Theoretical Concepts and the Emerging Role of Taxanes in Adjuvant Therapy

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ABSTRACT
The proven benefits of adjuvant chemotherapy on disease-free and overall survival in breast cancer can be explained by concepts of cell kill. Interventions which result in greater log kill can be expected to produce improved clinical results. The application of log-kill concepts to human breast cancer growth, which appears to follow Gompertzian kinetics, suggests not only that the use of non-cross-resistant drugs is important, but that dose-dense schedules may have an advantage over conventional schedules of drug administration. Sequential therapy may allow dose-dense administration of cytotoxic agents and encourage the integration of new biological agents into combination regimens, particularly with the taxanes. Ongoing trials in these concepts are reviewed. The Oncologist 2001;6(suppl 3):30-35

INTRODUCTION
Evidence for the existence of occult micrometastases at the time of diagnosis is overwhelming [1]. Equally clear is that some form of systemic therapy is the only treatment which may have an impact on the problem of occult disease [2]. This paper presents certain theoretical concepts important to our understanding of empirical data in the field of adjuvant therapy.

At the start of the development of medical oncology, Skipper et al. introduced the important concept of log kill [3, 4]. Although the model was based on murine tumors, it was soon extrapolated to human systems. A fundamental concept is that killing of cells is the ultimate determinant of outcome in an organism harboring a cancer. The extent of cell kill predicts disease-free survival, and improved disease-free survival translates into extended overall survival [1, 2, 5, 6].

Several methods of killing cells are relevant to the adjuvant setting: these include hormonal manipulation through selective estrogen receptor modulators such as tamoxifen and (historically) hormone manipulation through oophorectomy. However, this paper focuses on the effects of chemotherapy, and in particular, on how active agents can be administered together in combination and sequentially to maximize clinical benefit. In this context it is important to note that the pattern of growth seen in human cancers is not the same as that seen in murine tumors, and hence a more sophisticated view is needed of cell kill and its consequences.

EXPONENTIAL GROWTH, LOG KILL, AND CHEMOTHERAPY
Central to our understanding of tumor growth is the expectation that cell numbers will increase exponentially, i.e., that numbers double and continue doubling over a certain fixed unit of time [7]. Such a pattern of growth appears as a straight and rising line when a logarithmic scale is used on the y axis to represent cell number while time is represented on the x axis on an arithmetic scale.

Extrapolation of this pattern of growth, which is typical of murine leukemias, led to the idea that roughly one liter of tumor cells would represent a lethal volume of cancer in humans and that diagnosis of the disease could not be expected until somewhere between $10^{10}$ and $10^{11}$ tumor cells.

The concept of log kill is represented graphically in Figure 1. Exponential increase in tumor cell number can be interrupted by one or more cycles of treatment, each of which produces a substantial fall in the log number of cells. However, the effect of each treatment is simply to move the exponential growth curve to the right, at which point the rise in cell number resumes at its previous rate [5-9].

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This relatively simple picture is complicated by heterogeneity in the sensitivity of tumor cells to a particular drug. A resistant clone will not suffer a fall in cell number with initial treatment and will continue to grow exponentially [10]. This problem can be tackled by introducing a second drug into therapy [5, 6, 9-11]. Figure 2 shows how this might achieve a log kill of all cell populations. However, to maintain this effect, the two-drug combination needs to be continued for repeated cycles (Fig. 2). This concept forms the rationale for combination chemotherapy.

The clinical situation, of course, is considerably more complicated. Combining an agent which achieves a 50% response rate (RR) as monotherapy with another agent with a 50% RR achieves an RR of perhaps 60% or 65%, rather than 100%, since cell populations overlap in drug sensitivity [11].

**CELL KILL AND ADJUVANT CHEMOTHERAPY**

Figure 3 presents a series of curves taken from data presented recently at the overview meeting of the Early Breast Cancer Trialists Collaborative Group in Oxford, England [2]. The top left panel shows curves for overall survival and relapse-free survival which are based on data pooled from the control arms of all available studies of adjuvant chemotherapy. The panel below shows a set of four growth curves which can explain these results. On the left-hand side is a curve showing the 90th percentile growth rate: 90% of tumors grow at a slower rate than that indicated by this line. At the right is the 60th percentile growth rate.

The top right-hand panel shows the curves for relapse-free and overall survival using data pooled from the chemotherapy arms of all available studies. Below are the growth curves that can account for these data. Compared with the curves generated from data from control patients, they are all shifted to the right. In essence, they show that the improved relapse-free and overall survival seen clinically in trials of adjuvant chemotherapy could have been achieved through a one-log cell kill. This ignores any effects on variables such as regrowth kinetics but is important in showing that the basic concept of the log-kill model is valid in the adjuvant setting.

**Figure 1.** Concept of log-cell kill: the effect of each treatment to move the exponential growth curve to the right.

**Figure 2.** Combination chemotherapy is necessary to achieve log kill where populations of tumor cells are not equally sensitive to a single drug.
Importantly, the growth curves that fit the data generated by trials of adjuvant therapy are not the straight lines of exponential growth. They curve in the particular sigmoid shape known as “Gompertzian” [5, 12-14]. Since the rate of cell growth is faster in the early rather than the latter part of the curve, the effect of early intervention is greater than that of later intervention. The log kill is therefore probably greater in tumors of small volume than in those of larger volume, and this is reflected in Figure 4.

In this situation, administration of chemotherapy using conventional alternating schedules will not eradicate cell clones of different sensitivity [15]. As cells sensitive to one drug are being killed, resistant cells are growing; and the same is true when the second drug is used (Fig. 5).

In this situation, delays in drug administration or schedules which cycle drugs over a more prolonged period may actually work against the efficacy of treatment. An alternative is to compress the conventional schedule, giving doses closer together in time in so-called “dose-dense” therapy [5, 15, 16]. In simulations, this simple manipulation achieves a considerably greater efficacy by minimizing regrowth of cells between cycles of treatment (Fig. 6).

This concept can be extended to encompass situations of heterogeneous drug sensitivity through the use of sequential dose-dense regimens (Fig. 7) [5, 6, 17-19]. This represents a new view of the way to proceed. However, there is empirical evidence to justify it, and the approach underlies several important ongoing clinical trials involving agents such as the taxanes.

**ONGOING CLINICAL TRIALS**

In the Cancer and Leukemia Group B (CALGB) 9344 study, patients with T1-3 N1-2 breast cancer were randomized to receive a fixed dose of 600 mg/m² cyclophosphamide plus doxorubicin at either 60, 75, or 90 mg/m² for four cycles [20, 21]. This was followed by a second randomization to either four doses of 175 mg/m² paclitaxel or no further chemotherapy, with tamoxifen administered in hormone receptor-positive disease. The dose of doxorubicin given had no impact.
on survival. However, the intriguing aspect of the study is seen when its results are set in the context of data presented from other trials at the recent Oxford meeting [20-22].

Table 1 shows that single-agent adjuvant chemotherapy has a weak and non-significant impact on the odds of recurrence and death. However, combination chemotherapy using CMF has a large and significant effect, while epirubicin plus doxorubicin further increases the annual odds of survival by approaching 16%. The sequential use of doxorubicin plus cyclophosphamide (AC) followed by paclitaxel improved the odds of recurrence-free and overall survival by greater than 20% when compared with AC alone.

Since this trial, the CALGB has attempted to further explore the possibilities of clinical benefit by comparing a three-weekly regimen of AC followed by paclitaxel with a two-weekly, and hence, more dose-dense regimen using the same drugs with G-CSF support. In this Intergroup/CALGB 9741 study, patients are also being randomized to two arms of the study in which the three drugs are given sequentially as doxorubicin followed by paclitaxel and cyclophosphamide in two- or three-week cycles.

Several trials are also investigating the effects of combination chemotherapy in a more formal way. A Breast Cancer International Research Group (BCIRG) trial is randomizing patients to six cycles consisting of either docetaxel 75 mg/m² or 500 mg/m² 5-fluorouracil (5-FU), with each drug combined with doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (i.e., TAC versus FAC). An American Intergroup study is investigating a similar comparison between 60 mg/m² each of doxorubicin and docetaxel versus 60 mg/m² doxorubicin plus 600 mg/m² cyclophosphamide, each administered for four cycles.

The choice between taxanes and schedules is being investigated in an Intergroup/Eastern Cooperative Oncology Group study in which node-positive, HER-2 negative patients are randomized to one of four treatment arms. Following four cycles of doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m², patients receive either four cycles of 175 mg/m² paclitaxel

<table>
<thead>
<tr>
<th>Comparison</th>
<th>% Reduction (± SD) in annual odds of recurrence and death [20-22]</th>
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<tbody>
<tr>
<td>Recurrence</td>
<td>Death</td>
</tr>
<tr>
<td>Single agent versus Not (3932)*</td>
<td>+7.9 ± 4.8</td>
</tr>
<tr>
<td>CMF versus Not (12175)*</td>
<td>+23.0 ± 3.0</td>
</tr>
<tr>
<td>Dox/Epi versus CMF (13756)*</td>
<td>+10.8 ± 3.1</td>
</tr>
<tr>
<td>&gt;6 months versus ≤6 months (3611)*</td>
<td>+7.0 ± 5.0</td>
</tr>
<tr>
<td>AC + T versus AC (3121)**</td>
<td>+22 ± 6</td>
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</tbody>
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Abbreviations: AC = doxorubicin plus cyclophosphamide; T = paclitaxel; Dox/Epi = doxorubicin/epirubicin

*Early Breast Cancer Trialists Collaborative Group, Oxford, 9000
**CALGB 9344, U.S. Food & Drug Administration Hearing, 9/99

Figure 6. Effect of dose-dense therapy on log-cell kill in Gompertzian growth.

Figure 7. Sequential dose-dense therapy.
apy. Patients will receive either doxorubicin 60 mg/m² followed by CMF or to epirubicin followed by docetaxel alone. A multi-institutional French trial will randomize a similar population of stage II lymph node positive patients to either six cycles of 5-FU plus epirubicin and cyclophosphamide or three cycles of FEC followed by three of docetaxel.

NEW TARGETS IN BREAST CANCER THERAPY

In the new era of cancer therapy, the targets of intervention are extending from the DNA itself to include multiple features of the tumor cell. These new targets include tyrosine kinase receptors such as epidermal growth factor receptor and HER-2, adhesion molecules, matrix proteins, and signal transduction molecules [23-26]. Among these targeted therapies, the attack on HER-2 is ripe for clinical testing [26-30]. One important study in progress is the Intergroup/North Central Cancer Treatment Group trial in which patients with HER-2 positive disease all receive four cycles of AC. This is followed by the administration of weekly paclitaxel alone, weekly paclitaxel followed by Herceptin or paclitaxel accompanied by Herceptin with continuing Herceptin thereafter. Since this study includes a Herceptin-free arm, the study addresses issues of potential Herceptin cardiotoxicity as well as efficacy.

The BCIRG study is of similar design: randomization is to four cycles of AC followed by four of docetaxel 100 mg/m², four cycles of AC followed by four cycles of docetaxel plus Herceptin which then continues for one year, or six cycles of docetaxel plus platinum salts (either cisplatin 75 mg/m², or carboplatin area under the concentration time curve 6) accompanied from the outset by weekly Herceptin for one year.

This avenue of research promises to significantly improve our ability to extend disease-free and overall survival of patients with primary breast cancer, and even point the way towards better management of advanced disease.

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