New Paradigm in Dose-Finding Trials: Patient-Specific Dosing and Beyond Phase I

André Rogatko,1 James S. Babb,2 Mourad Tighiouart,1 Fadlo R. Khuri,1 and Gary Hudes3

Abstract We propose a new paradigm for the clinical evaluation of new cancer therapies. It entails adjusting the search for the optimal dose on the basis of measurable patient characteristics that may be predictive of adverse responses to treatment, and extending this search beyond phase I and into phases II and III. We provide examples of (a) how the fine-tuning of dose may involve utilization of patient-specific attributes to obtain a personalized treatment regimen, and (b) how novel methods for phase I design can be used to update the working dose for the conduct of phase II and III cancer clinical trials. These examples should be interpreted as an enticement for the development of new methods to implement the proposed new paradigm.

Cancer trials typically proceed through several distinct phases. The major objective in phase I trials is to identify a working dose for subsequent studies, whereas the major end point in phase II and III trials is treatment efficacy. Ideally, from a therapeutic perspective, clinical trials should be designed to maximize the number of patients receiving an optimal dose. Consequently, more patients would be treated with therapeutic doses of promising new agents, and fewer patients would have to suffer the deleterious effects of toxic doses.

With cytotoxic agents, it is a long-accepted assumption of cancer chemotherapy that toxicity is a prerequisite for optimal antitumor activity and that efficacy increases with dose. It could be argued that the paradigm used for cytotoxic drugs will not apply for newer molecularly targeted therapies. It has been assumed that inhibition of protein function, rather than toxicity, will determine the optimal dose of such therapies. However, early experience with epidermal growth factor and vascular endothelial growth factor receptor antagonists has shown that target inhibition in tumor tissue is difficult to quantify. Inhibition of the target is usually associated with toxicity, which influences the selection of an optimal dose. Therefore, it is unlikely that future therapies will be completely free of toxicity constraints. Furthermore, targeted agents such as angiogenesis inhibitors or growth factor receptor antagonists are likely to be used in combination with cytotoxic agents. For these reasons, the paradigm used for cytotoxic drugs should be applicable and relevant to molecularly targeted therapies.

Phase I studies assume that dose is the most significant determinant of toxicity. Our analysis of multiple phase I and early phase II trials revealed that dose is not always a significant predictor of toxicity (1). Even with conventional patient selection criteria that included the requirement for normal or near-normal hepatic and renal function, patient characteristics had greater predictive value than dose for the toxicity for several agents. Thus, the current eligibility criteria for most phase I and II trials do not provide populations that are uniform enough to conclude that differences in toxic response are primarily dose related.

Identification of the optimal dose is usually restricted to the phase I setting, although the number and type of patients evaluated are very limited. Typically, the dose selected for phase II may be based on the toxicity experiences of a few heavily pretreated patients with limited life expectancy. The assumption that the dose selected in such a patient population will be optimal for other populations may well be incorrect. Furthermore, as experience accumulates with a new therapy, it often becomes apparent that certain groups of patients tolerate greater or lesser doses due to differences in age, sex, organ function, and genetic profile that may affect clearance and metabolism. An example is the topoisomerase inhibitor irinotecan, which at recommended doses often causes unacceptable and unpredictable gastrointestinal and hematologic toxicity, a risk that increases with hepatic dysfunction (2, 3). Another example is capecitabine, a widely used fluoropyrimidine that requires dose reduction for elderly patients and those with mild to moderate renal insufficiency (4). The recommended starting dose of docetaxel, a microtubule inhibitor used in the treatment of lung, breast, ovarian, and other cancers, was reduced from the approved recommended dose based on subsequent clinical experience in larger and older populations (5, 6). These observations raise concerns for the dosing recommendations based on limited patient cohorts typically treated in phase I and II trials. Consequently, the limited information available from phase I trials is frequently insufficient for an accurate determination of the phase II dose, which should accommodate patient heterogeneity in susceptibility to adverse effects of treatment.

According to the current paradigm for the clinical evaluation of new cancer therapies, (a) the dose of a therapeutic agent is not adjusted to accommodate individual patient differences, and (b)
the identification of working dose of new cancer therapies are mainly restricted to phase I trials. We propose that \((a')\) the dose should be fine-tuned using patient-specific attributes, and \((b')\) the search for the optimal dose should be extended beyond phase I and into phases II and III. We provide examples of how phase I design methods can be used to update the working dose for phases II and III and how fine-tuning the dose may involve the utilization of patient-specific attributes to obtain a personalized treatment regimen. We present these examples to motivate the development of new and improved methods.

### Cancer Phase I Trial

The primary objective of a phase I clinical trial is to determine the dose of a new drug or combination of drugs for subsequent clinical evaluation of efficacy. The dose sought is typically referred to as the maximum tolerated dose (MTD) and its definition depends on the treatment under investigation, the severity and reversibility of its side effects, and the clinical attributes of the target patient population. Because it is generally assumed that toxicity is a prerequisite for optimal antitumor activity (1), the MTD of a cytotoxic agent typically corresponds to the highest dose associated with a tolerable level of toxicity. More precisely, the MTD is defined as the dose expected to produce some degree of medically unacceptable dose-limiting toxicity (DLT) in a specified proportion \(\theta\) of patients (2). Thus, if a population of patients is treated at the MTD, a proportion \(\theta\) of them is expected to manifest DLT. The value chosen for the target probability \(\theta\) would depend on the nature and consequences of the DLT; it would be set relatively high when the DLT is a transient, correctible, or nonfatal condition, and low when it is lethal or life threatening (7).

Table 1 summarizes the attributes that an optimal dose finding procedure should possess to achieve the goals \((a')\) and \((b')\). Whereas none of these characteristics are possessed by the usual modified Fibonacci phase I design, each can be addressed within a Bayesian framework (8).

In the next section, we outline a Bayesian dose escalation scheme permitting precise determination of the therapeutic working dose and at the same time directly controlling the likelihood of an overdose. The method, known as Escalation with Overdose Control (EWOC), has been used to design phase I clinical trials at the Fox Chase Cancer Center and at the Sylvester Comprehensive Cancer Center, University of Miami School of Medicine. Zacks et al. (9) discuss statistical properties of the method, and a comparison of EWOC with alternative phase I design methods is given in ref. 7. Babb and Rogatko (10) provided a summary of Bayesian phase I design methods (11) and studied the performance of EWOC under a rich class of prior distributions for \(\theta\). EWOC will be the basis for a more general method to be used beyond phase I trials. A computer program implementation of the EWOC method for Windows environment is available free of charge. Version 2 is a user-friendly, dialogue-based, stand-alone application and the self-extracting file can be downloaded from the web site http://www.sph.emory.edu/BRI-WCI/software.html.

### The Escalation with Overdose Control Method

EWOC was the first dose-finding procedure to directly incorporate the ethical constraint of minimizing the chance of treating patients at unacceptably high doses. Its defining property is that the expected proportion of patients treated at doses above the MTD is equal to a specified value \(\alpha\), the feasibility bound. This value is selected by the clinician and reflects his/her level of concern about overdosing. Zacks et al. (9) showed that among designs with this defining property, EWOC minimizes the average amount by which patients are underdosed. This means that EWOC approaches the MTD as rapidly as possible, while keeping the expected proportion of patients overdosed less than the value \(\alpha\). Zacks et al. (9) also showed that, as a trial progresses, the dose sequence defined by EWOC approaches the MTD (i.e., the sequence of recommended doses converges in probability to the MTD). Eventually, all patients beyond a certain time would be treated at doses sufficiently close to the MTD.

### Personalizing the Phase I Dose—Escalation with Overdose Control with Covariates

A key assumption implied by the definition of the phase I target dose (MTD) is that every subgroup of the patient population has the same MTD. That is, it is assumed that the

### Table 1. Attributes that an optimal dose finding procedure should possess to achieve the goals \((a')\) the dose should be fine-tuned using patient-specific attributes, and \((b')\) the search for the optimal dose should be extended beyond phase I and into phases II and III

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
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<tbody>
<tr>
<td>Freedom to choose any target probability (\theta)</td>
<td>Because cancer phase I and II patient populations typically differ with respect to treatment tolerance, a different target probability (\theta) might be chosen in each case. Consequently, a method for fine-tuning the working dose should allow any value of (\theta) to be targeted and permit its change during phases II and III.</td>
</tr>
<tr>
<td>Patient-specific dosing</td>
<td>The method should allow the dose level to be adjusted according to patient characteristics associated with susceptibility to treatment.</td>
</tr>
<tr>
<td>Assess the precision of the MTD estimate</td>
<td>To decide if and when to adjust the phase II/III dose, the method should provide an estimate of how precisely the MTD has been estimated.</td>
</tr>
<tr>
<td>Utilize all available information</td>
<td>The method used to adjust the dose should be fully adaptive. That is, it should be able to exploit all the information accumulated during both the current and previous phases of clinical evaluation.</td>
</tr>
<tr>
<td>Assess patient risk</td>
<td>Both the investigator and patient might benefit if updated assessments of the risk of toxicity were available during the trial.</td>
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patient population is homogeneous in terms of treatment tolerance and every patient should be treated at the same dose. As a result, no allowance is made for individual patient differences in susceptibility to treatment (12). Recently, however, improvements in our understanding of the pharmacokinetics and the pharmacogenetics of drug metabolism have led to the development of new treatment paradigms that accommodate individual patient needs (13, 14). For example, the observation that impaired renal function can result in reduced clearance of carboplatin led to the development of dosing formulas based on renal function, which permit careful control over individual patient exposure (15). Additionally, the National Cancer Institute accounts for the contribution of prior therapy by establishing separate phase II doses for heavily pretreated and minimally pretreated patients. For these reasons, the EWOC method was extended to permit the incorporation of patient-specific characteristics into the statistical design of phase I clinical trials. The extension of EWOC to include covariates will be illustrated in the context of a Food and Drug Administration–approved phase I study of PNU-214565 (PNU) involving patients with advanced adenocarcinomas of gastrointestinal origin (10). PNU is a murine Fab fragment of the monoclonal antibody 5T4 fused to a mutated superantigen staphylococcal enterotoxin A (SEA). Preclinical testing showed that the action of PNU is moderated by the neutralizing capacity of anti-SEA antibodies. Consequently, dose levels were adjusted during the trial according to each patient’s pretreatment plasma concentration of anti-SEA antibodies.

It was assumed that the probability of DLT is an increasing function of dose (for fixed anti-SEA) and, because anti-SEA has a neutralizing effect on PNU, a decreasing function of anti-SEA (for fixed dose). Because the probability of DLT depends on both the PNU dose level and the anti-SEA concentration, the dose toxicity model was chosen to be a logistic function of pretreatment anti-SEA and PNU dose level. The MTD was defined as a function of the anti-SEA concentration. Specifically, the MTD was defined, for patients with pretreatment anti-SEA concentration equal to a specific value \(a\), as the dose level of PNU (ng/kg) that produces DLT in a proportion \(\theta = 0.1\) of the patients with anti-SEA equal to \(a\) at baseline. The small value chosen for \(\theta\) reflects the severity of the treatment-induced toxicities (e.g., myelosuppression) observed in previous studies. A detailed clinical report on the PNU trial is given in ref. 16.

The amount of information gained during the trial was evidenced by the magnitude of change in the recommended dose levels. At the onset, the recommended PNU dose started as 25 ng/kg for patients with anti-SEA values ranging from 1 to 1,500 pmol/mL. By trial termination, the recommended PNU dose changed to 43.59 ng/kg for patients with anti-SEA value of 1 pmol/mL, and to 1,088.25 ng/kg for patients with anti-SEA value of 1,500 pmol/mL. Source code in Visual Fortran 90 used to implement EWOC with covariates as described in refs. 10 and 16 is available from the authors.

**Is the Phase I Maximum Tolerated Dose the Appropriate Dose for Phases II and III?**

Whereas the major end point in phase II trials is efficacy, the search for the optimal dose is usually restricted to the phase I setting. In this case, the phase II dose determination may be based on the data accumulated from a patient population with very different characteristics than the target phase II population. The implicit assumption that the dose selected in one patient population will be optimal for other populations may be incorrect. In a phase II trial, the frequent occurrence of toxicity leads generally to dose reduction. In contrast, dose increase due to lack of toxicity is much less common because such treatments are generally considered “well tolerated.” Because maximizing dose intensity is still regarded as an important condition to achieve an optimal therapeutic effect, failure to increase the dose in the absence of toxicity may result in patients being treated at subtherapeutic dose levels.

EWOC was retrospectively applied to dose-toxicity data from two trials completed at the Fox Chase Cancer Center. In the phase I study (17), 26 patients with a wide variety of malignancies and varying exposure to cytotoxic therapy and radiation were treated with paclitaxel and estramustine. Based on toxicity observed in the phase I population, the phase II dose of paclitaxel was chosen to be 120 mg/m\(^2\). Applying EWOC analysis to this data set yields \(\theta = 0.2\) for a dose of 120 mg/m\(^2\), indicating that approximately one in five patients would be expected to have DLT at the phase II dose of paclitaxel. In the phase II trial (18), 34 patients with hormone refractory prostate cancer and no prior chemotherapy received the recommended phase II dose, using the same treatment regimen and same definition of DLT as for the phase I trial. Only 2 of the 34 patients in the phase II trial experienced first cycle DLT, and only three other patients required dose reduction of paclitaxel over subsequent cycles. Because the incidence of DLT was lower in the phase II trial, EWOC analysis results in a lower value of \(\theta\) for this population. Figure 1 shows, for each trial, the recommended EWOC dose of paclitaxel for selected values of the target probability of DLT (\(\theta\)) and dose for the phase I and phase II populations. The recommended EWOC dose of paclitaxel for any selected value of the target probability of DLT (\(\theta\)) is higher for the phase II population. For this analysis, the feasibility-bound \(z\) was set to 0.5, implying that both underdosing and overdosing are of equal concern. If the object of the phase II trial had been to administer a paclitaxel dose to achieve \(\theta = 0.2\), then more aggressive dosing would have been possible. Although we...
analyzed this example retrospectively, one could envision a similar analysis conducted during the phase II trial after accrual of an initial cohort of 10 to 12 patients to adjust the dose using relationships similar to those in Fig. 1.

One sees that different doses are required in the two patient populations to obtain the same targeted probability of DLT. This example shows how EWOC can be used to aid the clinician in selecting a working dose for a cytotoxic treatment. Once the clinician decides on a target probability of DLT, θ, the phase II (or phase III) dose can be determined.

A phase II (or phase III) trial can be designed to permit dose modifications based on the number and type of toxicities observed during the trial. As a specific example, the following is the design of a phase II trial involving a combination of radiation and taxol. The design allows the dose to be adjusted according to an assessment of whether a desired level of toxicity is achieved. A portion of the protocol is given below and summarized in Table 2.

The adequacy of the selected dose will be assessed after 14 patients have been treated. We target the dose such that the probability of DLT, θ, is 0.2. If no DLTs are observed among the first 14 patients (assuming that θ = 0.2, the probability of this outcome is 0.044), the radiation will be increased from 45 to 60 Gy. If one, two, three, or four DLTs are observed, the treatment will remain unchanged. If five or six DLTs are observed, the taxol dose will be decreased from 50 to 40 mg/m² (assuming that θ = 0.2, the probability of this outcome is 0.118). If seven or more DLTs are observed, the trial will be terminated. When θ = 0.2, the probability of observing seven or more DLTs and incorrectly terminating the trial is 0.012.

The same design could be implemented to adjust the dose in the phase III setting. The main distinction between phase II and III trials is that larger samples are typically used in phase III, thereby permitting further refinement of the working dose and better adjustment to individual patient needs. This example should be interpreted as an enticement for the development of new methods to implement item (V) of the proposed new paradigm (i.e., to extend the search for the optimal dose beyond phase I and into phases II and III).

**Dose-Finding Beyond Phase I Trials**

The standard paradigm of clinical evaluation of new cancer therapies restricts the dose determination to the initial phase of the process (Fig. 2, top). Progress in DNA-array technology and pharmacogenetics undeniably argues against the concept of “one dose fits all.” At the same time, it would be unreasonable to design phase I trials with sufficient power to distinguish the important patient-specific characteristics for a given therapy.

One solution is to continue with the quest for determining the best dose throughout phases II and III (Fig. 2, bottom). Hence, clinical trials might progress as follows. First, a phase I trial is conducted to characterize the toxicity profile of the treatment and determine a starting dose for phase II investigation. Subsequently, the phase II and III trials can be designed in stages with the data from each stage used to determine if and what adjustment of the dose is needed. Dose modification would continue until either a specific number of patients have been treated or the dose has converged to the MTD according to some criterion (such as the posterior variance of the estimated MTD).

In the previous sections, it was shown that methodologies are available to improve the design and analysis of cancer clinical trials. We highlighted the importance of targeting θ, the proportion of patients treated at the MTD expected to manifest DLT, during all phases of treatment evaluation. We also presented methods that permit the incorporation of personal information thereby allowing dose levels to be tailored to the individual patient according to his/her attributes. It is important to note that, for any phase of the evaluation process, the working dose should be adjusted on the basis of accumulated toxicity and efficacy information. Therefore, each patient at each stage will be provided with the best dose possible, more patients will be treated with therapeutic doses of a promising new agent, and fewer patients will be overdosed and suffer from its toxic effects.

There has been a substantial effort from the cancer research and treatment community to translate basic science and laboratory findings faster into clinical trials, in an attempt to

<table>
<thead>
<tr>
<th>Number of DLTs in 14 patients</th>
<th>Probability when θ = 0.2</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.044</td>
<td>Increase radiation from 45 to 60 Gy</td>
</tr>
<tr>
<td>1, 2, 3, or 4</td>
<td>0.826</td>
<td>None</td>
</tr>
<tr>
<td>5 or 6</td>
<td>0.118</td>
<td>Decrease taxol from 50 to 40 mg/m²</td>
</tr>
<tr>
<td>7 or more</td>
<td>0.012</td>
<td>Terminate trial</td>
</tr>
</tbody>
</table>

NOTE: The design allows the dose to be adjusted according to an assessment of whether a desired level of toxicity is achieved.
accelerate the improvement in cancer patients' survival and quality of life. Research biostatisticians dedicated to the discovery and improvement of clinical trial design play a fundamental role in the process of drug discovery and treatment. As in many science, research biostatisticians generate new methods that are published in specialized journals using a language typical to the profession. Most of these new methods are rarely used, although they may offer advantages over the standard ones (19, 20). Despite a compelling rationale for their use, EWOC and other Bayesian methods are not commonly used in phase I trials. Some of the reasons include (a) lack of awareness and/or understanding of Bayesian methods among clinical investigators and industry sponsors involved in drug development; (b) fear that newer methods are complex, and may cause delay or loss of information, rather than increase efficiency and information gained—this is partly a consequence of (a); and (c) change from the status quo. If nothing else, the “modified Fibonacci” 3 + 3 has going for it conformity among its adherents.

The “modified Fibonacci” 3 + 3 dose escalation design remains a favored design for phase I trials despite the important limitations described above and by others (21–23). The consequence of using ineffective methods such as the “modified Fibonacci” 3 + 3 dose escalation in clinical practice is that more patients are treated with doses outside the therapeutic window (24, 25).

It is our responsibility to not only develop new and better designs but also to shepherd new approaches into clinical practice. This will require effective communication with clinical colleagues and active representation in scientific review boards and clinical research committees. The main goals of this article are to encourage additional work in the realm of cancer clinical trial design and to urge biostatisticians to actively participate in translating new methods into the real world of clinical trials.

References

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