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On the Design of Combination Cancer Therapy

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Abstract

Combination therapy programs are the hallmark of the successful treatment of all forms of human malignancies. In this issue of Cell, Palmer and Sorger present data suggesting that cell culture results indicative of synergistic anticancer drug interactions rarely translate clinically and that the results of combination therapies in mouse models or human clinical trials, even if successful, are best explained by the independent activities of the individually administered drugs.

Early in the development of cytotoxic cancer chemotherapy, basic principles guiding the use of combination therapies were established based primarily on the work of Frei and Freireich (Frei et al., 1965), Sartorelli (Sartorelli, 1969), and DeVita and colleagues (DeVita and Schein, 1973). As elucidated, these principles suggest that (1) drugs used in combination should cause measurable tumor regressions when employed individually, (2) each ought to demonstrate a different mechanism of action to minimize the development of resistance, (3) the clinical toxicities of each compound should not overlap to permit their use in effective doses, and (4) intensive intermittent treatment is preferred over continuous, low-dose therapy to enhance cytoreduction (Kummar et al., 2010). However, the molecular basis for the selectivity of the cytotoxic agents used for the first effective clinical trials of this approach, in their disease contexts, was not known. Over the past 15 years, the availability of anticancer agents with greater molecular specificity of action has engendered new rules for the development of combinations, which suggests that the prospective design of molecularly targeted combinations, inhibiting multiple pathway dependencies, might lead to complementary growth inhibition and enhanced therapeutic activity (Kwak et al., 2007).

In this issue of *Cell*, Palmer and Sorger suggest that most commonly used combi nation chemotherapy regimens provide benefit via a spectrum coverage mechanism based on the independent actions of individual drugs rather than through their additive or synergistic effects (Palmer and Sorger, 2017). The independent action model, illustrated in Figure 1, assumes that the population outcome for patients receiving the combination of drug A + drug B equals the maximum outcome the patient population would have experienced had they received the same doses of either drug A or drug B as single agents. Hence, even when no patient benefits from the combination relative to what he or she would have experienced with an optimally selected single agent, the number of patients that benefit following

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combination treatment could be greater than if all patients had only received one of the drugs.

The difference between population outcomes from either combination or single-agent treatment can be either small or large. For example, if the two drugs are functionally very similar, so that the same patients who respond to drug A would also respond to drug B, then according to the assumptions of the independent action model, the population outcome following treatment with the combination may be the same as if either single agent had been given to the population. Contrary to what we might expect based on pharmacological principles, no additive cytotoxicity takes place. On the other hand, suppose that the two drugs are functionally different, and the outcomes on either single agent are statistically independent. Then, under the independent action model, the probability of a greater outcome for the combination would be much higher, because a different set of patients would benefit from either drug. This can represent a very large effect corresponding to a substantial reduction in hazard for a proportional hazard model.

There are several important considerations worth bearing in mind while reading this study. The clinical trial results evaluated in the current paper have very limited follow-up, making it difficult to observe a substantial prolongation of disease control. A better way to test the independent actions model would be to evaluate best response or duration of response; these measures would be more informative than survival or progression-free survival. Also, the dose of each drug delivered in a combination is often less than for single agents. Also noteworthy is that for one-third of the combinations examined in this study, the independent action model could not sufficiently explain the observed clinical benefit—as might be exemplified by a well-established, mechanistically based combination, such as 5-fluorouracil + calcium leucovorin for colon cancer (Leichman et al., 1995).

Despite past successes that have led to the cure of certain childhood malignancies with combinations of cytotoxic agents and more recent therapeutic advances focused on targeting specific genomic alterations that underlie kinase addiction or vulnerabilities in DNA repair pathways, there remains no adequate theory to help us rationally design clinical combinations of anticancer agents. Despite clinical attempts to simultaneously target multiple forms of the same target, separate targets in the same pathway, or different pathways (Kummar et al., 2010), it has been difficult to reproduce the degree of success obtained fifty years ago in pediatric leukemias for patients with heterogeneous, advanced solid tumors. The authors suggest a “precision monotherapy” approach, focused on the development of pharmaco-dynamic markers of drug action in tumors. This is an attractive proposition because new multiparameter, three-dimensional assay methodologies now make it possible to quantify intra- and interpatient variability of molecular responses following either single-agent, sequential, or combination treatment programs *in vivo* (Parchment and Doroshow, 2016). In this fashion, an early mechanistic understanding of drug action could facilitate a clinical-trial-design approach based on precise measures of biochemical heterogeneity from patient-derived materials. This kind of translationally oriented systems biology approach may soon be required to provide adequate rationale for the design of targeted drug combinations in the future.

In summary, Palmer and Sorger have raised important questions about the mechanisms by which drug combinations provide better outcomes in populations than individual single agents do. It is likely that some combinations are effective via the independent action model while others provide deeper and more durable responses due to additive or synergistic effects. In their classic paper, Hewlett and Plackett pointed out that biological independence of two drugs in combination cannot be inferred from the probability of response as a function of the dose combination because joint action and non-interactive mechanism can produce the same results (Hewlett and Plackett, 1950). Nevertheless, the challenge today is to better understand signaling networks so that either combination regimens or adaptive sequential strategies that translate high partial response rates to durable complete responses can be developed.

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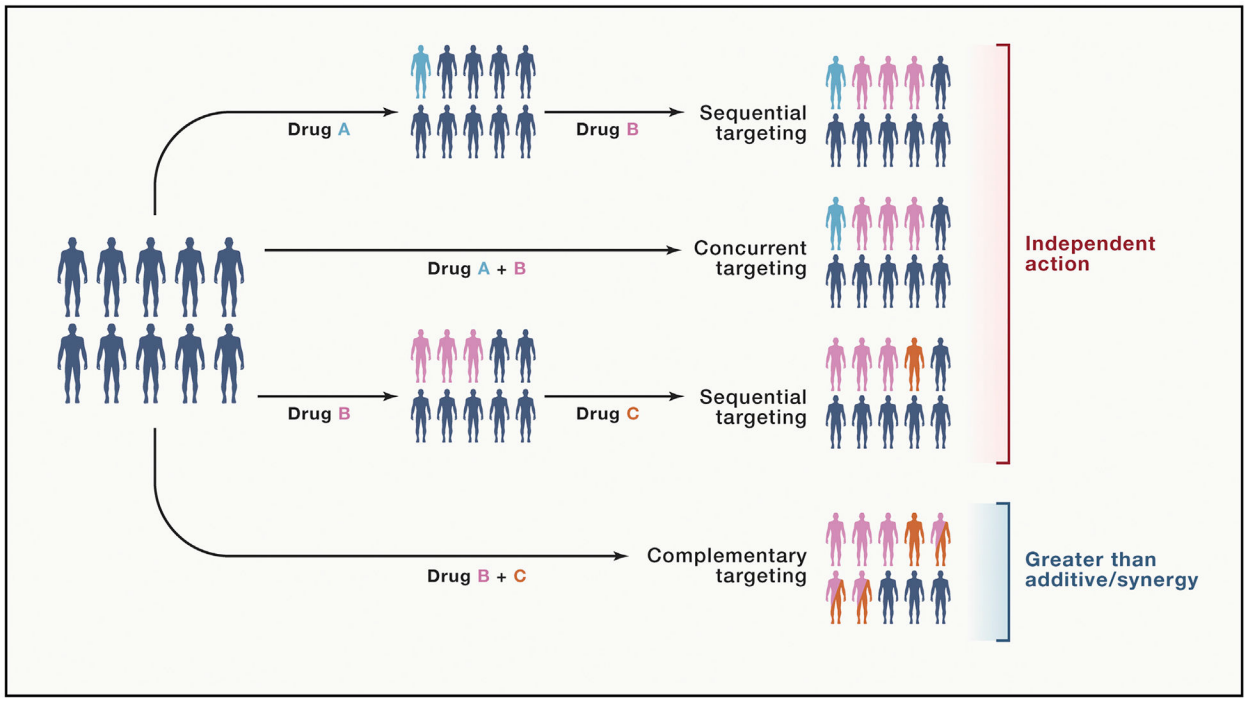

Figure 1. Possible Outcomes for Anticancer Agents Administered as Combinations

In this illustration, ten patients with cancer receive treatment with drugs A, B, and C. If drugs A and B are administered sequentially, the patient symbol shown in teal blue represents an objective clinical response to A. If the entire group is subsequently treated with B, three additional patients (shown in lavender) respond to B. Under the independent action model, the response of a patient to the combination of A + B is the best response to either A or B. In this example, all responses are assumed to be partial. If drugs A and B are delivered concurrently, the response of the tumor sensitive to either/both A and B is also partial and occurs in the same number of patients, since drug action does not combine to give a better response rate. However, under certain more limited clinical circumstances, sometimes based on known or hypothesized interactions between specific molecular pathways, drugs can be chosen (B + C) that produce complementary therapeutic effects, with acceptable toxicity, that encompass not only the independent actions of drugs B (lavender) and C (orange), but also engagement of novel mechanisms of growth control (patients in both lavender and orange), leading to greater therapeutic activity.
Adapted from Sartorelli (Sartorelli, 1969).