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ORIGINAL ARTICLE

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New concepts in the treatment of breast cancer using high-dose chemotherapy

Abstract High-dose chemotherapy is now frequently used for the treatment of primary and metastatic breast cancer. Two recent randomized trials have demonstrated that this treatment approach can result in extended disease-free and overall survival for patients with metastatic disease. However, treatment results have demonstrated that long term remissions from these treatments raise complex questions about traditional models of chemotherapy principles. A detailed analysis of the principles underlying high-dose therapy is presented in the context of principles of dose-response, the inverse rule and the total tumor cell kill hypotheses.

Key words Breast cancer · High-dose chemotherapy

Introduction

During the past 10 years there has been increasing interest in the use of high-dose chemotherapy with autologous bone marrow support for the treatment of metastatic and primary breast cancer. Analysis of data submitted to the North American Bone Marrow Transplant Registry indicates that breast cancer is now the most common diagnosis for which a transplant is performed in the United States. The number of bone marrow transplants performed for breast cancer is greater than the number of allogeneic bone marrow transplants carried out for acute and chronic myeloid leukemia combined. Even more autologous transplants are performed for breast cancer than for non-Hodgkin's or Hodgkin's disease. However, despite this enthusiastic adoption of the use of high-dose chemotherapy, only recently prospective randomized trials been completed that support the value of high-dose therapy in metastatic breast cancer. The results of prospective multicenter trials in high-risk primary breast cancer will not be reported for many years.

This rapid adoption of high-dose chemotherapy reflects the general dissatisfaction with the results of treatment with conventional-dose therapy and the uniform results of treatment with high-dose regimens in phase I and II trials reported from numerous centers. The latter studies demonstrate an increased objective response rate and provide suggestive evidence of a higher frequency of durable complete remissions (CRs) as compared to the general experience with conventional-dose therapy. Most reports of high-dose therapy have indicated that CR rates of 45–70% are achieved in patients with hormone-insensitive metastatic breast cancer, with overall CR and partial response (PR) rates being >85%. For young women with metastatic breast cancer these rates appear attractive, particularly when coupled with data from several series indicating that 15–25% of poor-prognosis patients remain progression-free for >3–5 years after treatment.

Phase II studies in high-risk primary breast cancer patients with ≥10 involved axillary lymph nodes were undertaken because the relapse rates associated with the use of conventional-dose therapy were consistently >60% at 5 years and are based on the hypothesis that the higher objective response rates observed in patients who received high-dose therapy might translate into significant improvements in disease-free survival rates obtained in the adjuvant setting, where the tumor volume is lower. These studies found that the use of high-dose combination alkylating-agent therapy as consolidation after conventional-dose chemotherapy resulted in unexpectedly high disease-free

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and overall survival rates. With the follow-up period exceeding a median of 7 years and a minimum of 5 years, 64% of patients with a median of 14 involved lymph nodes at diagnosis remained alive and disease-free at 5 years. These data prompted the initiation of two multicenter trials of high-dose consolidation chemotherapy in this patient population. The results of these trials will undoubtedly be influential in determining the ultimate place of high-dose therapy in the treatment of breast cancer.

Underlying concepts of high-dose therapy

The use of high-dose chemotherapy derives from laboratory and clinical observations of tumor-cell growth properties and the ability of chemotherapy to affect the growth of both quiescent and replicating tumor populations. The fundamental concepts were derived to a large extent by Howard Skipper and Frank Schabel from murine models exploring the dose, dose intensity, schedule, and class of chemotherapy. Many of these observations were published in a series of booklets by the Southern Research Institute that were circulated in limited numbers to investigators involved in chemotherapy program design and testing. This review concentrates on three of Skipper's rules, their application to high-dose therapy, and their interpretation in the light of data arising from two new prospective randomized trials using high-dose chemotherapy conducted by the authors.

Skipper rule 1: the total tumor-cell-kill hypothesis

Skipper rule 1 is: "In order to achieve cure, it is necessary to eradicate the tumor stem-cells (both T/0 and T/R cells in both the primary and metastatic sites) using tolerated local and/or systemic treatment." Although at first glance this hypothesis may seem obvious, there are several important implications of the rule that should be considered in the development and interpretation of high-dose studies. It is perhaps fundamental to the concept of high-dose chemotherapy that eradication of the tumor-stem-cell burden is the therapeutic aim. The total-body tumor-stem-cell burden represents one of the major barriers to the cure of metastatic cancer. It has thus become a principle of contemporary oncology that efforts targeted at smaller tumor burdens are more likely to be successful. The aim of all therapeutic strategies aimed at cure must be total eradication of all tumor stem cells. The manner by which these tumorcells are eradicated is to a large extent irrelevant. Surgery has the capability of rapidly reducing the body tumor burden of localized tumors; similarly, radiation therapy can effectively sterilize limited tumor burdens. Systemic cancer dissemination implies the necessity for systemic treatment using chemotherapy, immunotherapy, or other molecular therapeutic approaches. Clinical experience has demonstrated that localized tumors can be eradicated by either local or systemic treatment but not by the same mechanisms; metastatic tumors are more likely to be cured by a combination of both local and systemic treatment.

As the tumor-stem-cell burden increases, the potential for multiple drug resistance to limit the efficacy of the therapeutic regimen increases, an observation derived from the above-mentioned rule. Skipper constrains the rule by noting the necessity of eradicating both sensitive and resistant cell populations from both primary and metastatic sites. The implication is that if a few or, potentially, even one tumor stem-cell remains at the end of treatment, it may successfully proliferate to kill the host. This observation has been consistently observed in animal models and is likely to be true in humans. Immune responses, natural or induced, that can deal with small tumor burdens may be capable of modifying this limitation but do not fundamentally alter the underlying principle.

The biological tendency of tumors to undergo spontaneous drug resistance mutations is generally accepted as a major reason for the inherent chemoresistance of large tumors. Goldie and Coldman have mathematically modeled this drug resistance and postulated that the transition from sensitive to resistant tumor populations can occur over a time as short as six tumor-cell-doubling periods.

In studies of high-dose chemotherapy these observations have implications for both the selection of disease setting as well as for the selection of multiple drugs and modalities of therapy for combination in the high-dose chemotherapy setting. Observations in the metastatic disease setting have relied on a combination of conventional-dose chemotherapy programs consolidated with high-dose chemotherapy. Many studies have demonstrated that bulky tumors at pretreatment sites of disease are frequently the sole sites of recurrence, and this has resulted in the combined use of surgery and radiation therapy at sites of pretreatment bulky disease.

The selection of earlier disease settings, such as the adjuvant treatment of breast cancer, would also be expected to improve the results of high-dose chemotherapy; the shorter natural history provides less opportunity for the development of multiple drug resistance, and the total-body tumor-stem-cell burden is smaller. Other considerations, such as the kinetic properties of smaller tumors, probably also play a role but are not addressed herein.

Skipper rule 2: the dose-response and first-order-kinetics rule

Skipper rule 2 reads: "There is an invariable direct relationship between the single dose of a given chemotherapy agent and the number of drug-sensitive tumor stem-cells killed. In a given cancer, the same dose of a given drug will kill the same fraction or percentage (not the same number) of widely different tumor burdens of drug-sensitive cancer stem-cells. It follows that in vivo dose-response curves or in vitro concentration-response curves should be (and are) exponential for homogeneous drug-sensitive tumor stem-cell populations."

The fractional kill doctrine, i.e., that in a given cancer the same dose of a drug will kill the same fraction of drug-sensitive cancer stem-cells, implies that the total-body burden of cancer will quickly become limiting for any given dose of chemotherapy. One potential way to overcome this limitation is to escalate the dose of chemotherapy substantially. For certain classes of drugs, especially the alkylating agents, the dose-response relationship is log-linear within the clinically relevant dose range. This means that doubling of the dose of chemotherapy will result, even in resistant tumor types, in a 10-fold or greater increase in tumor-cell kill. Thus, for the more resistant epithelial phenotypes the use of dose-intensified chemotherapy offers the potential to enhance the tumor-stem-cell kill sufficiently to eradicate the body burden of cancer cells.

The limitation on the use of dose intensification is the damage to normal cell populations for which the dose-response relationship also holds. Among the alkylating agents the common dose-limiting side effect is myelosuppression. This can be avoided by the use of autologous bone marrow transplantation and, more recently, by peripheral blood progenitor-cell (commonly called stem-cell) transplantation, which can repopulate the marrow after an otherwise lethal dose of combination chemotherapy. The limiting toxicity to dose escalation is then relegated to the next major toxicity, generally to a visceral organ. Among the alkylating agents the nonmyelosuppressive toxicities differ substantially. For example, the dose of cyclophosphamide is limited by cardiotoxicity; that of cisplatin by nephrotoxicity; and that of carmustine by pulmonary or hepatic toxicity. Although these toxicities are substantial and formidable challenges, that they differ offers the potential to combine several agents in high-dose autologous stem-cell-supported regimens with nonoverlapping toxicities. These predictions from animal and phase I clinical trials have largely been supported by subsequent clinical observations.

Over the past 5 years, rapid developments in the supportive care of patients have markedly changed the tolerability of high-dose regimens. The treatment-related mortality associated with high-dose chemotherapy has fallen rapidly from $>20\%$ to 2–5% in most experienced centers. To a large extent this is the result of the use of peripheral blood progenitor cells and hematopoietic growth factors, which has resulted in shorter periods of myelosuppression and in improved patient tolerance of high-dose chemotherapy regimens.

The dose-escalation increment that has generally been achieved in these settings is in the range of 2-10-fold, although in selected cases, higher dose increases have been possible. Such dose escalations, particularly for the more sensitive epithelial tumors, would reasonably be expected to improve the tumor-stem-cell kill. The consistent clinical observation of frequent CRs is consistent with this hypothesis. Furthermore, the fraction of patients with metastatic breast cancer who achieve durable progression-free responses is consistent with the potential for high-dose therapy to eradicate the tumor-stem-cell burden. Our group has reported that a single treatment with high-dose cyclophosphamide, cisplatin, and carmustine with autologous bone marrow support has resulted in 3 of 22 (14%) patients with measurable, hormone-insensitive metastatic breast cancer achieving a CR and remaining continuously disease-free for >10 years. In this trial the therapeutic result can be attributed only to the high-dose treatment, since no other intervention, including surgery, radiation therapy, induction chemotherapy, or hormonal therapy, was utilized. Although the patient series is small, the demonstration that a single high-dose treatment can result in the eradication of a metastatic malignancy is supportive of Skipper rule 2.

The dose-intensity rule is derived from Skipper rule 2 and states that: "The dose intensity (dose per unit time) of anticancer drugs is the dominant treatment design variable with respect to the degree of therapeutic response (cure or nearness to cure at the nadir); however, duration of treatment and total dose often correlate best with the duration of response in treatment failures." The implication of this rule is that comparisons among various high-dose chemotherapy regimens are most appropriately done by examination of the percentage of long-term progression-free patients, not the median duration of response. The latter is more indicative of the ability of treatment to modify the growth characteristics of cellular populations that remain after chemotherapy.

Skipper rule 3: the inverse rule

Skipper rule 3 is: "There is an invariable inverse relation between the cancer stem-cell burden and curability by chemotherapy used alone or in an adjuvant setting." This rule has at once an obvious and also an obscure relationship to the total tumor-cell-kill hypothesis discussed above. There is the obvious relationship that as tumor volume becomes larger, the tumor-stem-cell kill necessary for cure increases. Given the inherent limitations on tumor-cell kill imposed by the dose-response rule, large tumor burdens will be killed less effectively than small tumors. Thus, the inverse-rule prediction of curability would clearly obtain.

Less obvious is the relationship of this rule to the development of spontaneous drug resistance by mutation as espoused by Goldie and Coldman. This interpretation of rule 3 takes the form of an invariable direct relationship between the tumor-stem-cell burden and the presence of specific resistant cells. In other words, the longer or larger a tumor has grown, the greater the probability that the development of drug resistance will manifest and result in reduced curability.

The two interpretations of this rule are operative at the same time and reflect different populations within a tumor. The first interpretation relates to the effect of the total tumor burden on the effectiveness of a given chemotherapy regimen in chemotherapy-sensitive cell populations; the latter interpretation relates to the effect of the total tumor burden on the development of drug-resistant cell populations. The operative effect of both of these interpretations is that an increase in the tumor burden rapidly alters the

curability of tumors by chemotherapy for reasons related to both chemotherapy effectiveness and intrinsic drug resistance.

Randomized trials of high-dose chemotherapy in metastatic breast cancer

Recently, two prospective randomized trials using high-dose chemotherapy to treat metastatic breast cancer have been reported. The first, reported by Bezwoda et al., randomized patients with metastatic breast cancer to either two cycles of high-dose chemotherapy [cyclophosphamide, mitoxantrone, etoposide (CNV)] or six to eight cycles of conventional-dose CNV chemotherapy. The study demonstrated a significantly higher objective response and CR frequency for high-dose therapy and a significantly improved disease-free and overall survival rate.

The second trial, called the AFM randomized trial, reported by Peters, evaluated a high-dose chemotherapy strategy in 423 patients with hormone-insensitive metastatic breast cancer. Patients were treated with up to four cycles of doxorubicin, 5-fluorouracil, and methotrexate (AFM), and if a CR was achieved the patients were randomized either to immediate consolidation with high-dose combination alkylating agents [cyclophosphamide, cisplatin, and carmustine (CPB)] plus autologous bone marrow support or to observation with the use of high-dose CPB if the disease recurred. The trial demonstrated that the use of induction AFM followed by immediate high-dose CPB resulted in a significantly improved disease-free survival rate as compared to induction with AFM alone but showed that the strategy of AFM induction, observation, and CPB plus autologous bone marrow support at recurrence resulted in a better overall survival rate. In this group the overall survival rate at 5 years was $>40\%$ as compared to 22% in the patients treated with immediate high-dose consolidation chemotherapy. This result, which at first appears counterintuitive, can be interpreted in the context of the Skipper rules described above, particularly when considered in the context of the results of the South African trial.

The South African trial is consistent with the operation of the total tumor-cell-kill hypothesis, the dose-response rule, and the inverse rule. Conventional chemotherapy, when applied in metastatic disease, appears to be incapable of efficiently eradicating the total tumor-stem-cell burden. Consistent with this are the data indicating that all patients randomized to conventional-dose therapy relapsed and have since died. However, approximately 20% of the patients treated with the high-dose regimen remain progression-free at lead follow-up. The dose-response rule appears operative in that there is an increased frequency of CR and in that both disease-free and overall survival rates were improved with the high-dose consolidation regimen. The most effective evidence for the dose-response rule is the finding that the median time to treatment failure was prolonged in patients receiving high-dose therapy. The median duration of remission is indicative of the effect of the treatment in treatment failures, and the long-term remission rate (i.e., plateau) was also better in patients receiving high-dose therapy. Nonetheless, it is also relevant that the high-dose treatment resulted in a 20% disease-free survival rate, which is consistently reported in patients with metastatic disease and is also similar to that obtained with immediate high-dose consolidation in the AFM randomized trial.

At first appearance the AFM randomized trial would appear to be a violation of the inverse rule. Since the patients on the observation arm are subsequently treated with high-dose therapy at the time of recurrence of disease after CR, by definition the tumor burden of these patients is greater than that of those who are treated with immediate high-dose therapy while in CR. The observation that overall survival was superior in this population would appear to argue that for these patients, either the inverse rule was not operative, the dose-response rule was not operative, or other factors intervened to negate the effect of the rules. Closer analysis, however, indicates that the data are consistent with all of the rules and that the results of the South African study and the AFM randomized trial are reconcilable.

The reconciliation begins with a consideration of the dose-response rule as described above. The dose-response rule states that for a given tumor and drug the same dose of drug will kill the same fraction of drug-sensitive cells. In this regard the results of both the South African study and the AFM randomized trial are consistent with a fractional kill that is greater than that obtained with conventional-dose therapy. In both studies, disease-free survival was significantly prolonged, and in the South African study the median duration of overall survival was also significantly prolonged, indicating that high-dose therapy had a greater effect in the failing population. The interpretation of overall survival is more complicated in the AFM randomized trial because both arms received high-dose therapy, but on a different schedule or, more precisely, at a strategically different time.

The key to the interpretation of these studies is a consideration of the Skipper rules as modified by drug resistance in the inverse rule. Fundamental to the interpretation of the inverse rule is the hypothesis that the presence of drug-resistant cell populations is directly related to the tumor-stem-cell burden. Thus, at the time of the administration of high-dose chemotherapy in either study at either time there is a probability of the presence of drug-resistant populations (T/R in Skipper terminology) that will not be sensitive even to high-dose therapy. This T/R population limits the effectiveness of the treatment; this is reflective not of the effectiveness of the high-dose regimen on the sensitive cell population (the first interpretation of the inverse rule above) but rather of the limit on effectiveness resulting from the development of intrinsic resistance.

Within the tumor-burden difference that occurs between patients who achieve a PR or a CR the approach to eradication of the total tumor-cell burden is limited not by the magnitude of the cell kill but by the development of intrinsic resistance. This analysis is presented schematically in Fig. 1. Assume that high-dose chemotherapy can kill 10^8

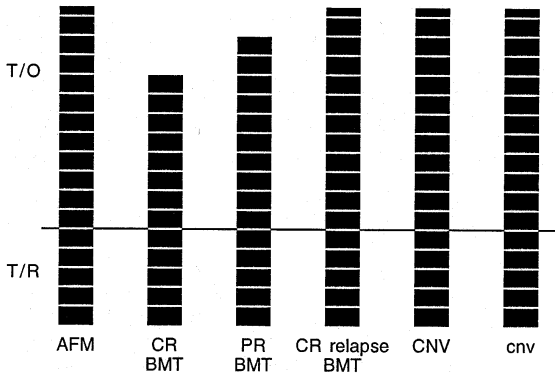

Fig. 1A, B Tumor-stem-cell kill achieved during high-dose treatment programs and the effects of tumor resistance on the total tumor-cell-kill hypothesis: concepts derived from the AFM randomized trial and the South African trial of high-dose therapy. Shown are the log-tumor volumes estimated at each of the major treatment points for A the AFM randomized trial and B the South African trial. At the time of presentation with metastatic disease, the tumor burden is highest in both the AFM randomized trial and the South African trial. AFM induction chemotherapy or conventional-dose CNV can produce a reduction in the tumor-cell burden but does not eradicate the tumor. T/0 refers to the drug-sensitive tumor-cell population and T/R to intrinsically resistant cell populations. High-dose chemotherapy is sufficiently cytotoxic to eradicate the T/0 population but is incapable of eradicating the multiply resistant T/R population. Treatment of patients in either CR or PR or at the time of relapse from a CR results in different total cell-kill rates because of the differences in tumor burden at the time of treatment and the limitation on total eradication in the presence of the T/R cell population

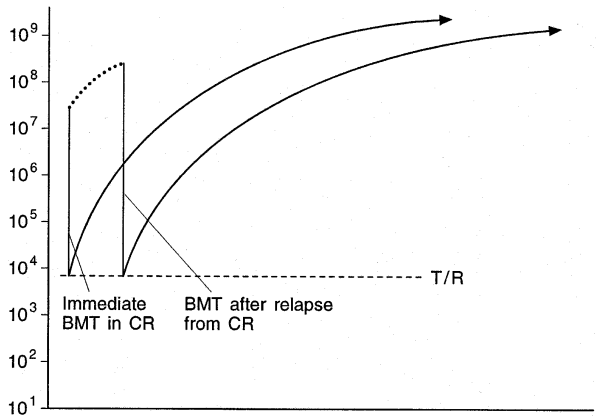

Fig. 2 Regrowth of tumor-stem-cell populations after high-dose chemotherapy carried out at different times during the AFM randomized trial. Due to the limitation of total tumor-cell kill by the presence of T/R cells, the regrowth of tumor populations from their minimal level after high-dose chemotherapy could explain the difference in overall survival data. The results seen, with regrowth from the minimal level being reached when patients who achieve a CR or PR receive autologous bone marrow transplantation, are consistent with the data shown for overall survival. The longer overall survival that results after recurrence during patients observation is the result of the additional time over which the patient has been under observation. Other hypotheses raised to explain these observations are discussed in the text

T/0 (sensitive) tumor cells but that by the time of the administration of high-dose chemotherapy there are 10^3 T/R (resistant) tumor-cells. At the time of CR, assume that the total tumor-cell burden is 10^6 cells (composed of 10^3 T/R cells and $9.97 \cdot 10^5$ T/0 cells). At the end of high-dose chemotherapy, 10^3 T/R cells remain because the high-dose therapy has killed all of the sensitive (T/0) cells but has not affected the T/R cells. Therefore, the result would not be different if the patient were in PR with a total burden of 10^8 cells, including a resistant cell population of 10^3 T/R cells, because the total kill of T/0 cells would be affected by the high-dose chemotherapy, but the limitation to achievement of Skipper rule 1 (total tumor-cell kill) is the presence of resistant cells (T/R).

If this is the case, then what is the explanation for the longer overall survival noted in patients who are treated with the strategy of induction therapy, observation, and bone marrow transplantation at recurrence? In this case the explanation is most easily seen by addition of the time under observation to the effect of tumor-cell kill. If the limitation to cure is the presence of resistant cells, the median duration of the survival curve reflects the growth characteristics of the surviving cell population (presumably T/R). The regrowth characteristics of tumor stem-cell populations from a "floor" of a T/R population would be expected to be similar and would therefore add to the overall survival by the amount of time added by the total cell kill of T/0 cells at whatever time the chemotherapy is carried out.

In reality, the data suggest tumor growth characteristics that are consistent with a fraction of the patients (approximately 20%) who have not, at the time of high-dose treatment, developed a cell population resistant to the high-dose regimen. This also implies that the relatively short interval between randomization to observation and recurrence (approximately 4 months) is not a sufficient period to change substantially the total number of T/R cells in the host. The fraction of T/R cells present will differ substantially between the arms since high-dose chemotherapy will be expected to have killed a much larger fraction of the T/0 cells.

The above-mentioned analysis is based upon the number of T/R cells remaining essentially unchanged from post-induction therapy until the use of high-dose therapy on either arm. This could be incorrect and the number of T/R cells might either increase or decrease. Assuming that the T/R cells were entirely unaffected by the induction chemotherapy, they would continue to grow and perhaps develop additional resistance through spontaneous mutation. The longer the interval between induction chemotherapy and the administration of high-dose chemotherapy, the greater the likelihood of this effect being operative. In contrast, it is possible that the resistance characteristics of the tumor might change favorably due to reversal of the resistant phenotype. The basis for this hypothesis is that although alkylating agents are effective anticancer agents in G_0-phase cells, they are more effective when the cells are cycling. It would not be unreasonable to expect that T/R cells might not be killed by induction therapy but that their kinetic activity would be significantly affected due to sublethal drug injury. These cells would at this point be

less sensitive to high-dose chemotherapy if the latter were given immediately. However, if there were a delay in the administration of high-dose chemotherapy and tumor-cell repair were to occur, followed by an increase in the kinetic activity of the tumor, the effectiveness of the same high-dose chemotherapy would be improved because of the greater effectiveness of the alkylating agents in this tumor with a high growth fraction. Although this hypothesis could adequately explain the results of the AFM randomized trial, it is less satisfying as an explanation of the difference in overall survival seen between the South African study and the delayed-transplant arm of the AFM trial. The available data, however, are inadequate to decide among these hypotheses.

Implications for future trials

These data raise important questions and suggest significant opportunities in the administration of high-dose chemotherapy in breast cancer. The testing of high-dose therapy earlier in the natural history of breast cancer, such as the high-risk setting, is important, and considerations derived from the inverse rule and the dose-response relationship would argue that this would be a better setting for improving the efficacy of the treatment. In contrast, these studies and their interpretations raise questions about the appropriate timing of high-dose chemotherapy and as to whether there might be any role for the use of induction chemotherapy in affecting the plateau seen after high-dose therapy. It is conceivable that the early and single use of high-dose chemotherapy would allow maximization of the tumor-cell kill and obviate any additive advantage of combination with conventional-dose therapy. The data indicate that there will be a need for additional therapy to attempt to eliminate the residual tumor-cell populations after high-dose chemotherapy. Combination of this approach with alternative strategies utilizing different mechanisms of killing may be important.

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