Formal Discussion: The Clinical Pharmacology of Anti-Leukemia Agents

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The toxicity of anti-leukemic drugs with special reference to clinical problems can be epitomized in the old adage that "if wishes were horses, every beggar would ride; if turnips were watches, I'd wear one by my side."

The sum total of adverse effects on normal tissues of the host, viewed as a negotiable price, is my definition of the toxicity of anti-leukemic agents. Not included are those effects caused by tumor destruction or alteration of tissues where a tumor had been, but only effects of the drug *per se* on normal body function and structure. One should consider these effects in the context of the adage. It would would be proposterous to pay the price of a watch and get a turnip in exchange. But we have not yet reached that Utopian agriculture where one can have the beauty of a diamond timepiece free.

The therapeutic index of many of the compounds that we have used is small, and, in fact, other than with those agents which have found their way into established practice, much of the time we have labored at chemopraxis rather than chemotherapy (4). It is a duty of the clinical investigator to distinguish between these purposes and to indicate the toxicity permissible today in clinical practice and that which is still a part of investigational leukemic research.

In human leukemia one does not have the liberty of some of the considerations of therapeutic index that have been discussed, such as a ratio of effective dose for 90% at a toxic cost of 10% lethality (ED_{90}/LD_{10}). Neither of these is obtainable. I would choose to introduce a new term, which is the clinically effective dose/the investigatively tolerated toxicity (CED/ITT). One cannot reduce this to a simple ratio. For example, at a ratio of 4, one has purchased a turnip if he settles for a dose active for 20% of patients, with a toxic dose in 5%, no matter how serious the toxicity, if in effect he had been able to achieve a ratio of 4 at an effective dose for 60% despite a higher, but still relative, cost of investigationally tolerated toxicity.

The status of the host is one of the major factors which influence chemotherapeutic index. This may be intrinsically disease-related: profound host differences exist in florid leukemia and in the remission state. A residual biochemical, physiologic, or structural abnormality from prior radiation or chemotherapy may markedly affect host response. Impaired marrow function, necrosis and inflammation in the alimentary canal, renal or hepatic dysfunction, and nutritional depletion all may modify subsequent toxic phenomena. Iatrogenic alterations of the host may drastically improve the observed therapeutic index of candidate compounds. Whole blood or red blood cell transfusions, the administration of γ-globulin, platelet transfusions, and leukocyte transfusions are technics which have found their way to clinical implementation. Marrow hyperplasia or hyperfunction, induced by androgen administration, has been advocated as a possible means of extending therapeutic index. The effects of corticosteroids on the total organism, often used but poorly understood, may modify to some extent the effects of drug toxicity encountered.

The nature of the disease, and its effect on the host, are of prime importance in the expression of drug toxicity. Thus patients with acute lymphocytic leukemia may be susceptible to lower doses of the drugs presently in use than patients with acute myelocytic leukemia (e.g., methylglyoxal-bis-guanylhydrazone, parenteral methotrexate). This seems to hold true for host as well as tumor.

A singular advance was made by Freireich *et al.* (3) in demonstrating anti-leukemic drug activity in the leukemic child in remission in contrast to the child in the florid leukemic state. This has led Acute Leukemia Group B to adopt this type of design almost routinely because of lesser toxicity and higher efficacy. In a study currently in progress (8, 9), children under 15 with acute lymphocytic leukemia were induced into complete remission with vincristine and prednisone in combination. Approximately 85% of these children who were floridly leukemic at the onset were induced into the complete remission state. At that point they were randomly allocated to 1 of 2 drug regimens: methotrexate, either (*a*) 3 mg/sq m of body surface, per day p.o., which is quite comparable to standard clinical regimens, or (*b*) 30 mg/sq m twice weekly, i.v. in the hospital and then i.m. during maintenance.

There is a significant difference in the duration of complete remission. The oral group sustained a median duration of 2 months; the parenteral semiweekly methotrexate group, which in fact had 3 times as much drug per unit time, still has $\frac{2}{3}$ of the patients in remission 9 months later. Subsequently, median complete remission was found to be 1 year. These results have been achieved at essentially comparable rates of toxicity. There clearly seems to be a superior therapeutic effect which should, some 16–17 years after the first exhibition of methotrexate, find its way rapidly into clinical practice as the desired way of administering methotrexate. These data have led us, of course, to embark on a study of the same interrupted high dose schedule of methotrexate by mouth (Acute Leukemia Group B, unpublished data).

Drug toxicity should be looked upon as a two-tailed phenomenon. Omission of drug studies, to avoid toxicity in a still uniformly fatal disease, is a course purchased at

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the expense of no chance for new information or possible therapy and without assurance that the patient will enjoy remaining life more. Surely this is a turnip purchased at the cost of a watch. Drugs can be viewed as biochemical dissecting tools. As we pick new ones and perform the dissections, some compounds may well prove to be selectively to the host's advantage. Some examples follow.

Alterations in the route and schedule of cytoxan administration in acute leukemia have shown higher efficacy when the dose was administered once weekly instead of daily (6). The drug is better tolerated by leukemic children i.v. rather than p.o. As much as 1 gm/sq m of body surface per week can be given intravenously.

Druckrey *et al.* (1) have reported the treatment of a sensitive ascites tumor from the rat with small doses of cyclophosphamide. During the animal's lifetime, a resistant tumor strain develops, which, upon administration of a large dose of the drug, demonstrates inconsequential therapeutic response. The same large dose of cyclophosphamide given *de novo* can lead to far more effective therapy of the tumor. Clinically one suspects that there is a decrease in the chemotherapeutic index associated with prior administration of a drug by suboptimal technic.

We have found, with combinations of methotrexate and 6-mercaptopurine, that there are acceptable increments of toxicity. These drugs have been given in full dose for each, and have led almost to a doubling of the induction of A1 marrow status (2). There is difficulty in picking the appropriate dose of drugs in combination at the outset; more often one can start with a full dose of both and then is obliged to reduce the dose in later maintenance administrations. There has been a substantial experience, however, to indicate that drugs whose toxicity is seen in many ways to affect the same sensitive tissues can be combined acceptably. We have had substantially greater experience and success in combining drugs whose toxicities do not affect the same tissues.

I would like to outline briefly the study to which Dr. Skipper's data gave paternity. Vincristine and prednisone, as described, are used in combination to diminish the lethal risk of active florid leukemia by inducing a complete remission state. The subsequent treatments are designed with the concept of delivering a lethal injury to the leukemic population in an attempt to arrive at minimum leukemic cell number and even, optimistically, possibly at the nonleukemic state.

Children are treated with 1 of 4 treatment programs assigned at random. Each program has 3 courses of treatment separated by as short as possible an interval to recover from the toxicity induced. This toxicity has not proved to be formidable with the doses chosen. No maintenance therapy is used thereafter, and the duration of unmaintained remission, together with marrow studies, will be used to estimate the leukemic population at the nadir. The treatments consist of 6-mercaptopurine, 1 gm/sq m, daily for 5 days in each course; methotrexate, 15 mg/sq m, for 5 days; cytoxan, 1 gm/sq m, once only in each course; or the sequential administration of a course of 6-mercaptopurine, a course of methotrexate, and a course of cytoxan. We hope to be able to report results to you shortly.

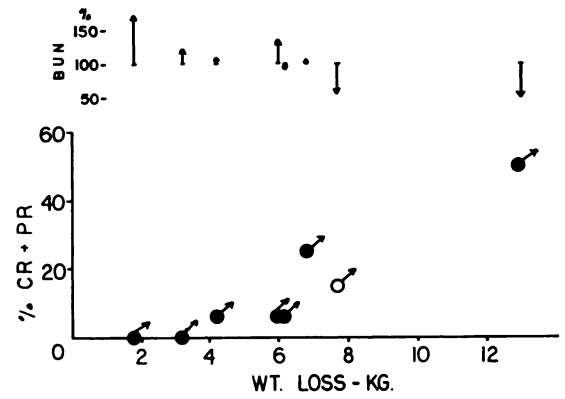

CHART 1.—Response to, and toxicity of, methylglyoxal-bisguanylhydrazone in men with acute myelocytic leukemia. Each point represents an institution's cases, plotted to show % remissions and median weight loss. Increase or decrease of BUN is shown as percentage of initial level for each institution shown.

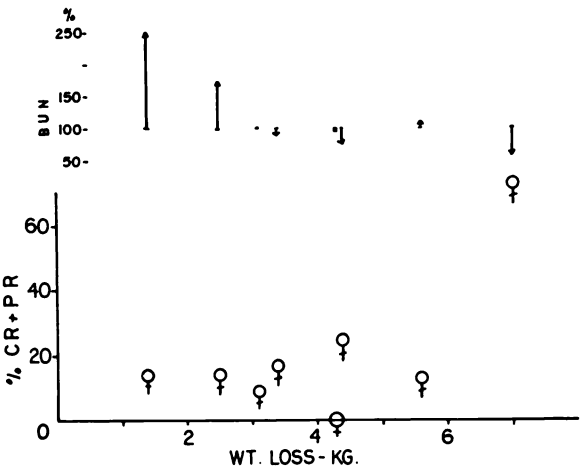

CHART 2.—Response to, and toxicity of, methylglyoxal-bisguanylhydrazone in women with acute myelocytic leukemia. See the text for additional details.

Our own experience with the terephthalanilides has been limited. They have not been studied exhaustively anywhere, but Burchenal's experience is as extensive as any and is presented below. We were impressed by the thrombophlebitis described by Louis *et al.* (7) upon the intravenous administration of the parent terephthalanilide (NSC 35843). It seemed to us they had not achieved a therapeutic trial because of this toxic limitation of administration. We therefore undertook to give the drug by the intracavitary route in man.

Unfortunately, the drug is a microcrystalline suspension, not a solution. It produced chemical peritonitis in 2 patients and chemical pleuritis in a 3rd, and we saw no therapeutic effects during this period. One of the requests that clinicians might make of chemists is a technic for dissolving currently insoluble substances so that they are physiologically tolerable.

Some data of Acute Leukemia Group B illustrate the point that there may be a level of effective dose at an investigationally tolerated dose (Chart 1). The charts represent patients with acute myelocytic leukemia, all of whom have been treated for more than 21 days, at doses

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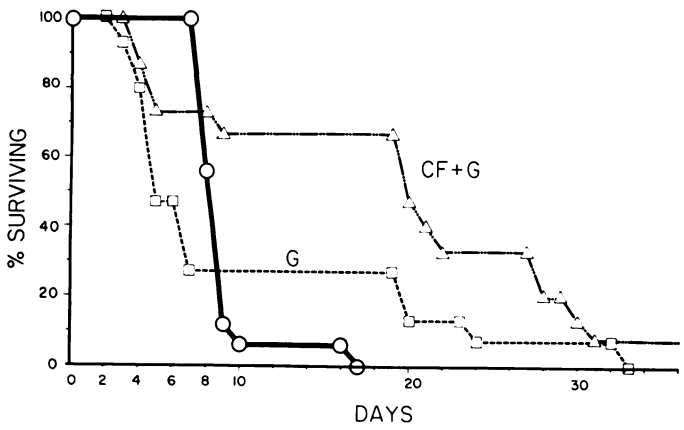

CHART 3.—Survival of AKD2 mice bearing subcutaneous Leukemia L1210. The heavy line represents saline-treated controls. *G* represents mice treated with 100 mg/kg of methylglyoxal-bis-guanylhydrazone. *CF + G* represents the same dose of *G* plus citrovorum factor, 140 mg/kg, administered 30 min prior to each dose.

greater than 4 mg/kg or an equivalent dose based upon body surface, with methylglyoxal-bis-guanylhydrazone (MeGAG).

A remission rate of approximately 50% was achieved in males in 1 institution. This correlates with the amount of toxicity that was induced. The cost can be measured in part as a median weight loss of 12.8 kg. In addition, a substantial reduction in the BUN occurred without other hepatotoxicity, possibly relating to the structural similarity of MeGAG and arginine, a precursor of urea biosynthesis. There is an apparent relationship between the amount of toxicity, the cost one is willing to pay, and the induction of remission from the disease. This must be viewed in the context of the other available remission inducers, of which there are precious few, and the short mean survival time.

The same phenomena are not so clearly demonstrated in women similarly treated (Chart 2). The remission rate for the group of patients with the maximum weight loss, however, was of the order of 70%. Again the reduction in BUN and weight is notable. To be sure, this degree of toxicity in the hands of some might be considered unconscionable. But it is my belief that the investigation is laudable and has opened a path toward the possibility of greater leukemic control. It is necessary to induce remission before one has substantial prospects of survival to receive other anti-leukemic treatments. What may be considered "clinically tolerable toxicity" is less than "investigationally tolerable toxicity."

Kensler referred to our data of selective protection against MeGAG toxicity. In mice bearing Leukemia L1210, premature death from MeGAG toxicity can be prevented by treatment with citrovorum factor (5). One can apparently spare the host and keep the residual anti-leukemic effect (Chart 3). Unfortunately, we were unable to recognize this increase in therapeutic efficacy in man (Acute Leukemia Group B, unpublished observations), possibly because the MeGAG dose we used in man was not at a level which needed this kind of amelioration of its toxic side effects, and the citrovorum factor dose was of necessity much less.

Modification of toxicity of nitrogen mustard with thiosulfate, of methotrexate with citrovorum factor, and of iododeoxyuridine with localized thymidine all have been demonstrated in clinical explorations. Conspicuous success by this approach in acute leukemia has not yet been reported.

The importance of the study of a placebo, even in marrow disease, should not be overlooked. A number of years ago we undertook a study of the chemotherapeutic effectiveness of urethan, a time-honored anti-leukemic agent, in multiple myeloma, a disease surely related in some of its pharmacology to chronic if not acute leukemia. We were not convinced of the activity of urethan in this disorder, and thus chose to administer to patients with myeloma optimal medical care with or without urethan on a random basis. We found that in a large group of patients, those who received urethan died earlier than those who received a placebo (J. F. Holland, Eastern Solid Tumor Group, Blood, in press). There is, then, a two-edged sword in any drug that we use with respect to selective activity on tumor and host. When significant effects on the tumor are encountered, one hopes they are not those that cost the host the price of a watch instead of a turnip.

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