1552 Innovative Phase I/II Statistical Design in Combination Chemotherapy That Combines Toxicity and Efficacy Parameters to Increase Study Efficiency: Bendamustine and Idarubicin in *De Novo* Adult AML

Program: Oral and Poster Abstracts
Type: Poster
Session: 615. Acute Myeloid Leukemia - Therapy, excluding Transplantation: Poster I
Saturday, December 10, 2011, 5:30 PM-7:30 PM
Hall GH (San Diego Convention Center)

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Background: Novel drugs or drug combinations are conventionally tested first in Phase I studies (in which therapeutic decisions are based solely on toxicity) with Phase II (efficacy) evaluations following as a separate trial. This process not only slows new drug development, it is challenging for patients during the informed consent process, because they usually enter trials not merely in hope of "no toxicity" but in hope of response. Response rates in Phase I at doses less than the maximum tolerated dose (MTD) may be irrelevant to efficacy, but this common assumption remains unproven. An equally plausible alternative is efficacy failure at these lower doses augurs failure at the MTD in Phase II. This hypothesis prompted development of a Phase I-II Bayesian design that uses both efficacy and toxicity to find a clinically relevant dose (Biometrics 2004;60:684-93). In the current study, we apply the innovative Bayesian approach to the design of a Phase I-II trial using bendamustine + idarubicin in older patients (>50 yo) with newly-diagnosed AML or high risk MDS (>10% marrow blasts). We then compare and contrast our trial operation with that of the standard 3+3 Phase I design. *Methods:* The design specifies anticipated probabilities ("priors") of response (CR or no CR) and toxicity (grade 3-4 or not) at each of 4 doses of bendamustine (45,60,75,90 mg/m^2 daily X 5 together with idarubicin 12 mg/m^2 daily on day 1 and 2). Patients are entered in groups of 3 beginning at the 45 mg/m^2 dose. As response/toxicity data became available for each cohort, Bayes theorem is used to update the priors and derive current probabilities ("posteriors") of response/toxicity at each dose. The priors are set to be relatively non-informative allowing the posteriors to be primarily influenced by the data from the trial. The posteriors are referred to a minimum acceptable probability of response (here 40%) and a maximum acceptable probability of toxicity (30%). If the posteriors indicate that it is highly unlikely (< 2% chance) that any dose is associated with both of these probabilities the trial stops. Otherwise the next cohort of patients is treated at a dose so associated. This process is repeated iteratively to a maximum sample size of 48 patients. The parameters noted above were chosen to give desirable probabilities of selecting for future study doses meeting the minimum acceptable response and maximum acceptable toxicity rates. *Results:* *Table 1: Comparative Operating Characteristics: Our Design vs. 3+3:*

A: Bendamustine Dose (mg/m^2 daily X 5)	B: Response	C: Toxicity	D: (Phase I-II design) Next Dose	E: (3+3) Next Dose
45	0/3	0/3	60	60
60	2/3	0/3	75	75
75	1/3	2/3	60	60 is MTD Phase I stops:
60	2/3	0/3	60	N/A

Table 1 compares the operation of this trial with a standard 3+3 Phase I trial. Given that 2/3 patients had toxicity at the 75 dose, a Phase I 3+3 design would have declared 60 the MTD. Subsequently, an "expansion cohort" as a Phase II trial would be treated at this dose without any possibility of revisiting the 75 dose. This conclusion flies in the face of basic notions of statistical reliability and ignores the possibility that patients experiencing toxicity may have been particularly old, had significant comorbidities, or have a variable functional reserve for undefined reasons. In contrast, the Phase I-II design allows the trial to continue, and potentially revisit higher doses of therapy depending on the collective outcome of a greater number of patients. Based on our actual data, this trial continued to treat patients at the 60 mg/m^2 dose level, and in the next three patients there was no toxicity. In this case response data becomes the determining factor, which improves the efficiency of the trial. If 0/3 patients had a response, the trial would return to 75 mg/m^2, however, because 2/3 patients had a response, the trial continues to accrue at 60mg/m^2, with the statistical force of twice the number of patients. *Conclusion:* Accounting for response during dose finding seems to permit more sophisticated/flexible decisions about dosing in addition to improving efficiency.

Disclosures: Shannon Dorcy: *Cephalon:* Consultancy, Honoraria, Speakers Bureau.

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