Hypothesis

The Relationship between High-Dose Treatment and Combination Chemotherapy: The Concept of Summation Dose Intensity

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Abstract

The most important variables for the clinical use of antitumor agents (AAs) are dose and combination chemotherapy. The objectives of this study were to analyze the relationship between these two variables and to propose a unified conceptual framework for the construct and interpretation of clinical trials. Definitions and variables with respect to dose include potency, therapeutic index, standard dose, efficacy, relative efficacy, dose-limiting toxicity (DLT), dose rate, dose density, dose intensity, and fractional dose intensity. Our overarching concept, that is, summation dose intensity (SDI), was calculated in several ways, depending upon the nature of the data, and included the relative efficacy method, the unit regimen method, and the high dose method. The SDI concept was then applied to disease categories and strategies to determine its usefulness and effectiveness in integrating dose and combinations. The tumors and settings were: mustargen-vincristine-procarbazine-prednisone in Hodgkin’s disease, combination chemotherapy for acute lymphocytic leukemia in children, metastatic breast cancer including dose and combinations, selected other solid tumors, alternating chemotherapy, and high dose studies in the leukemias and lymphomas. SDI was effective in integrating and quantifying dose and combination chemotherapy. For classical AAs, the implication of SDI for the construct and analysis of clinical trials was emphasized. In addition to new drug development, emphasis should be given to reducing or eliminating DLTs, such as those of the marrow, now and, in the future, those of the gastrointestinal tract toxicity and other DLTs. The above was derived from and applies to the classical AAs. Whether they will apply to, with appropriate adjustment, agents with significantly different dose-response curves, such as biotherapeutics and hormonal agents, remains to be determined.

Introduction

What is the relationship between dose and combination chemotherapy? The two approaches developed separately, in that dose was the central theme for bone marrow transplantation investigators, whereas combination chemotherapy occupied the interest of hematologists, oncologists, and pharmacology-oriented researchers (1–3). Today, we are witnessing a synthesis of these two paradigms. Here, we develop the concept of SDI, propose that it can be used to explain much of what has been achieved in the past with combination chemotherapy, and, by applying it to high-dose treatment, link the two approaches.

A formula for curative chemotherapy is presented in Fig. 1. Almost without exception, the cure of a given form of clinically evident cancer requires the combination of at least three active agents. Here, an active agent is defined as one that, when used alone, produces at least a 30% response rate in a given tumor. The major rationale of basic science for using combinations to cure cancer has been to overcome tumor cell heterogeneity, particularly as it relates to drug resistance (4–6). The curable tumors include ALL, AML, Hodgkin’s disease, non-Hodgkin’s lymphoma, testis cancer, choiociarcinoma, hairy cell leukemia, Burkitt’s lymphoma, Wilms’ tumor, and embryonal rhabdomyosarcoma (7–9). Although it is true that very chemosensitive tumors such as choriocarcinoma and localized Burkitt’s lymphoma can be cured with one agent, the cure rate is generally higher with combinations of agents, and the more common and generalized forms of these tumors require combinations of three or more agents (7–9).

There are a few tumors for which there are three or more active agents that cannot be cured by chemotherapy. These include follicular lymphoma, small cell lung cancer, and chronic lymphocytic leukemia (7–9).

As is evident in Fig. 1, a major research objective is the identification of clinically active agents and their combination, where appropriate, into dose, combination, and multimodality treatment strategies (2, 4, 7).

A major principle of dose effect is that it depends upon the intrinsic chemosensitivity of the tumor. An insensitive tumor (zero effect at standard doses) is unlikely to respond to higher doses. On the other hand, a highly sensitive tumor (4-log kill
with standard dose) may be curable by a 3–5-fold increase in
dose, made possible by stem cells (3). Randomized studies
confirm the highly important effect of dose in chemosensitive
tumors such as lymphoma, AML, ALL, myeloma, and testis
cancer. Tumors of intermediate chemosensitivity include breast
cancer, ovarian cancer, and small cell lung cancer (7–11). For
these tumors, comparative studies often, but not always, indicate
a significant dose effect on response rate, but the effect on
survival has been limited (7–12). On the other hand, a large,
statistically powerful study has demonstrated a survival benefit
as a result of increasing dose intensity in the adjuvant chem-
otherapy of primary breast cancer (12). For less chemosensitive
tumors (non-small cell lung cancer and bowel cancer), a signif-
icant dose effect has not been demonstrated.

Supportive care and toxicity have a reciprocal relationship
(Fig. 1). Lessened morbidity and improved dosing with chem-
otherapy have been increasingly attained by advances in sup-
portive care. Examples include platelet transfusions, antibiotics,
antiemetics, marrow transplantation, and, more recently, periph-
eral blood stem cells and growth factors (13–15).

The potential for cure is inversely related to tumor burden
(Fig. 1). There are circumstances in which clinically evident
(macroscopic) tumor is generally not curable by chemotherapy
but the same tumor in microscopic form (adjuvant setting) is
curable. These tumors include breast cancer, osteosarcoma,
colorectal cancer, ovarian cancer, and several of the childhood
solid tumors. Although single agents can increase long-term
tumor-free survival in selected adjuvant programs (e.g., melpha-
lan in breast cancer), one can almost always do better with
combinations, generally of three or more agents (6–12, 16–20).

An additional adverse factor is prior chemotherapy. As will
be discussed later, more recent clinical and laboratory observa-
tions with respect to drug resistance, particularly mechanisms
relating to multidrug resistance and apoptosis, have significant
bearing on this prognostic factor (21–24).

Our thesis is that the final outcome of either a high-dose or
combination treatment must, in part, be related to the sum of the
dose intensities of all of the agents used in that treatment. Until
now, there has not been a satisfactory method of describing or
deriving this parameter, so that it can be applied across all
treatments and all diseases. We propose that such a parameter
can be derived and that it be designated SDI, and we suggest
several approaches for its derivation.

\[ \text{Curative Cancer} \quad \frac{\text{Combination}}{\text{Chemo-}} \quad \frac{\text{Supportive}}{\text{therapy}} \quad \text{Active Agents(a)} \times \text{Chemotherapy(b)} \times \text{Dose(c)} \times \text{Care(d)} \]

\[ \text{Tumor burden} \times \text{Prior Chemotherapy} \times \text{Toxicity} \] or radiotherapy

Fig. 1 Formula for curative cancer chemotherapy. (a), active = 30% response rate; non-cross-resistant. (b), concurrent combined administration of three or more active agents. (c), full dose maintained in combination (i.e., nonadditive toxicity). (d), particularly stem cells, blood products, and growth factors.

Dosage Definitions, Calculations, and Evaluation

The definitions and variables to consider concerning dose
include the following.

Potency is usually expressed in vitro as the molar concen-
tration required to inhibit or kill 50% of the cells (i.e., IC₅₀). The
lower the dose (or concentration) required to produce a given
effect, the greater the potency will be.

Therapeutic index is sometimes referred to as tumor select-
vivity and is defined as the relative effects of the agent on the
tumor as compared to the host, as follows:

\[ \text{Therapeutic index} = \frac{\text{Toxicity to tumor}}{\text{Toxicity to host}} \]

The full or "standard" dose of the individual agent when
used alone is that which produces acceptable and reversible
clinical toxicity. The efficacy of the agent is its antitumor effect
when it is used at its full dose. For the purposes of our study, it
was assumed that the dose-response curve for AAs in the
therapeutic range was linear (i.e., a 50% reduction in dose would
reduce effectiveness by 50%) and, conversely, that doubling the
standard dose would double its effectiveness in terms of initial
response (see below).

The relative efficacy of an agent in a combination is the
response rate for that agent divided by the median response rate
for all of the agents in the combination (Table 1).

DLT includes host effects up to the point that is acceptable
to the patient. The dose that produces DLT approximates the full
or standard dose and is that which would ordinarily be used in
a Phase II study. This is also true for nonmyelosuppressive
agents, as well as high-dose protocols in which myelosuppres-
sive agents are given together with stem cells.

The dose rate is the dose delivered per unit time. The
classical expression for dose rate over the course of treatment,
that is, dose intensity, is that developed by Hryniuk and Levin
(25, 26) that expresses dose intensity as mg/m²/week. This
allows for comparisons within studies and, in many circum-
stances, across studies. For practical reasons, the schedule of
drug administration has been disregarded, except in selected
circumstances. Comparisons of the effectiveness or of the
importance of dose rate may sometimes more conveniently be
expressed by the use of other units of time. For example, when
treatment is altered on a monthly basis, it may be convenient to
use 2 months as the time unit. Clearly, the duration of drug
administration must be constant if the impact of dose rate is to
be compared. Because development of resistance is a major
problem, the effectiveness of a given treatment diminishes over
time. Thus, the major effect of treatment may occur within the
first 2–4 months, depending on the disease (25, 26).

1 H. E. Skipper, personal communication.
Relative efficacy of an agent was calculated by dividing the response rate by the reference standard; e.g., relative efficacy was calculated as the product of fraction of full dose divided by dose rate when used in the combination divided by the dose rate when used as a single agent. This derived by the fraction or percentage of full dose delivered three methods for calculating SDI.

- **Relative Efficacy Method.** With this method, the SDI is derived by the fraction or percentage of full dose delivered multiplied by the relative efficacies of individual agents. This gives the fractional dose intensity for each agent, and the sum of these intensities is the SDI. The relative efficacy method, as applied to Hodgkin's disease and to metastatic breast cancer, is illustrated in Tables 1 and 2.

**Unit Regimen Method.** An entire regimen is assigned an SDI value of 1 unit, and fractions thereof can be calculated when there are variations in its time of delivery or the interposition in part or whole of other equiactive regimens. This method is most appropriate for analysis of the complex trials of ALLs and of alternating (cycling) chemotherapy (Tables 3 and 4).

**High Dose Method.** This method is similar to the unit regimen method, which can be adapted to high-dose regimens (Tables 5 and 6). The doses that are maximally tolerated when drugs are given singly with stem cell rescue are assigned an SDI of 1 unit. Fractions thereof are then assigned to each drug when given the fractional dose intensity for each agent, and the sum of these intensities is the SDI. The relative efficacy method, as applied to Hodgkin's disease and to metastatic breast cancer, is illustrated in Tables 1 and 2.

The fraction of the full dose for combination chemotherapy is the dose rate when used in the combination divided by the standard dose rate (i.e., the dose rate when the agent is used alone).

The fractional dose intensity for individual agents in a combination is the product of the relative efficacy of the agent and the fraction of full dose.

**SDI**

The term SDI is meant to integrate the contributions of the individual agents to a combination regimen. Here, we present three methods for calculating SDI.

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Table 3  First-line therapy of metastatic breast cancer and SDI

<table>
<thead>
<tr>
<th>Agent(s)a</th>
<th>Fraction full dose</th>
<th>Relative efficacy</th>
<th>Fractional dose intensityb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>0.60 (0.10)</td>
<td>1.33</td>
<td>70</td>
</tr>
<tr>
<td>C</td>
<td>0.45 (0.05)</td>
<td>1.0</td>
<td>1500</td>
</tr>
<tr>
<td>F</td>
<td>0.35 (0.05)</td>
<td>0.77</td>
<td>150</td>
</tr>
<tr>
<td>M</td>
<td>0.35 (0.05)</td>
<td>0.77</td>
<td>180</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>0.40 (0.05)</td>
<td>0.89</td>
<td>100</td>
</tr>
</tbody>
</table>

**Combination chemotherapy**

<table>
<thead>
<tr>
<th>Agent(s)a</th>
<th>Fraction full dose</th>
<th>Relative efficacy</th>
<th>Fractional dose intensityb</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.4</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>M</td>
<td>0.33</td>
<td>0.77</td>
<td>0.25</td>
</tr>
<tr>
<td>F</td>
<td>0.50</td>
<td>0.77</td>
<td>0.37</td>
</tr>
<tr>
<td>A</td>
<td>0.37</td>
<td>1.33</td>
<td>0.48</td>
</tr>
<tr>
<td>F</td>
<td>0.63</td>
<td>0.77</td>
<td>0.48</td>
</tr>
<tr>
<td>F</td>
<td>0.18</td>
<td>0.77</td>
<td>0.24</td>
</tr>
<tr>
<td>A</td>
<td>0.5</td>
<td>1.33</td>
<td>0.66</td>
</tr>
<tr>
<td>C</td>
<td>0.44</td>
<td>0.77</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Dose chemotherapy**

<table>
<thead>
<tr>
<th>Agent(s)a</th>
<th>SDI</th>
<th>Response [CR + PR (CR)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF</td>
<td>0.27</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>0.62</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>0.98</td>
<td>0.48 (0.04)</td>
</tr>
<tr>
<td>CAF</td>
<td>1.37</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>2.10</td>
<td>0.63 (0.13)</td>
</tr>
</tbody>
</table>

**Notes:**

- C, CPA; M, Mtx; F, FU; A, Adriamycin.
- Taken from Refs. 7–11 and 72–81; also W. HryniUk, E. Frei, III, and F. Wright. A single scale for measuring dose intensity chemotherapy in breast cancer: summation dose intensity, submitted for publication.
- Reference standard was the median of response (0.45). Relative efficacy = response/reference standard = (for doxorubicin) 0.60/0.45 = 1.33.
- Taken from Refs. 7–9, 11, and 72–80; also W. HryniUk, E. Frei, III, and F. Wright. A single scale for measuring dose intensity chemotherapy in breast cancer. Summation dose intensity, submitted for publication.
- DLT, marrow.
- Fractional full dose = dose used in combination divided by dose used as a single agent.
- Fractional dose intensity = fraction full dose × relative efficacy.

**Conclusion:** It is used within high-dose combinations, and the sum of these fractions is the SDI of the combination.

**SDI for Hodgkin’s Disease**

Combination chemotherapy was introduced early and effectively for both Hodgkin’s and non-Hodgkin’s lymphoma (27–29). Although the initial studies of curative combination chemotherapy were made in ALL, the Hodgkin’s protocols were less complex and were used here to introduce the application of SDI. The relative efficacy method for calculating the SDI was used.

The CR plus PR values for patients with Hodgkin’s disease are presented in Table 1. A median response rate of 42.5% for the individual components of the MOPP program was calculated. The relative efficacies of the individual agents were then determined by dividing the response rates of the individual agents by the median or reference standard response rate. For mustargen, the relative efficacy was 50%/42.5% = 1.2. The fractional dose intensity of the individual agents was calculated as the fraction of the full dose within the combination times the relative efficacy. SDI was then the sum of the individual fractional dose intensities (Table 1).

A response rate (CR plus PR) of 35–50% (Table 1) could be achieved with the individual agents at full doses, but CR rates were low (5–10%), and no patients were cured. For the combination of four agents (MOPP), the SDI was 3.30. This increased the CR rate from 10% to 70%, and the cure rate was increased from 0% to 40% (7–10, 29).

A similar analysis of the Adriamycin-based four drug combination ABVD (data not shown) revealed an SDI of 3.5, which is consistent with the evidence that ABVD is slightly superior to MOPP (Table 4; Refs. 7–10 and 30).

**ALL in Children**

After gestational choriocarcinoma, ALL was the first systemic cancer to be cured (31–33). Curative chemotherapy was introduced in the 1960s, and the cure rate has increased incrementally to the present level of 70–80% (Table 1; Refs. 34–36). Major contributions include platelet transfusions and central nervous system prophylaxis (31, 33, 36). However, systemic treatment with an increasing number of AAs was critical. Here, we used a modification of the unit efficacy method to calculate the SDI (see above).

With two drug combinations, a marked increase in CR rate occurred. Cure rates appeared with combinations containing four agents and SDIs approaching 3. With six to nine agents, a SDI of 5–7 could be achieved. The almost parallel increase in number of active agents and SDI was made possible by agents with nonadditive toxicity. Certainly, the dose, schedule, and sequence of agents were important, but clearly, SDI is a very important factor in the cure of ALL and is the factor that correlated most clearly with increasing cure rates (Table 3).

**Metastatic Breast Cancer Combination Chemotherapy and SDI**

Progress of chemotherapy for breast cancer has been slower than in the hematological malignancies because the disease is less sensitive to chemotherapy and CRs to standard doses of the single agents are uncommon (e.g., 5–10% in Table 2; Refs. 7–9 and 12). Most of these agents have myelosuppression as their DLT, and Mtx, FU, and Adriamycin have mucositis as well. Therefore, the doses have had to be reduced proportionately to accommodate combination chemotherapy.

We used the relative efficacy method. The relative efficacies for each drug separately and in combination were determined. Then, to calculate SDI, the dose intensities of the constituent drugs in each regimen were expressed as fractions of 1. The median value for CR plus PR (0.45) was chosen as the reference standard. All of the combinations were from randomized trials. There was good correspondence between the overall
response rate and SDI and, to a lesser extent, between CR rate and SDI. Note that marrow toxicity was dose limiting for all of the agents used in combination. Mainly because of this, dose reduction was required, and the SDIs for the combinations ranged from 1.02 to 1.36, which is similar to the range of the response rate and SDI and, to a lesser extent, between CR rate and SDI. Note that marrow toxicity was dose limiting for all of the agents used in combination. Mainly because of this, dose reduction was required, and the SDIs for the combinations ranged from 1.02 to 1.36, which is similar to the range of the best two agents, CPA and doxorubicin, when they are used alone. This is in accordance with with response rates for CAF, CMP, and FAC, which were 60, 55%, and 55%, respectively. The “good news” is that marrow toxicity can be largely prevented with stem cells. Thus, breast cancer is a major target for the HD-SCR approach. A significant dose effect has been found for combination chemotherapy regimens within the standard dose range of 0.27–2.1.

### Cisplatin and Solid Tumors

Cisplatin is the first nonmyelosuppressive agent that, when used in combination, consistently increases response rates in many solid tumors. For example, the PR rate for non-small cell lung cancer to cisplatin used as a single agent is 15–20%. For other active agents, such as vindesine, etoposide, FU, and CPA, the single-agent response rate is in the range of 10–20%. Combinations, excluding cisplatin, produce a 15–20% response rate, whereas those that include cisplatin produce response rates of 30–45%. This may be because of some biochemical interaction of cisplatin with the other agents or simply because cisplatin is presently the only agent with broad-spectrum solid tumor activity that is nonmyelosuppressive and, therefore, can be combined with most other agents at full doses, thereby increasing the SDI (7–9, 37).

### Alternating (Cycling) Chemotherapy and SDI

Alternating or cycling courses of chemotherapy were proposed and studied many years ago as an approach to delaying the development of drug resistance (38–40). It was reasoned that resistance takes a finite length of selection pressure time before it is stable. There is substantial evidence that short-term exposure to AAs will produce transient resistance. Thus, short courses of treatment with agent “A” might produce resistance that is transient and reverses during treatment with agent “B”; the same is true for B followed by A. Thus, it might be possible to cycle back and forth between A and B without the development of sustained resistance. In addition, Goldie and Coldman (39, 40) proposed that cycling therapy would allow for the delivery of more agents.

### Table 4 Alternating (cycling) chemotherapy and SDI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR (%)</th>
<th>DFS (%)</th>
<th>Toxicity</th>
<th>Relative dose intensity</th>
<th>SDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s disease (stages IIIB and IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOPP</td>
<td>70</td>
<td>40</td>
<td>4+</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ABVD</td>
<td>88</td>
<td>58</td>
<td>2+</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MOPP alternating with ABVD</td>
<td>80</td>
<td>52</td>
<td>3+</td>
<td>0.5 + 0.5</td>
<td>1</td>
</tr>
<tr>
<td>Osteosarcoma (adjuvant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mtx/LCV</td>
<td>40</td>
<td>1-2+</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>40</td>
<td>2-3+</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin alternating with Mtx/LCV</td>
<td>40</td>
<td>2-3+</td>
<td>0.5 + 0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin + Mtx/LCV</td>
<td>60</td>
<td>2-4+</td>
<td>1.0 + 1.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>ALL (remission maintenance)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mtx</td>
<td>2+</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-MP</td>
<td>2+</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mtx alternating with 6-MP</td>
<td>2+</td>
<td>0.5 + 0.5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mtx + 6-MP</td>
<td>2+</td>
<td>0.5 + 0.5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data were taken from Refs. 30 and 38–49.

* Relative dose intensity for control was set at 1. Control for Hodgkin’s disease was MOPP; for osteosarcoma, it was Mtx/LCV; and for ALL, it was Mtx.

### Table 5 Dose-intensive (marrow transplant) regimens for the leukemias/lymphomas

<table>
<thead>
<tr>
<th>Regimen</th>
<th>DLT (nonmyelosuppressive)</th>
<th>MTD (mg/m²) with marrow transplant when used</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alone</td>
<td>In combination</td>
</tr>
<tr>
<td>CPA + TBI</td>
<td>Heart</td>
<td>7000</td>
<td>7000</td>
</tr>
<tr>
<td>CPA</td>
<td>Lungs, liver</td>
<td>1200–1400 cGy</td>
<td>1200–1400 cGy</td>
</tr>
<tr>
<td>TBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BU + CPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BU</td>
<td>Liver, gastrointestinal</td>
<td>640</td>
<td>640</td>
</tr>
<tr>
<td>CPA</td>
<td>Heart</td>
<td>7000</td>
<td>7000</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>SDI = 2 (of 2)</td>
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</tbody>
</table>

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provide improved SDI because both programs were given every other month, which led to a dose rate or intensity reduction of 50% (to 0.5) and, therefore, an SDI of only 1, i.e., the same as that for the nonalternating programs (30, 41).

Adjuvant chemotherapy studies of osteosarcoma also illustrate this point (Table 4). Numerous historical studies indicated that the cure rate with amputation only was 15–20% (42). It was then discovered that adjuvant chemotherapy with either high-dose Mtx with LCV rescue (Mtx/VCV) or doxorubicin resulted in a 40% cure rate. When doxorubicin and Mtx/VCV were alternated at monthly intervals, there was no difference, as would be expected if SDI were the critical factor (43). Because the DLTs for doxorubicin and Mtx/VCV were different, it was possible to deliver them in combination without compromise in dose intensity. This required careful monitoring of the pharmacokinetics of Mtx and of renal function. It was predicted that an additive effect would increase the cure rate to 56%. The actual result of the combination, which had an SDI of 2, was a cure rate of 60%. Subsequent studies including multi-institutional randomized studies confirmed the prediction (Table 4; Refs. 44–49).

When patients with ALL in complete remission were randomized to receive (a) concurrent 6-MP plus Mtx and (b) alternating 6-MP and Mtx at monthly intervals, concurrent 6-MP plus Mtx had to be given at reduced doses because of the additive marrow DLT. Thus, for both programs, an SDI of 1 was achieved, and there was no difference in the duration of complete remission (Table 4; Ref. 38).

A comparative study by the CALGB, in which treatment was alternated after 6 months, demonstrated that 6 months of CMFVP followed by 6 months of VATH was superior to CMFVP for 12 months. This could mean that developing resistance to CMFVP did not cross over to VATH or that VATH, which includes Adriamycin and thiopeta, is more effective than CMFVP (50).

### Table 6 Triple-drug high-dose regimens (STAMP regimens) developed at the Dana-Farber Cancer Institute

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose-limiting toxicity transplant</th>
<th>MTD with transplant when used</th>
<th>Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Heart</td>
<td>6,500</td>
<td>0.93</td>
</tr>
<tr>
<td>BCNU</td>
<td>Liver, lung</td>
<td>800</td>
<td>0.75</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Nerve, kidney</td>
<td>160</td>
<td>1.00</td>
</tr>
<tr>
<td>CTC</td>
<td>Heart</td>
<td>6,500</td>
<td>0.9</td>
</tr>
<tr>
<td>CPA</td>
<td>Liver</td>
<td>800</td>
<td>0.63</td>
</tr>
<tr>
<td>TSPA</td>
<td>Mucositis</td>
<td>2,000</td>
<td>0.48</td>
</tr>
<tr>
<td>Carboplatlin</td>
<td>Liver</td>
<td>16,000</td>
<td>2.00</td>
</tr>
<tr>
<td>ICE</td>
<td>Nerve, renal</td>
<td>2,000</td>
<td>0.9</td>
</tr>
<tr>
<td>IFF</td>
<td>Liver</td>
<td>2,500</td>
<td>0.5</td>
</tr>
<tr>
<td>Etopside</td>
<td>Mucositis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> MTD in combination/MTD when used alone.

<sup>b</sup> BCNU, bis(2-chloroethyl)-1-nitrosourea; TSPA, thiopeta; IFF, ifosfamide.

SDI and HD-SCR for Solid Tumors

The evidence is substantial that combinations of chemotherapeutic agents are superior to single agents in HD-SCR (Table 5). The MSD of TBI that can be given in the marrow transplant situation is ~1200 cGy, depending on dose rate and shielding technology. The most common DLT is pulmonary. For CPA, the MSD is 6.5–7 g/m². DLT, excepting myelosuppression, is cardiac. With stem cell myeloprotection, TBI and CPA can be combined with minimal compromise in the dose of each modality. More recently, BU plus CPA has proven as effective as CPA plus TBI. With BU plus CPA, it also has been possible to use nearly full MTDs of the individual agents in combination (see Discussion; Refs. 51–54).

The myelosuppression that occurs with many chemotherapeutic agents has precluded their use at full or nearly full doses in combination. However, in recent years, stem cell rescue has provided increasingly effective myelo-protection. What is the SDI potential for combined HD-SCR therapy?

We examined three combination regimens developed at the Dana-Farber Cancer Institute for HD-SCR treatment of solid tumors (Table 6). The first combination was CBP (55–57). The DLTs in the transplant setting for these agents are cardiac for CPA; liver and lung for 1,3-bis(2-chloroethyl)-1-nitrosourea; and kidney and peripheral nervous system for cisplatin. Do these nonoverlapping toxicities allow for improved SDI in the HD-SCR setting (57, 58)?

The MTDs in the transplant setting for these agents used alone and in combination are presented in Table 6. Here, we use the high dose method of calculating SDI, as described above. The fractions of the individual doses in the combination, as compared to when they are used alone, are also presented. If toxicity were completely additive, the SDI would be 1; if toxicity were totally independent, SDI would be 3. The ratios shown are high, i.e., 0.93, 0.75, and 1.00. This provides an SDI of 2.7. The selection of the three agents for the CBP combina-
Table 1. Summary of Dose Intensity and Response Rates

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Summation Dose Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>ALL Response</td>
<td></td>
</tr>
<tr>
<td>CR rate</td>
<td>20-50</td>
</tr>
<tr>
<td>Cure</td>
<td>10</td>
</tr>
<tr>
<td>Hodgkins Disease</td>
<td></td>
</tr>
<tr>
<td>CR rate</td>
<td>5-20</td>
</tr>
<tr>
<td>Cure rate</td>
<td>45m</td>
</tr>
</tbody>
</table>

Fig. 2. Correlation of SDI with response. Each enclosure represents results as above. X axis, SDI; Y axis, response by disease. 1, single agent; m, MOPP; a, ABVD; ma, MOPP alternating with ABVD; cmf, CMF; caf, CAF; aBMT, autologous bone marrow transplantation.

Discussion

There is an ongoing synthesis of two chemotherapy paradigms for common adult solid tumors: dose and combination chemotherapy. Dose increase was made possible by supportive care, particularly stem cells from the blood, and combination chemotherapy was made possible by an increasing number of effective agents. The occasion for the paradigm synthesis was the observation of Schabel et al. (59) in 1978 that AAs were commonly not cross-resistant and could be used successfully in combination in preclinical systems. These findings were confirmed in human tumor cells in vitro (60). Finally, the broadly available technology for autologous bone marrow transplantation and the need for improved treatment of solid tumors resulted in the rapid clinical expansion of this modality.

Here, we present the concept of SDI, which integrates and interrelates these two modalities, i.e., dose and combination chemotherapy, and provide evidence from clinical trials of the correlation between SDI with overall response. This evidence is summarized in Fig. 2. The correlations within a given tumor are methodologically secure. The correlations across tumors are provocative.

Although platelet transfusions and central nervous system prophylaxis played a significant role in childhood ALL, it is the number of active agents that correlates the most impressively with CR and cure rates (Fig. 2 and Table 3). Moreover, the increased number of agents (total of nine) provided a major SDI increase (to >7.5) because of nonadditive toxicity. Major dose compromise to accommodate the combinations was not necessary as in other tumors (see below). For both Hodgkin’s disease and ALL, the cure barrier is at about three to four active agents (SDI = 3). So-called third-generation combinations, such as Promace-MOPP, have not been found to be superior to MOPP or ABVD. This is because, although Promace-MOPP contains eight agents, the SDI is only 3–4. Thus, dose rate had to be sacrificed to accommodate the increased number of agents (27–29).

For metastatic breast cancer there are two limitations: (a) the agents are less active than in the leukemia/lymphomas producing PR rates only (CR rate, <10%), and (b) combinations provide limited improvement because essentially all of the ac-
tive agents are myelosuppressive and, thus, require dose reduc-
tion to accommodate combination chemotherapy.

Comparing dose intensity over the standard to HD-SCR range is difficult. There is a ~3–4-fold increase in dose of AAs or TBI made possible by myeloid stem cells. This constitutes a 6–8-fold increase in SDI, which is quite comparable to what can be achieved with combination chemotherapy as above. In ALL, Hodgkin’s disease, and non-Hodgkin’s lymphoma, SDIs in the range of 3 can be achieved with combinations such as MOPP, ABVD, CPA-Adriamycin-vincristine-prednisone, and related programs. These produce cure rates in the range of 50% (Table 1 and Fig. 2).

These data, taken together and summarized in Fig. 2, indicate a good correlation between SDI and response, suggesting that SDI will be useful in the construction and interpretation of clinical trials.

What are the implications and predictions of SDI? The classical view is that combination chemotherapy addresses the heterogeneity of tumors and decreases, therefore, the risk of drug resistance. High-dose therapy, on the other hand, increases log tumor cell kill. But, clinical drug resistance is often at low levels, such that a major increase in dose may decrease substantially the drug resistance population (3, 37). Combination chemotherapy may do the same because, at the downstream level, the mechanisms for programmed tumor cell death enter a common channel. These results suggest that combination chemotherapy is an approach to increasing dose.

The above would predict that the toxic and antitumor effects of chemotherapy are additive, that synergism and antagonism do not occur, and, indeed, that there is no qualitative interaction between agents used in combination. They would also predict that, given two agents, agent A and agent B, of equal antitumor activity, doubling A or B should equal A plus B. Clinical trials directed at this are not feasible, but the fact that the same SDI can be reached by two agents given at transplant doses (e.g., AML) and five to nine agents given in combination (e.g., childhood ALL) is consistent with that conclusion.

An important therapeutic principle that derives from SDI analysis is that the addition of an active agent, D, if it does not compromise the doses of the other agents, will have an additive therapeutic effect. A common design problem is the addition of one or several agents that are additive in terms of therapy but require comparable dose reductions because of additive toxicity. Examples here include many of the third-generation combinations for Hodgkin’s disease (61). Related examples include alternating schedules that double the number of agents but halve the dose rates (Table 4).

In the solid tumors, in which response to the individual agents is substantially less than that in the hematological neoplasms and in which myelosuppression is dose limiting for all agents except cisplatin, one must, out of necessity, compromise dose to accommodate combinations. It is not surprising, therefore, that combinations such as CMF, CAF, and FAC require substantial reduction in doses of the individual agents and that the limited increase in response correlates with the SDI. Randomized studies of two dose levels in metastatic breast cancer indicate a close correlation between SDI and response (Table 2).

Studies made possible by stem cell myeloprotection allow a 3–4-fold increase in dose of the individual agents. For example, many years ago, high-dose CPA was combined with TBI and, later, BU at full transplant doses of each agent. One explanation is that the nonmyelosuppressive DLT is cardiac for CPA, hepatic (i.e., venous occlusive disease) for BU, and pulmonary and liver for TBI. The vagaries of differences in treatment groups over time and overall advances in treatment make it quite impossible to know how much more effective are the combined treatments with either CPA plus TBI or CPA plus BU compared to either component alone.

It has been suggested that any one of the agents, such as CPA, might be as active at maximum high dose with stem cell protection compared with the combination. The MSD of CPA used alone was 7 g/m². The MTD of CPA that can be used in the trialkytator CBP program, however, was 6 g/m². Given these figures, it seems most unlikely that CPA alone would be as effective as the trialkytator combination. This is consistent with the findings of Antman and Gale (58).

Methodological Problems. Ideally, single-agent effectiveness should be known with reasonable precision. This can be a problem, given heterogeneity with respect to experimental design, including the sample of patients, treatment protocol, criteria for response, and the time period and setting of the study. This problem is addressed in a manuscript in preparation in which we found good agreement between analyses of primary publications, textbooks, compendiums, and the opinions of experts. What variation existed would not affect the general conclusions here.

Another methodological problem relates to the dose effect. For calculation of efficacy within a combination regimen, we assumed a linear relationship between dose and response: if half the full dose intensity were used in the combination, the antitumor effect would be correspondingly reduced. This would apply only to the straight-line portion of the sigmoidal dose curve, but we believe it is a reasonable assumption for the classical cytotoxic AAs. Selected classes of AAs such as hormones and biotherapeutics differ substantially from the cytotoxics in terms of the dose effect. Pharmacokinetics may effect the dose curve, e.g., saturation of a catabolic enzyme. Analysis of the contribution of dose in the SDI context is a complex subject and will be dealt with in a separate communication.

A corollary of the statement that SDI accounts for most of the therapeutic effect of combinations is that the major rationales commonly invoked for combination chemotherapy have not contributed in a major way to improved responsiveness and cure. Such rationales include those relating to pharmacology, biochemistry, cytokinetics, recruitment, synchronization, bio-therapeutics (anti-soil and anti-seed), and alternating schedules. In addition, there is no clinically established evidence that alternating therapy is superior independent of SDI. As illustrated earlier, the Goldie-Coldman hypothesis, based on drug resistance, has not yet been borne out by clinical studies (39, 40). The impact of schedule and drug administration on SDI and response and the outcome of alternating chemotherapy can largely be explained through changes in SDI (3).

We do not mean to imply that there is no important inter-
action at a biochemical or cytokinetic level that contributes to the superiority of combination chemotherapy. Rather, we emphasize that such interactions do not have to be invoked and that much (possibly most) of the clinical data are consistent with the effectiveness of combination chemotherapy results from dose increase, as expressed by SDI.

Another rationale for combining drugs has related to a potential lack of cross-resistance. Although this may be so, our clinical analysis, which focuses on SDI, again indicates that combining agents may simply be a technique of increasing overall dose, i.e., the importance of summation dose is overriding and that lack of cross-resistance is less important. Indeed, in experimental systems, drug resistance is almost always relative and can be overcome by dose increase (3, 37).

Recent molecular studies support the position that drug resistance is multifactorial and that cross-resistance is common. Thus, the upstream effect of an agent may be specific, such as inhibition of dihydrofolate reductase by Mtx or DNA damage by an alkylating agent. Such effects are not lethal directly but rather may activate a downstream mechanism, e.g., the setpoint for apoptosis (programmed cell death), which may be determined by such characteristics as p53 mutations. Thus, the upstream specific effect, expressed as cell death, must be of sufficient magnitude to trigger the downstream effect, which is nonspecific. These and other studies of the determinants of drug sensitivity/resistance suggest that cross-resistance is more general than thought previously. Thus, the dose effect is highly complex. These observations, however, are not inconsistent with the notion that the primary mechanism of the superiority of combination chemotherapy is dose and summation dose, as expressed by SDI (37, 62–70). 5

The concept of SDI is not new. It goes back at least to our first attempts at combining Mtx and 6-MP in the mid-1950s. We believe that it is somewhere between a hypothesis and a fact. We did not include the more recent agents such as the taxanes and gemcitabine because SDI-type studies require an established and mature database.

Conclusions. From our analysis, we conclude that progress in cancer chemotherapy has largely depended on the identification of active agents (minimum requirement = 30% response rate; Fig. 1) and their use in increasing SDIs, made possible either by nonadditive toxicity or advances in supportive care, such as stem cell myeloprotection. This predicts that an active agent for a given tumor should provide an additive effect when it is added to a combination, provided there is no significant dose attenuation and provided the relevant studies documenting the effect of its addition have adequate statistical power. The next level, after myelosuppression, of DLT for cancer chemotherapy is oropharyngeal mucositis. Prevention of this complication is an active area of clinical investigation, in which transforming growth factor β, interleukin 11, keratinocyte growth factor, and amifostine are under study. Control of mucositis, as a component of supportive care, should extend the effectiveness of agents such as FU and doxorubicin and, in the transplant dose range, melphalan and thiotepa. We would predict that the improved results that would follow would largely be due to the increased SDIs of the new combinations (71).

References


The relationship between high-dose treatment and combination chemotherapy: the concept of summation dose intensity.


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