor support, or every 3 weeks without growth factor support. The study results demonstrated that patients receiving dose-dense treatment experienced an improvement in disease-free and overall survival, however, there was no difference between sequential or concurrent drug administration. Toxicity was similar in both arms, however, there was an increase in red blood cell transfusions on the concurrent dose-dense arm, and grade 4 neutropenia was less common in the dose-dense treatment. Based on these results, dose-dense chemotherapy has become an approved regimen for the adjuvant treatment of node-positive breast cancer [22]. Another study from Germany found dose-dense, sequential epirubicin and paclitaxel to be superior to the combination of these agents given according to a standard 3-weekly schedule. This trial combined both dose intensity and dose density but did not control for total cumulative doses which were higher in the dose-dense arm [23]. Another German trial, presented by Jakisch et al. [24], found that a dose-dense doxorubicin-docetaxel regimen given for 4 cycles was inferior to a more conventional regimen of sequential doxorubicin/cyclophosphamide-docetaxel preoperative chemotherapy in terms of complete and pathologically complete responses, as well as breast conservation rates.

Tailored Chemotherapy

Almost all cancer drugs are delivered according to body surface area and individually modulated doses. It is well established that this will not compensate for pharmacokinetic and pharmacodynamic variations of most cytostatics [25]. Body surface area-based dosage will therefore result in severe toxicity for some patients and no or minor toxicity for others. Five retrospective studies showed statistically significant worse outcome for patients with fewer side effects [26]. These retrospective observations have been further explored in 2 randomized studies, Scandinavian Breast Group (SBG) 9401 and 2001–1 study. Tailored FEC with granulocyte colony-stimulating factor (G-CSF) support resulted in a significantly improved relapse-free survival and fewer grade 3 and 4 toxicities compared with marrow-supported high-dose chemotherapy as adjuvant therapy in women with high-risk primary breast cancer in the SBG 9401 study [27]. A major complication in the study was the high incidence of acute leukemia or myelodysplastic syndrome in the tailored arm with 3.6%.

The concept of tailored therapy is more efficacy at the price of more side effects. In a cooperation between the Scandinavian Breast Cancer Group, the Austrian Breast and Colon Cancer Study Group, and the German Breast Group, a randomized study was started to investigate whether tailor-

ing and dose densification is superior to a fixed-dose strategy without dose intensification. The ‘Panther Trial’ compares the use of dose-dense and tailored epirubicin/cyclophosphamide followed by dose-dense and tailored docetaxel with 3-weekly FEC followed by docetaxel in lymph node-positive or high-risk lymph node-negative breast cancer patients.

Conclusion

‘Is higher efficacy always at the price of more side effects during chemotherapy?’ – The answer must be ‘Yes’. Only the dose-dense approach seems to have a marginal decrease of side effects combined with a superiority in efficacy. But more studies are needed to underline this assumption. For the future, microarrays as well as pharmacogenetic and pharmacogenomic technologies will be a rational basis for tailored therapy strategies based on individual tumor biological characteristics, aiming towards a more effective and selective therapy.

Conflict of Interest

The author did not provide a conflict of interest statement.

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