High Dose Chemotherapy in Breast Cancer - A Thin Red Line Between Hype and Hope

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INTRODUCTION

By the year 2000, half a million women will die from breast cancer annually. Adjuvant chemotherapy improves survival in patients with operable primary breast cancer and chemotherapy also improves palliation in metastatic breast cancer (MBC)[1]. However, a survival benefit of chemotherapy in MBC is debatable, but has been estimated in months compared to historical survival MBC patient data[2]. Combination chemotherapy, if at all, confers only a marginal survival benefit over single agent chemotherapy in MBC[3]. So it has been the hope that high dose chemotherapy with stem cell transplantation (HDCSCT) will not just confer higher complete responses, as is well established, but that it will significantly result in better overall survival (OS) and progression-free survival (PFS) in responding breast cancer patients.

More is better?

The principal of high dose chemotherapy is simple. If conventional bombing of the enemy (tumour) can inflict impressive damage but yet not defeat the enemy, let us then intensify the bombing with one or two megadoses (5 to 30 folds higher than conventional chemotherapy doses), necessitating haematopoietic rescue with blood stem cell transplantation after collateral damage to the bone marrow[4]. This strategy was based on increased tumour log-kill with dose intensification in laboratory in vitro and animal models. With the steep dose-responses seen in the laboratory, it was also hypothesised that drug resistance in cancers could be overcome with combinations of very high doses of mainly alkylating chemotherapy agents with improved cure rates. The Gompertzian model of tumour kinetics infers that a small tumour volume has increased tumour growth fraction[5]. So why not punch the opponent (breast cancer) with a few regular jabs to daze him (induction chemotherapy), and then deliver a huge knock-out punch (HDCSCT) to put the enemy out? After all, this 'more is better' approach has proven value in leukemia, multiple myeloma and lymphoma. So can breast cancer, a heterogenous disease with protean manifestations, be knocked out by high dose chemotherapy for a full head count? More than 15 years, over 300 related publications and 12,000 US breast cancer patients treated with HDCSCT later, we now have some early answers.

High noon in Atlanta

In May last year, at the 35th ASCO Annual Meeting, the highly-charged post lunch plenary session featured four seminal studies of HDCSCT in breast cancer.

The Philadelphia Intergroup Study reported their results of the largest Phase III randomised trial of HDCSCT in responding MBC with 184 eventual patients analysed, patients in both arms having responded to standard induction chemotherapy[6]. At a median follow-up of 31 months, there was no significant difference in OS and PFS. There was also no difference in serious toxicity between the two arms. A criticism of this study is that the conventional chemotherapy arm received a total of up to 18 months (or until progression) of maintenance chemotherapy. A small randomised French study of 61 women followed up for 5 years presented as a poster also reported no significant OS advantage of HDCSCT in MBC over conventional chemotherapy[7]. However, PFS was significantly better in the HDCSCT arm. The remaining three plenary reports focused on the efficacy of HDCSCT as adjuvant therapy in high risk node-positive breast cancer patients. The largest of these trials is the Cancer and Leukemia Group B (CALGB) randomised multicentre study by Peters et al, analysing 783 patients at a median follow-up of 37 months, a time line too short for final analysis[8]. Following identical induction chemotherapy, patients were randomised to receive either high dose cyclophosphamide, cisplatin and melphalan followed by SCT, or intermediate doses of the same chemotherapy with growth factor support to quicken haematopoietic recovery. These preliminary results reported no statistical difference in OS and event-free survival at 3 years between the two groups, although there was 11% less relapses in the HDCSCT arm. There were more deaths in the high dose arm, blamed partly on the use of melphalan, a toxic first generation chemotherapy. Quality of life analysis was no different between the two groups. However, comparing a HDCSCT arm with a non-standard intermediate dose regimen makes the data difficult to interpret and apply to standard oncology practice. Both arms demonstrate superior survival compared to previous reports of conventional chemotherapy in this setting. The study will be re-analysed in 2 years. The Scandinavian Breast Group study compared a HDCSCT regimen against a six-cycle dose-intense tailored chemotherapy regimen of 5-fluorouracil, epirubicin and cyclophosphamide with growth factor support, posing the same problem of not having a standard conventional chemotherapy arm as the yardstick by which HDCSCT should be measured against and too short a follow-up[9]. With a median follow-up of 23.7 months analysing 274 patients, this study was negative. Quality of life and toxicity appeared better in the HDCSCT arm, and late leukemic complications occurred in the tailored chemotherapy arm with none in the HDCSCT arm. The only positive randomised study of HDCSCT in high-risk breast cancer patients came from South Africa[10]. This study had the smallest cohort of 154 patients but the longest median follow-up at more than 5 years. The study design brought HDCSCT upfront without induction chemotherapy and employed two sequential tandem high dose cycles both supported by blood stem cell infusion after each cycle. At a median follow-up of 277 weeks, 17% had died in the HDCSCT arm compared with 35% in the conventional chemotherapy arm ($p < 0.01$). The PFS is also significantly better in the HDCSCT arm ($p < 0.001$). This lone positive trial has the longest follow-up of all the four plenary reports and, unlike the other two adjuvant studies, used a standard chemotherapy comparison arm. In other words, the best HDCSCT strategy may be to leap out of the seat at the bell in round one and deliver a one-two knock-out punch to breast cancer without prior regular jabs. However, Dr Werner Bezwoda and the South African study is currently under investigation for data discrepancies and possible scientific misconduct. Thus one has to look elsewhere for validation of the upfront tandem high dose chemotherapy approach. The most ideally-designed large US prospective randomised study of HDCSCT in high-risk node-positive breast cancer will not be reported until after year 2001. This completed study randomised patients to HDCSCT or no further treatment following identical standard induction chemotherapy with 5 fluorouracil, adriamycin and cyclophosphamide. Also, we await the completion of four large randomised European trials addressing the same issue.

The plenary studies will challenge the oncology community to relook at how best to use the concept of dose in killing human breast cancer and review the lessons learnt from this great Sisyphian struggle.

From mouse to man - eyes wide shut

Even if HDCSCT for breast cancer eventually shows a survival benefit with longer follow-up and larger patient numbers, it will be no home run. Megadoses of chemotherapy are not going to destroy enough invisible (micrometastatic) or bulky breast cancer to give patients a dramatic survival advantage. It is also clear that animals, like mice with tumours, enjoy better cancer cures than humans. That 9 out of 10 US women with breast cancer chose HDCSCT instead of joining a randomised trial is testament to the early hubris of transplant oncologists based on laboratory-driven hypotheses, uncontrolled clinical data and popular media hype that this appeared to be their best available treatment. So is HDCSCT for breast cancer the 'Emperor's New Clothes' or the 'Cinderella' of cancer treatment? We now know it works as well as conventional chemotherapy (and with time, may even be better), its toxicities are much less with improved technology (0% – 1% mortality in three of the four studies), and it has the advantage of being a one-hit wonder with one or two megadoses compared to prolonged cycles of chemotherapy lasting many more rounds of slugfest in the ring with the same outcome. The main issues then become quality of life, toxicity to the patient and the cost-benefit ratio.

Tomorrow

Newer ways of harnessing the powerful tumour-reducing ability of HDCSCT include the use of different high dose regimens or scheduling, using tandem cycles of chemotherapy[4], augmenting HDCSCT with non-cross-resistant immunotherapy or biological therapies[11] and also the use allogeneic stem cell transplant to induce a graft-versus-tumour effect known to be powerful against haematologic malignancies[12]. Heavy bombing alone in this current form may not win this long drawn war against a resistant foe that is not well understood.

After over three decades of research into the biology of breast cancer, the translation of this knowledge into therapeutic tools has, until now, been less than gushing[13]. The explosion of the new biology is yielding potentially important and novel anticancer agents. Cytotoxic drugs such as the taxanes, newer hormonal therapies, monoclonal antibodies to growth signalling receptors and to tumour-specific antigens like its glycoproteins, differentiation agents, small molecules to inhibit oncogenic drive, immunogene therapy like vaccine strategies, pro-apoptotic, anti-angiogenesis and antimetastatic agents are all poised to audition for centre stage and join the main players of chemotherapy, radiation therapy and surgery[14]. In the war on breast cancer, there is every reason to believe that tomorrow will definitely be a better day.

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