Clinical Strategy for the Development of Angiogenesis Inhibitors

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ABSTRACT

Angiogenesis inhibitors differ from conventional cytotoxic chemotherapy agents by targeting normal cells rather than tumor cells, which may contain multiple mutations. Because of this, the traditional strategy used in clinical development of cytotoxic agents may not be appropriate for these novel agents. Many clinical studies are now evaluating these agents with a new approach, referred to as the cytostatic paradigm. The cornerstone of the cytostatic paradigm is the use of time to progression (TTP) of disease as the decision-making criterion for “go/no go” in the early phases of clinical development. However, the use of TTP as the main criterion for clinical trials is complicated for a variety of reasons, including: A) the lack of standardized criteria accepted by regulatory authorities; B) the heterogeneity of the historical database, and C) the larger number of patients needed for the “go/no go” decision-making process. In addition, clinical trials of cytotoxic agents have traditionally used objective response (despite the controversy regarding objective response as a surrogate for clinical activity) as the main criterion for determining whether the results of phase II studies justify the pivotal phase III studies.

Another aspect of the clinical development strategy is combining angiogenesis inhibitors with cytotoxic chemotherapy. The rationale for combination of angiogenesis inhibitors with cytotoxic agents is based on: A) different targets for these agents; B) lack of cross-resistance patterns; C) lack of myelosuppression with angiogenesis inhibitors allows administration of full doses of all agents, and D) the assumption that combining these agents will result in additive antitumor activity. Combination therapy with angiogenesis inhibitors may be attractive to both clinicians and their patients because it allows cytostatic agents to be used upfront in treatment while contributing to drug registration strategy (cytostatic/cytotoxic combination therapy versus cytotoxic therapy).

The clinical development of the angiogenesis inhibitor SU5416, a small molecule inhibitor of vascular endothelial growth factor, is currently ongoing. In phase I trials, SU5416 demonstrated activity in both colorectal and non-small-cell lung cancer patients. Based on these encouraging results, phase III studies to evaluate combination of SU5416 with established cytotoxic therapy are planned. These studies will include an interim analysis, the equivalent of a phase II evaluation of clinical activity. If successful, this strategic approach will save significant time in the clinical development process. The Oncologist 2000;5(suppl 1):51-54

Angiogenesis inhibition is a new and exciting target for anticancer drug development. The drugs being developed against this target pose both conceptual and strategic challenges. Currently, there is no track record of success to help guide the development pathway. In addition, the cytotoxic drug development model is most likely not an appropriate one, since angiogenesis inhibitors will probably act in a cytostatic manner.

This paper will briefly outline the approach being taken by SUGEN, Inc. (South San Francisco, CA) in its development of SU5416, a small molecule inhibitor of the vascular endothelial growth factor (VEGF)-Flk-1 pathway.

The strategic assumptions being made by SUGEN are outlined in Table 1. These assumptions are mainly driven by the proposed cytostatic mechanism and the implication that the criterion of objective response—which served as the basis for registrational development of every cytotoxic drug currently approved in the United States—cannot be utilized as a surrogate marker for “go/no go” drug development decision-making in cytostatic agents. While it is well understood that
survival is the gold standard end point for registration of an experimental anticancer drug, its use for guiding early clinical development decisions is not practical.

For a cytostatic drug, if the phase II decision-making criterion cannot be objective response, what is the alternative? One alternative would be an end point of time-to-progressive disease (TTP). This implies that stable disease will result from cytostatic therapy; this translates into prolonged TTP. From this follows the implication that chronic administration will be required, which feeds back into the phase I decision-making criterion. For a cytostatic drug, the maximum tolerated dose (MTD) based on acute toxicity will not be the optimal dose to be chosen for phase II evaluation. What is needed is the highest dose that permits chronic administration, which is unlikely to be the traditional acute MTD that has guided cytotoxics in their development.

Another key strategic assumption made by SUGEN is that cytotoxic chemotherapeutic agents are not viewed as competitive to angiogenesis inhibitors and other cytostatics. Cytotoxics are potential partners that will optimize the goal of improving survival for cancer patients. In this view, success of cytostatics is likely to increase the usage of cytotoxics and expand their market. This conceptual approach is driven by the view that when used alone in metastatic disease, cytostatics will not be powerful enough to keep in check large tumor cell burdens. This will be particularly true if the single-agent phase II evaluation of a cytostatic drug had to take place in the second- or third-line treatment of metastatic disease because of ethical considerations, as other approved agents are available for later-stage cancer patients.

SUGEN has therefore shifted its development strategy to the view that combination of an angiogenesis inhibitor with chemotherapy has a strong rationale (Tables 2 and 3) and will accomplish the following: A) allow cytostatics to be used as front-line treatment for metastatic disease, and B) optimize the possibility of a survival improvement for metastatic cancer patients.

Table 4 compares cytostatics and cytotoxics from a strategic, disease-oriented placement perspective. The crucial difference is that with cytotoxics, the tradition is single-agent initial usage in advanced metastatic disease no longer amenable to “standard” therapy. With cytostatics, the move is quick after phase I to combination usage to attack first-line therapy situations.

Tables 5 and 6 compare cytostatics and cytotoxics in terms of the actual (cytotoxic) and the proposed (cytostatic) phase I and II development paradigms. In phase I for cytostatics, the key is that toxicity should be supportive of long-term chronic administration. In phase II, the dominant assumption is that TTP will be a surrogate for activity that allows a sponsor to take the risk of investing millions of dollars on survival-based, large-scale, registrational trials.
The use of TTP as a decision-making end point is not as simple as it may appear. TTP reflects stable disease, which has not been generally accepted as a “response” criterion (Table 7). Use of TTP as an end point within specific tumor types involves risks, as the criteria for determining progressive disease and their diagnostic correlates have not been standardized in the past. This is a concern of the Food and Drug Administration in the United States, which is one of the principal reasons that TTP is not an acceptable registrational end point except in rare “individu- alized” accelerated approval circumstances. Some of the difficulties in accurately measuring a standardized TTP across multiple centers—as would be in a phase III registrational trial—are listed in Table 8. These include the intensity and frequency of evaluation.

A further challenge in the use of TTP is the heterogeneity of the historical control databases. These data are frequently not analyzed or have not been collected in a systematic fashion correlated with prognostic variables. Thus, appropriate analyses are often difficult to perform, and the historical control groups are not well regarded as providing true comparison groups. With cytotoxics, a single-arm phase II study in colon cancer looking for a minimum of 20% response is viable in relation to the massive historical database. A single-arm study in the same disease with an end point of five months TTP would be problematical.

The conclusion reached by SUGEN was that the only phase II study design utilizing TTP as the end point was a randomized, controlled approach in which chemotherapy plus an angiogenesis inhibitor versus chemotherapy alone would be compared. Such a study utilizing 80 patients would allow an educated risk-taking decision on spending the dollars required for a survival-based registrational phase III study. Such a phase II “go/no go” study would in itself be expensive in terms of money and time. Given the importance of speed in the development process, however, it is the time factor that weighs more heavily on sponsors as they contemplate a traditional phase I-II-III sequence for angiogenesis inhibitors and other cytostatics (Table 9).

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With this in mind, SUGEN has undertaken a development strategy with SU5416 that involves the following sequence (Table 10): single-agent phase I—phase I pilot combination with an established cytotoxic regimen—combination phase II/III large scale registrational study with an early phase II-based interim analysis for safety and estimation of efficacy.

The potential value of this approach is that if it is successful in achieving registration, at least one year would be saved in the clinical development process. Saving one year can provide an extra year of exclusivity, which for a major new cancer drug could result in hundreds of millions of dollars in sales, as well as making the drug available for cancer patients one year earlier.

We felt this was an appropriate risk to take with SU5416 for the following reasons: A) the phase I study had shown 145 mg/m² i.v. twice weekly to be well tolerated in chronic administration; B) blood levels achieved had been above levels required for preclinical activity; C) the toxicity spectrum did not overlap with cytotoxics, and D) clinical and biological activity had been observed in cancer patients.

With the above facts in mind and the intrinsic logic of combining angiogenesis inhibitors and cytotoxics, SUGEN has undertaken registrational strategies for first-time use in colon cancer and non-small-cell lung cancer (outlined in Table 11) beginning subsequent to the initial single-agent phase I study. We are excited about this approach because it allows the registrational study to attack first-line therapy of metastatic disease where the chance to benefit a large number of cancer patients is the greatest.

Angiogenesis inhibitors are perhaps the most exciting new therapeutic target in oncology today. SU5416 is the first small molecule compound to enter registrational development in this area. With no track record of past success to guide us, we have attempted to modify the cytotoxic paradigm to fit the needs of cytostatic drug development in both a rapid and logical manner.