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Editorial

The Clinical Evaluation of Analogues

I. The Overall Problem

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One of the major manifestations of the success of cancer chemotherapy is the fact that a wide variety of chemical structures have been shown to have antitumor activity. This diversity of active structures has offered significant opportunity for analogue development. At this moment in time analogue development rivals the search for new structure as the major thrust of drug development programs throughout the world. Drug development is a complex activity which begins with synthesis and moves through bioassay, pharmacology, toxicology, pharmaceutical development arriving ultimately at clinical trial. Each of the various steps in the drug development process require a modification of strategy in comparison to the strategy utilized for new structure development. This is particularly true for the clinical trial which is often given less thought from a strategic point of view as regards the unique problems of analogues.

Clinical trials of new agents are divided into three phases which have been described in great detail [3]. Phase I can be described as clinical pharmacology with the end-point being determination of a maximally tolerated, or optimally tolerated, dose and the elucidation of the clinical toxicology pattern. Phase II can be described as an efficacy screen in which evidence of clinical activity is sought which would warrant widespread trial. Phase II trials need to be approached from a disease-oriented point of view and ideally a phase II trial should be performed for each kind of cancer for which it is hoped that the drug might prove of value. This ideal is rarely, if ever, possible and a variety of compromises have to be made [2].

Phase III trials are the studies which attempt to elucidate the role of the drug in clinical practice. These trials usually involve larger numbers of patients and more complex experimental design and analysis techniques. Phase IV trials have been described as trials which validate the research findings in actual community clinical practice within a cancer control or technology transfer setting. The strategy of phase IV trials is a newly developing science which is in its early evolutionary stages. Another kind of drug trial is the combined modality trial where drugs are used as adjuvants to surgery and/or radiation therapy for the therapy of clinically localized or regional disease with a high likelihood of microscopic dissemination [5]. These trials are extremely complex and require both large numbers and a long term complex analysis which involve a range of survival and toxicologic parameters [4]. Each of these clinical trial phases have to be analyzed from a different point of view for analogues as compared to new structures. The major, and most obvious, reason for this is that the analogue must always be compared in some way to its parent clinical structure while the new drug stands alone and need only search for its role in competition with currently available therapeutic regimens.

There are four possible ways that an analogue can be an improvement over its parent clinical structure:

1. The analogue can show greater activity in responsive tumors.
2. It can show a broader spectrum of activity giving a meaningful response rate in a tumor type unresponsive to the parent compound.
3. It can show diminished acute toxicity.
4. It can show diminished chronic toxicity.

Each of these four possible ways to improve the therapeutic index requires a different strategy for experimental bioassay and for clinical evaluation. It is the purpose of this paper to briefly review the clinical trial strategy for analogues highlighting the unique aspects of this strategy as required by the four possible end-points of superiority.

All new drugs must begin with a phase I trial. The initial starting dose and schedule are derived from animal studies. The starting dose is usually derived from large animal toxicology studies [6] and the schedule from experimental tumor schedule dependency studies with a large dash of clinical empiricism. For some drugs the analogue strategy is geared toward diminished acute

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toxicity. For example the clinically used nitrosoureas have profound delayed marrow toxicity [1] and an active non-myelosuppressive nitrosourea would be of great clinical value. A variety of nitrosourea drugs with sugar moieties have been synthesized in hope that they would be less myelosuppressive. Drugs such as chlorozotocin in the United States, GANU in Japan, and RFCNU in France have entered clinical trial with such a hope. For such drugs the phase I study would give important data about the predictive value of the experimental logic. If such compounds showed profound delayed myelosuppression in phase I study further phase II study might not be worth undertaking. Acute toxicities for which amelioration in analogues would be of clinical value include the myelosuppression of mitomycin C, the vomiting of hexamethylmelamine, the cystitis of cyclophosphamide, the skin toxicity of bleomycin, the anaphylaxis of asparaginase, and the stomatitis of methotrexate.

For any analogue the toxicologic pattern at the conclusion of phase I study must be compared to the toxicologic pattern of the parent clinical structure. If the acute toxicity pattern shows either a quantitative increase in severity of a toxicologic index or a qualitative new toxicologic manifestation then phase II study might not be indicated.

The phase II strategy needs to be specifically tailored for each analogue area from the point of view of which tumor types are selected. The options include choosing only responsive tumors to the parent structure, choosing only unresponsive tumors to the parent structure or some mixture of the two. Difficulties arise if the parent structure is part of highly successful multidrug regimens for the responsive tumor types [2]. In this situation single agent phase II evaluation of the agent in previously treated patients becomes unrealistic unless experimental studies indicate some possibility of a lack of cross-resistance between the analogue and its parent structure. An example of this difficulty can be seen in contemplating the phase II evaluation of a vincristine analogue in Hodgkin's disease, where MOPP or other vincristine containing combinations are so highly efficacious. Other examples of this difficulty include a bleomycin analogue in testicular cancer, a methotrexate analogue in childhood leukemia, an adriamycin analogue in sarcomas, a procarbazine analogue in Hodgkins disease, and an arabinosyl cytosine analogue in adult leukemia.

If one restricts phase II study exclusively to unresponsive tumors for the parent structure the problems of design are diminished but the clinical test for the analogue becomes more rigorous. It is possible to restrict phase II studies of new adriamycin and bleomycin analogues to colon and melanoma patients or arabinosyl cytosine analogues to solid tumors but then one could miss a valuable therapeutic index increase for the responsive tumors. On the other hand however, one could argue that only an analogue good enough to have a broader spectrum of clinical activity should be tested for a superior therapeutic index in responsive tumors, given the difficulties in doing so for some tumor types.

From a toxicologic point of view, both the acute and chronic toxicity need to be looked at as comparative parameters in the evaluation as to whether large scale phase III studies are indicated. If comparable activity to the parent structure is observed for an analogue in a phase II trial but the acute toxicity is less, then further study might be warranted. If a slight increase in activity is seen but this is accompanied by either a new qualitative toxicity pattern or a greater severity of the existing pattern, then further study might not be indicated. Examples of analogues with new toxicity patterns include the jaw pain and postural hypotension of cyclocytidine as compared to arabinosyl cytosine and the central nervous system toxicity of ftorafur as compared to 5-fluorouracil. Examples of a greater severity of an expected toxicologic pattern include the acute bladder-renal toxicity of isophosphamide as compared to cyclophosphamide and the nausea and vomiting of imidazole mustard as compared to dacarbazine.

The chronic toxicities of some of the most active recent drugs have proven to be significantly self limiting to their use and have become specific targets of analogue development programs. The two most prominent examples are the cardiac toxicity of adriamycin and the pulmonary toxicity of bleomycin. The renal toxicity of cis-platinum diammine dichloride will be a third important area for future consideration. While chronic toxicity comparisions will be most feasible with the larger numbers of patients usually placed into phase III studies some data in phase II studies may well be available. The pulmonary toxicity, or lack thereof, of a new bleomycin analogue should be evaluable within the framework of a phase II analysis and extremes on either end of the scale could tip the balance for or against phase III trials.

Phase III trials introduce the full complexity of the disease oriented strategy which has begun to play its important role in the phase II area. A drug shown active for a given tumor in a phase II study is no longer then commonly compared in a controlled fashion with other active single agents in that disease. What is more likely to occur is that the active drug will be placed into combination regimens involving the other active drugs. These new combinations then become in many ways like a new drug again requiring a phase I and phase II process which is often covered under the rubric of pilot study. Assuming a positive pilot study, which will establish the dosage regimen for the combination and evidence of activity, then a phase III comparative study with another regimen will be most likely undertaken. The phase III decision concerning an analogue in comparison to its parent structure will in many cases be

whether a combination regimen including the analogue has been therapeutically superior to older regimens utilizing the parent compound. Randomized comparisions of two combinations which differ only in containing either an analogue or its parent compound are unusual. Therefore, the phase III analysis is often made with historical controls with all of the comparability problems involved in such analyses. Such analyses in many cases do not give clear answers and so one is left with many analogues which co-exist in the clinical trials arena for years with their parent structure without a clear answer being forthcoming. Some prominent examples of this include BCNU, CCNU, and Methyl CCNU for a range of tumors, adriamycin and daunomycin for acute leukemia, a wide variety of alkylating agents for a range of diseases, and 6-mercaptopurine and 6-thioguanine in acute leukemia. In many cases a phase III strategy for analogues is nonexistent and after phase II study analogues bounce around for years in a wide range of inconclusive trials which are wasteful of precious clinical trials resources. This is further complicated when analogues become commercially competitive as well as scientifically competitive. In this situation only a comparable therapeutic index may be considered acceptable as a criterion for commercial development.

Another aspect of the disease oriented strategy that impacts on analogue clinical evaluation is the combined modality strategy. The parent compound may be found to have as one of its important roles adjuvant treatment after surgery or concomitant with radiation therapy for apparent local control situations. In such situations chronic toxicity such as organ damage or carcinogenicity become highly important and comparisons between analogues frought with great strategic and analytical difficulties. Analogues of alkylating agents such as cyclophosphamide and L-phenylalanine mustard may have to be compared in areas such as adjuvant breast or adjuvant ovary trials. The endpoint in such studies will not be an objective response, but will be initially relapse free survival versus acute toxicity and ultimately overall survival versus chronic toxicity [7].

The phase IV, or community outreach, trial is a new area. These trials attempt to take regimens shown to be clearly valuable, in a clinical research setting, and demonstrate a positive impact for them in a community clinical practice setting. The methodology for evaluation of such demonstrations is an area of great debate currently. The major problem with evaluation of such community outreach, or cancer control demonstration, trials is that the classic techniques of experimental design are difficult to apply in such a way that endresults can be shown to have been improved by the new approach introduced. Analogue evaluation in the phase IV setting is just an added complexity which will have to wait its turn in the methodology lineup.

In conclusion it may be valuable to select out the four possibilities for analogue improvement and look at the strategy applicable in broad terms. It must be recognized that the clinical exigencies of any given structural class will call for modifications and most clinical trial strategies for analogues will mix these four approaches in some way. Future papers in this series will look at some specific structural classes and attempt to detail a specific strategy.

For greater efficacy in tumors responsive to the parent structure the ideal strategy would be one that most closely mimics the strategy outline given in drug development text books and review papers;

Phase I Study
↓
Phase II to see if a reasonable activity level can be demonstrated.
↓
Phase III controlled trial against parent drug.

For a broader spectrum of activity the strategy would be;

Phase I
↓
Phase II in unresponsive tumors to parent structure to see if any level of activity is seen.
↓
Phase III to establish a level of activity.

For diminished acute toxicity the strategy would be;

Phase I to compare acute toxicity patterns and severity.
↓
Phase II to establish a reasonable level of activity in responsive tumors to parent type.
↓
Phase III to establish at least comparable activity with diminished acute toxicity.

For diminished chronic toxicity the strategy would be the most complex of all;

Phase I
↓
Phase II to establish a reasonable expectation of activity and to get an early feel for chronic toxicity in responding patients given maintenance therapy on reasonable follow-up.
↓
Phase III trial to establish comparative activity as against comparative chronic toxicity.

Recognizing again that this is a gross simplification of a highly complex problem, future papers in this series will explore some specific drug classes such as the anthracyclines, bleomycins, nitrosoureas, fluorinated pyrimidines, antifoles and platinum coordination complexes to attempt to elucidate some specific strategies.

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