

PHASE I (DOSE-FINDING) TRIALS

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Cytotoxic agents:

Treat cohorts of patients with escalating doses until unacceptable toxicity is seen, and then recommend the next lower dose level for further testing.

Rationale: Increased dosage of an agent will offer more anti-tumor benefit, provided the dose has acceptable toxicity.

“Standard design” - cohorts of 3 or 6 patients

“Accelerated designs” - start with cohorts of 1 patient until some toxicity is seen, and then expand the cohorts

OR

-start with large jumps in dose between successive cohorts and decrease jump size when some toxicity is seen

Accelerated designs are most useful when you have no good idea of a starting dose level.

Would not appear to be important in the present “pediatric rule” setting in which you have some idea of a starting dose to examine from the adult studies.

Note: It is, of course, important to do a dose-finding trial in children. In fact, one may want to have a relatively large phase I trial if the next step is a going to be a large randomized trial rather than a small phase II trial.

Cytostatic agents and agents directed at novel molecular targets

For these agents, the maximum dose that has tolerable toxicity may not be the best to use in further studies, because a lower dose may be just as effective.

Instead of using toxicity to determine the recommended dose, there is the possibility of using other information:

- (1) Blood concentrations of the agent
- (2) Targeted biologic response

(1) Minimum effective blood concentration of the agent (or its active metabolite) known

One possible trial design:

Treat a cohort of patients at a dose level and measure their concentrations. Depending upon these concentrations, treat additional cohorts at higher or lower doses.

Example:

Treat 5 patients and observe concentrations
95, 103, 112, 120, 120

If the minimum effective level is 80, treat next cohort at a lower dose.

If the minimum effective level is 130, treat next cohort at a higher dose.

Treat 5 patients and observe concentrations
95, 103, 112, 120, 120

If the minimum effective level is 100, ...

observed mean is 110

lower 90% con. int. for true mean = 102.5

80% (=4/5) of the observations are >100

But 90% confident only that the true
proportion of observations above 100 is
49%

- (2) Targeted biologic response available
- Find a dose that ensures a specified minimum biologic response rate

Example:

11 patients treated at a dose level and all 11 have biologic responses, i.e., observed response rate=100%

Implies that we can be 90% confident that the true response rate is $>81\%$.

Example:

11 patients treated at a dose level and 10 have biologic responses, i.e., observed response rate=91%

Implies that we can be 90% confident that the true response rate is $>69\%$.

- (2) Targeted biologic response available
- Find a biologic efficacious dose

In the context of a dose escalation, rather than trying to ensure that there is a minimum biologic response rate, only ensure that if the true response rate is low then there is a high probability of escalating, and if the true response probability is high then there is a low probability of escalating.

One possible trial design (similar to standard 3-6 phase I escalation):

Initially treat 3 patients at a dose level. With 0 or 1 responses, escalate dose for next cohort. With 2 or 3 responses, expand the cohort to 6 patients. With 5 or 6 responses, declare this dose to be the “biologically efficacious dose”.

$\text{true} \leq 40\% \Rightarrow .96$ probability of escalating
 $\text{true} \geq 90\% \Rightarrow .11$ probability of escalating

(2) Targeted biologic response available

- Ask if there is a dose-response relationship

Not really trying to determine a dose for further studies, but instead trying to show whether the response rate is associated with the dose level at all.

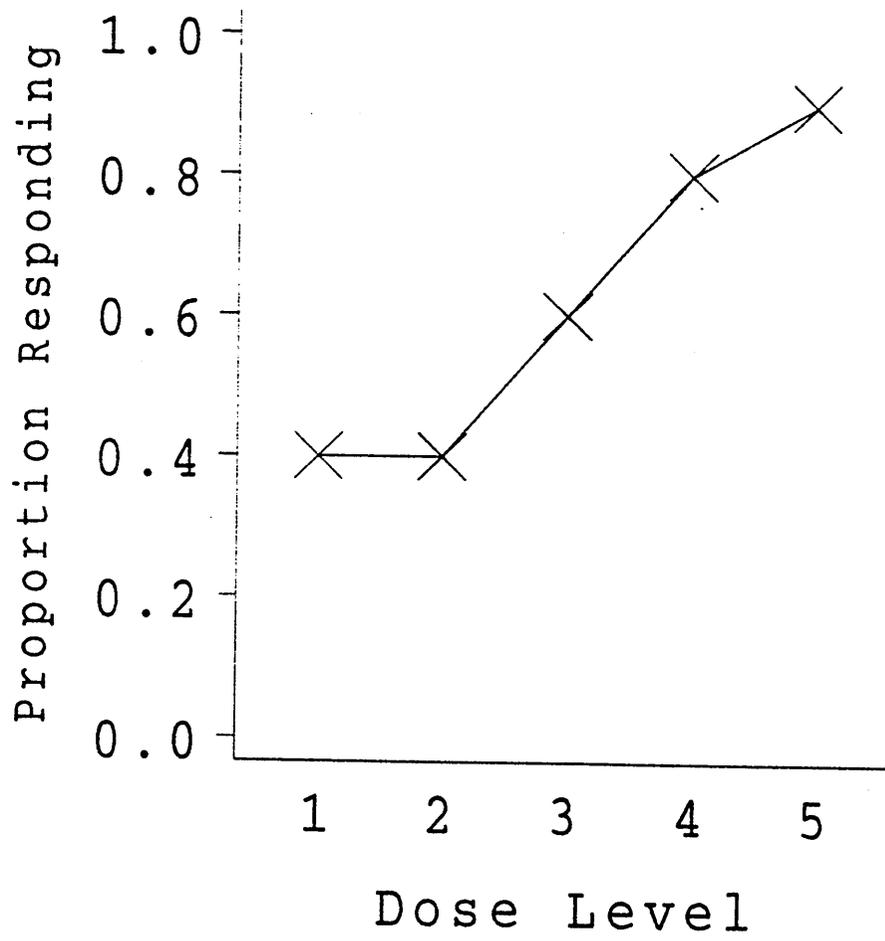
One possible trial design:

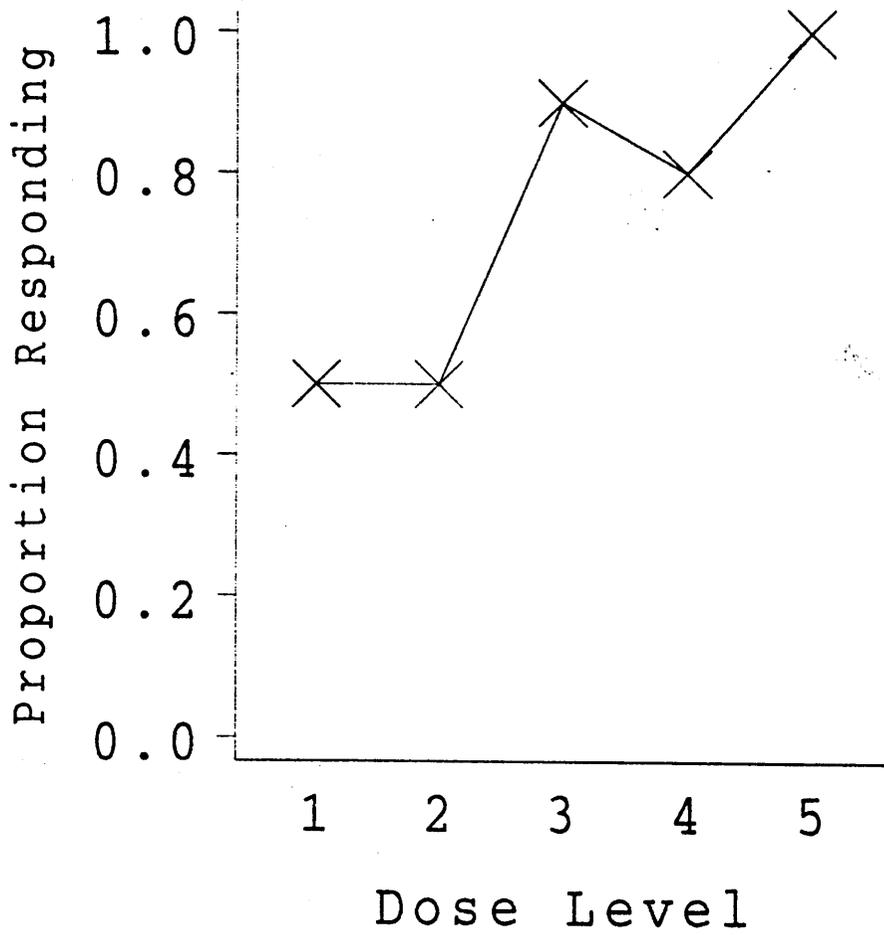
Treat 20 patients at a low dose and 20 patients at a high dose and compare the biologic response rates between the two doses.

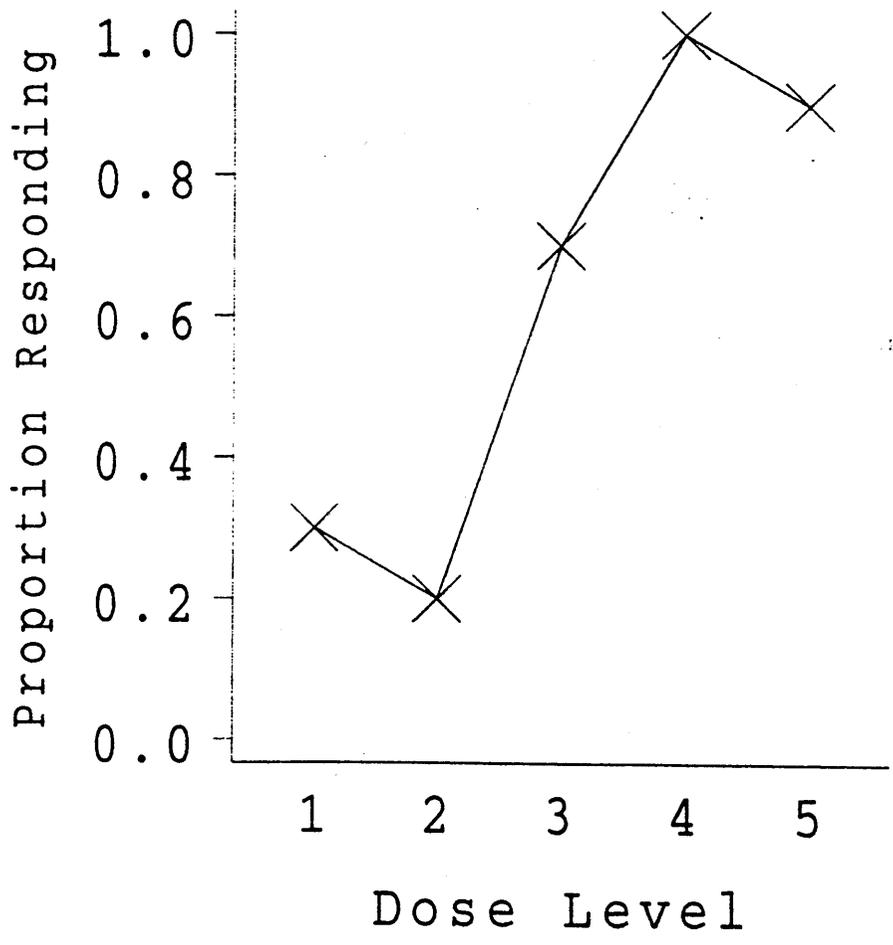
This design would reliably detect true response rates of 50% versus 90% (power=.9, alpha=1).

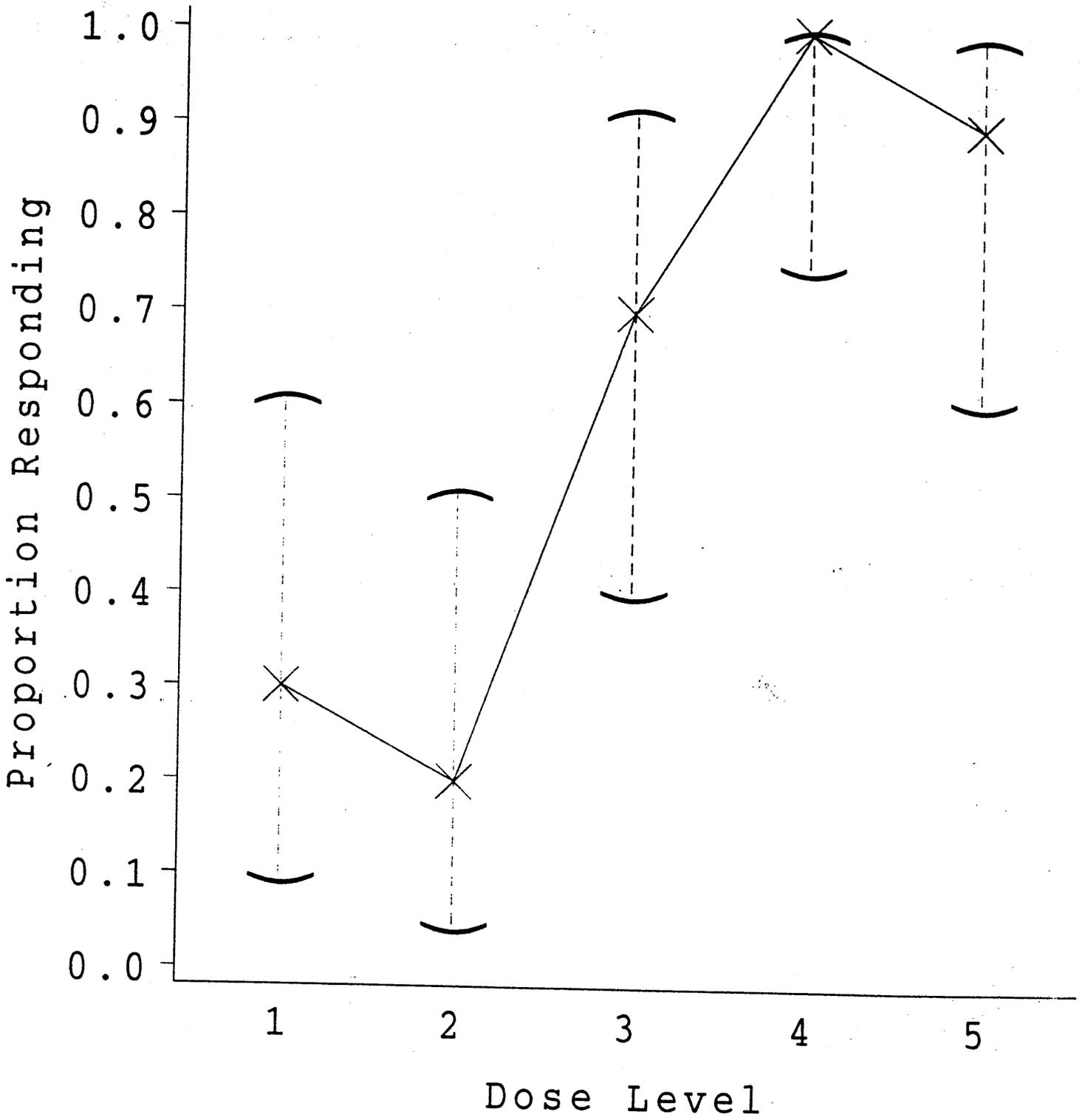
- (2) Targeted biologic response available
- Assess the shape of the dose-response relationship

Even larger sample sizes required than those needed to detect whether or not there is a positive dose-response relationship









Summary - Cytotoxic Agents

Standard designs should work well since one typically knows about where the recommended dose will be from the adult studies.

Summary - Non-Cytotoxic Agents

Minimum effective blood concentration known

- Find a dose that ensures that concentration in a specified proportion of patients

Targeted biologic response available

- Find a dose that ensures a specified minimum biologic response rate
- Find a biologic efficacious dose
- Ask if there is a dose-response relationship
- Assess the shape of the dose-response relationship

Usually, using targeted biologic responses is problematic because the assays and techniques are being developed simultaneously with the ongoing clinical trials. In this “pediatric rule” setting, there may be more opportunities since the pediatric trials will be occurring later in the agent’s development.