A Dynamic De-Escalating Dosing Strategy to Determine the Optimal Biological Dose for Antiangiogenic Drugs

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The concept and application of antiangiogenic therapy for the treatment of cancer has been on a long roller coaster ride. After years of promising, and sometimes exciting, preclinical studies, the first antiangiogenic drug clinical trials began in the early 1990s with the fumagillin analogue, TNP-470, eventually followed by phase III trials evaluating such diverse agents as SU5416, a small-molecule vascular endothelial growth factor receptor-2 antagonist, matrix metalloproteinase inhibitors, and bevacizumab (Avastin), the humanized anti-vascular endothelial growth factor monoclonal antibody (1). The first such trials yielded negative results, and the inevitable feeling of disappointment (2). The mood changed dramatically in May 2003 with the announcement of positive results in a randomized phase III trial of bevacizumab and irinotecan, fluorouracil, and leucovorin chemotherapy for the first-line treatment of metastatic colorectal cancer—the results of which were published in 2004 (3). Bevacizumab was approved for this indication by the U.S. Food and Drug Administration in February 2004, and more recently in many other countries. The drug has been on a tear since then with a string of positive results involving randomized phase III clinical trials in second-line colorectal cancer, first-line metastatic breast cancer, and late stage nonsquamous non-small-cell lung cancer, as a first-line therapy. All these final results (or interim trial results in the case of breast cancer) were presented recently at the 2005 American Society for Clinical Oncology meeting (4). There were also encouraging results presented involving single-agent (but multitargeted) small-molecule receptor tyrosine kinase inhibitors, notably Sutent (SU11248) and Sorafenib (BAY 43-9006) in renal cell carcinoma (4).

The results highlight several important questions. Why does a tumor-starving drug, such as bevacizumab, which presumably suppresses blood flow within a tumor and increases hypoxia, enhance rather than diminish the efficacy of chemotherapy? Could the modest survival benefits detected in the aforementioned trials using such combination treatments be improved by selecting different doses of a drug such as bevacizumab? Furthermore, related to the latter question, how does one go about determining the best dose of an antiangiogenic drug?

Limitations of Traditional, Toxicity-Guided Trial Designs for the Development of Antiangiogenic Drugs

Given their mainly cytostatic nature, conventional response criteria based on tumor shrinkage that have been historically used for cytotoxic chemotherapy are not necessarily appropriate for the assessment of many antiangiogenics, at least when they are used in monotherapy settings, and perhaps not even in combination treatment regimens involving cytotoxic chemotherapy (i.e., a survival benefit may be response-independent; ref. 5). Common side effects of many conventional cytotoxic drugs (e.g., myelosuppression) are not usually encountered when testing most antiangiogenics, although some of the small-molecule multitargeted receptor tyrosine kinase inhibitors could be exceptions to this rule (6). In fact, some antiangiogenic drugs are rather well tolerated and dose-limiting toxicities (DLT) may not be reached (7, 8). When DLTs do occur, the most efficacious dose, the optimal biological dose (OBD), may not necessarily coincide with the maximum tolerated dose (MTD). Because dose-escalation is usually toxicity-guided in traditional phase I trials (Fig. 1A; ref. 9), such designs may therefore be inappropriate for optimizing the use of some antiangiogenic drugs. For example, the MTD of bevacizumab in humans is ~20 mg/kg because of severe migraine headaches in some patients (10). In a randomized phase II trial of the drug (albeit with chemotherapy), however, a 5 mg/kg dose (but not a 10 mg/kg dose) was found to be effective in prolonging the survival of metastatic colorectal carcinoma patients (11). A more recent phase III trial of bevacizumab using the 10 mg/kg dose and FOLFOX4 chemotherapy for the second-line treatment of colorectal cancer was found to be effective (12). The question still remains: would the 5 mg/kg dose, if it had been used, be just as effective, if not more effective? Therefore, how might one go about testing several different doses in a phase I clinical trial and determining which one might be best? This is where new surrogate pharmacodynamic markers and clever new clinical trial designs are sorely needed, which brings us to the article by Dowlati et al. (13) in this issue of Clinical Cancer Research, in which they report a dynamic de-escalating dose trial design using the oral small-molecule vascular endothelial growth factor receptor-2 inhibitor, SU5416.
A, standard toxicity-guided phase I dose escalation trial design. The starting dose of a given drug is usually one-tenth of the LD_{10} in the most sensitive species (dose at which 10% of the animals die). Cohorts of three (to six) patients are treated per level and stepwise dose escalation is commonly based on a modified Fibonacci series. In the absence of DLT, the next cohort of patients is treated with the next higher dose level (\textbf{A}). If DLT is observed in 33% of cases, another group of patients is treated at the same dose level. If no further DLT is detected, dose escalation continues. Otherwise, it stops. If DLT occurs in >33% of cases, dose escalation is stopped without further testing. The dose for subsequent phase II trials corresponds for the most part to the level with <33% DLT. Modifications of this design such as accelerated titration and continual reassessment have been described.

B, novel pharmacodynamically guided phase I dynamic dose de-escalation design described by Dowlati et al. (13). Cohorts of 10 patients are treated per dose level. The starting dose (SD) corresponds to the MTD of a given drug, or a dose that should translate into plasma concentrations with antiangiogenic activity (AAA) in the case where MTD information is not available. The nature and extent of the AAA considered as being biologically meaningful is predefined. If >5 responses are noted with the starting dose, the next cohort of patients is administered a reduced dose. If this de-escalated dose results in an equal or greater number of responding patients compared with the starting dose (in which response is defined on the basis of a surrogate marker of angiogenesis), further dose de-escalation ensues. If the number of responding patients is reduced by 1-2 compared with the starting dose, that particular (de-escalated) dose is the candidate dose selected for further study in a randomized phase II setting. In case the number of responding patients is reduced by 3 or more compared with the starting dose, another cohort of patients is treated at an intermediate, higher (\textbf{B}) dose level. SD minus 1, 2, 3: number of responding patients = number of responding patients with starting dose (\textbf{B}) minus 1, 2, 3. C, individualized maximum repeatable dose (iMRD) dose-finding system by Takahashi et al. (28). Metastatic pancreatic cancer patients were started at half the MTD of weekly gemcitabine (500 mg/m^2). For a period of 5 weeks, toxicity was assessed weekly and the dose was maintained or adjusted in ±100 mg/m^2 steps based on the degree of toxicity observed. The individualized maximum repeatable dose is defined as the dose associated with minimal but detectable toxicity (\textbf{C}) during chronic administration of the drug.

Fig. 1. A, standard toxicity-guided phase I dose escalation trial design. The starting dose of a given drug is usually one-tenth of the LD_{10} in the most sensitive species (dose at which 10% of the animals die). Cohorts of three (to six) patients are treated per level and stepwise dose escalation is commonly based on a modified Fibonacci series. In the absence of DLT, the next cohort of patients is treated with the next higher dose level (\textbf{A}). If DLT is observed in 33% of cases, another group of patients is treated at the same dose level. If no further DLT is detected, dose escalation continues. Otherwise, it stops. If DLT occurs in >33% of cases, dose escalation is stopped without further testing. The dose for subsequent phase II trials corresponds for the most part to the level with <33% DLT. Modifications of this design such as accelerated titration and continual reassessment have been described. B, novel pharmacodynamically guided phase I dynamic dose de-escalation design described by Dowlati et al. (13). Cohorts of 10 patients are treated per dose level. The starting dose (SD) corresponds to the MTD of a given drug, or a dose that should translate into plasma concentrations with antiangiogenic activity (AAA) in the case where MTD information is not available. The nature and extent of the AAA considered as being biologically meaningful is predefined. If >5 responses are noted with the starting dose, the next cohort of patients is administered a reduced dose. If this de-escalated dose results in an equal or greater number of responding patients compared with the starting dose (in which response is defined on the basis of a surrogate marker of angiogenesis), further dose de-escalation ensues. If the number of responding patients is reduced by 1-2 compared with the starting dose, that particular (de-escalated) dose is the candidate dose selected for further study in a randomized phase II setting. In case the number of responding patients is reduced by 3 or more compared with the starting dose, another cohort of patients is treated at an intermediate, higher (\textbf{B}) dose level. SD minus 1, 2, 3: number of responding patients = number of responding patients with starting dose (\textbf{B}) minus 1, 2, 3. C, individualized maximum repeatable dose (iMRD) dose-finding system by Takahashi et al. (28). Metastatic pancreatic cancer patients were started at half the MTD of weekly gemcitabine (500 mg/m^2). For a period of 5 weeks, toxicity was assessed weekly and the dose was maintained or adjusted in ±100 mg/m^2 steps based on the degree of toxicity observed. The individualized maximum repeatable dose is defined as the dose associated with minimal but detectable toxicity (\textbf{C}) during chronic administration of the drug.
A Novel, Pharmacodynamically Guided Phase I De-Escalation Trial Design

Although de-escalation steps can be part of modifications of traditional phase I designs (9), the unique feature of the approach proposed by Dowlati et al. is to de-escalate to the OBD (referred to as a biological modulatory dose) based not on toxicity, but rather pharmacodynamic information (hopefully relevant to the drug’s mechanism of action), as outlined in Fig. 1B. The starting dose of SU5416 at 145 mg/m² i.v. twice weekly (which corresponds to the MTD), the DLTs of which are projectile vomiting, severe headache, and nausea (14), was given to patients with various advanced malignancies without curative or otherwise effective treatment options. Presumptive antiangiogenic activity was monitored by dynamic contrast-enhanced magnetic resonance imaging to measure changes in blood flow and vessel permeability in tumors, microvessel density counts in tumor biopsies taken serially, and by various plasma/serum markers. Four of the 19 patients had stable disease for ≥4 months, but no objective tumor responses were seen in any of the patients. No significant antiangiogenic activity of SU5416 was shown, even at the starting (maximum tolerated) dose, and consequently, the benefits of the trial design could not be explored. Nonetheless, the very minor antitumor effects and the absence of antiangiogenic activity of SU5416 at the doses used are not completely unexpected based on the published literature using this drug (7). The apparent absence of antitumor efficacy and the poor pharmacokinetics, as well as the greatly increased incidence of thromboembolic complications of SU5416 in combination with cisplatinum plus gemcitabine chemotherapy (15) resulted in the discontinuation of further clinical development of SU5416. This also highlights the need for predictive markers regarding such complications as recently described (16), and for assessing and monitoring antiangiogenic drug activity (17).

The choice of the particular angiogenesis surrogate markers used by Dowlati et al. is an unlikely explanation for their findings, although all the variables chosen for analysis have their shortcomings. Moreover, the decision of requiring a reduction of at least 35% in tumor blood flow and/or microvessel density as a measure of an antiangiogenic effect seems reasonable based on preclinical (cited in ref. 13) and clinical evidence (18). Even if the road taken by Dowlati et al. would have allowed the definition of the OBD of SU5416, some limitations of the design are obvious. As discussed by the investigators, the MTD or a dose with proven/predefined biological activity needs to be known beforehand. The number of patients per dose level (e.g., 10) is clearly greater than in traditional phase I trials for statistical reasons. In addition, a randomized phase II trial might be necessary to have better statistical proof of the clinical equality of the OBD compared with the MTD/starting dose. Yet only very few patients will be exposed to drug concentrations <OBD, a potential advantage compared with standard escalating designs. Finally, the application of such a trial design requires clinically validated surrogate markers of angiogenesis that can be assessed in a timely fashion to enable advancing rapidly from one dose level to another.

Surrogate Markers to Assess Antiangiogenic Activity

The advantages and drawbacks of various surrogate markers of angiogenesis have been extensively reviewed (19, 20). A noncomprehensive list includes (anti)angiogenic factors measured in various body fluids, cellular markers, such as circulating endothelial cells and endothelial cell progenitors, various imaging methods, in particular dynamic contrast-enhanced magnetic resonance imaging and biopsy analyses (e.g., microvessel density, endothelial cell apoptosis/receptor phosphorylation). An ideal surrogate marker would have the following properties: it should be noninvasively and repetitively available with minimal consequences to the patient, affordable, robust with respect to variations in the preanalytic and analytic phase, reasonably sensitive and quantitative, highly reproducible, as specific as possible for tumor-associated angiogenesis, and correlating closely with antiangiogenic (and antitumor) efficacy in different tumor stages, preferentially in a broad range of different neoplasias and under various therapies. As is the case with other disorders, it is likely that several variables assessed concurrently, not only one, will be needed for providing a comprehensive picture of the antiangiogenic activity. Once the OBD is determined, pharmacokinetic information might be used either in a complementary manner or as the main variable for guiding further clinical development. To base therapeutic decisions solely on pharmacokinetic information, however, could be misleading. First, the OBD is not an absolute value and might, for instance, vary depending on the tumor entity and the pharmacogenetic background of the tumor patient. Second, the dose with the most pronounced antiangiogenic effect might not necessarily correspond to the dose with the optimal antitumor activity in combination regimens comprising conventional cytotoxic drugs, as discussed below. Although in the literature, synergism or additivity is seen mostly (or at least reported, e.g., ref. 21), antagonistic activity has sometimes been described (22).

Do We Need to Know the Optimal Biological Dose if the Maximum Tolerated Dose is Known?

The antiangiogenic effects need to be fine-tuned and adapted over time to obtain the best antitumor response possible because suboptimal antiangiogenic therapy might, in some cases, lead to potentially more aggressive tumor progression (23). Combined with conventional cytotoxic drugs, the extent of the antiangiogenic activity might determine whether the combination is synergistic, for instance, by transient normalization of the tumor vasculature resulting in temporarily better oxygenation and drug deposition (24), otherwise, the combination could be antagonistic. A further layer of complexity derives from the finding that most conventional, and many targeted antitumor agents, exert “accidental” antiangiogenic effects (25). Indeed, if given in a metronomic fashion (i.e., administered frequently in comparatively low doses over prolonged periods with no prolonged breaks), traditional cytotoxic drugs might act primarily via antiangiogenic mechanisms that are accompanied by only low-grade toxicity (26, 27). As a corollary, the OBD of a given antiangiogenic agent might be context-dependent, necessitating an individualized approach. Such a strategy, for example, has been outlined recently.
by Takahashi et al. for metronomic-like weekly dosing of bevacizumab in metastatic pancreatic cancer (28). The authors describe a dynamic dose-finding system that potentially incorporates both escalation and/or de-escalation steps (Fig. 1C). Patients receive a starting dose of half the MTD (500 mg/m²) and are then dose-de-escalated or escalated to attain grade 1 toxicity (in most instances, based on hematologic toxicity). For some patients, this might be 300 mg/m², for others, 600 or 700 mg/m². Thus, weekly dose modifications are still toxicity-guided, but allow one to approach, stepwise, the presumed optimal dose (referred to as individualized maximum repeatable dose), defined as the dose associated with minimal but detectable (≤ grade 1) toxicity during chronic administration of the drug. This approach is appealing in terms of its ease of implementation and the antitumor effects seen; it remains to be seen whether the individualized maximum repeatable dose corresponds to the antiangiogenic OBD for weekly metronomic-like gemcitabine. Another cellular biomarker approach involves the use of four-color flow cytometry to monitor changes in the levels of circulating endothelial progenitor cells to determine the OBD for metronomic chemotherapy (29).

Besides the biological aspects of the OBD for antiangiogenics, practical considerations have to be taken into account as well. Although generally well tolerated, the side effects of antiangiogenic drugs such as bevacizumab are dose-dependent (10). Any reduction from the MTD is therefore preferable. Last but not least, optimal biological dosing might also help reduce the costs of such very expensive drugs, an economic issue taking on increasing urgency (30, 31).

In the light of the results obtained with bevacizumab combined with conventional cytotoxic regimens in colorectal, breast, lung, and other cancers, it would seem that antiangiogenic therapies will become the sixth main treatment modality for neoplastic diseases, after surgery, radiation, conventional chemotherapy, antihormonal-based therapies, and onco gene-targeted antitumor agents. Development of strategies to help determine the OBD will surely improve the successes of antiangiogenic drugs already observed. In this regard, it will be of considerable interest to investigate the dynamic de-escalating approach of Dowlati et al. with other, known active antiangiogenic agents, such as bevacizumab, Sutent, and Sorafenib, using new and promising surrogate markers of angiogenesis such as circulating endothelial cells or circulating endothelial progenitor cells (17).

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References

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