

Maintenance Therapy to Suppress Micrometastasis: The New Challenge for Adjuvant Cancer Treatment

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Abstract The palliative efficacy of cytotoxic drugs is routinely assessed using tumor shrinkage (response) rates shown in clinical trials. Although adjuvant drug therapy has a goal distinct from that of palliative therapy (i.e., to prolong survival by inhibiting progression of micrometastatic disease), it is widely assumed that the adjuvant efficacy of a drug will parallel its response rate ("activity") in advanced stages of the disease. Reconsideration of this assumption seems timely in view of recent developments: the realization that many predictors of short-term tumor response correlate inversely with long-term survival outcomes; the characterization of tumor progression as a discontinuous process that may include dormant phases; the understanding that micrometastasis is therapeutically suppressible by a variety of mechanisms including direct tumor cell kill, cytotoxic disruption of paracrine growth signals from normal tissues, and targeted inhibition of prometastatic pathways; the recognition that tumor dormancy not only blocks the antimetastatic efficacy of cytotoxic drugs but also represents a therapeutic end point for metastasis-suppressive noncytotoxic drugs such as hormone inhibitors; and the insight that optimal adjuvant drug therapy is likely to include both induction and maintenance components. The traditional view of cytoreductive response as a prerequisite for adjuvant drug efficacy thus merits reappraisal, with a view to accelerating incorporation of novel noncytotoxic maintenance therapies into controlled studies.

Anticancer drugs are characterized in the clinic via a sequential process—phase I, II, and III studies—involving end points such as maximum tolerated dose, tumor response, and survival, respectively. Because shrinkage of established tumor masses is necessary for symptom relief in advanced cancer, this drug development process has been well suited to the identification of cytotoxic drugs capable of palliating advanced disease. More recently, the therapeutic emphasis of oncology has shifted towards the use of adjuvant drugs to improve patient survival by delaying micrometastasis (1). This change in treatment philosophy has been accompanied by expanding knowledge of the biological pathways underlying tumor progression, as well as by development of molecularly targeted ("smart") drugs that modulate these pathways. How these changes affect the design of adjuvant trials is considered here.

Defining Chemosensitivity: Response versus Survival

Reduction of tumor size is a time-honored measure of drug suitability for treating a given cancer type (2), consistent with

longer survivals of drug-responsive versus refractory patients in both the neoadjuvant (3, 4) and metastatic settings (5–7). However, some reports have indicated that chemotherapy nonresponders tend to survive less long than untreated patients (i.e., implying that nonresponse *per se* is a biological marker of bad prognosis; ref. 8), casting doubt on the extent to which treatment itself influences survival outcomes (9, 10). To put this in another way, the relationship between nonresponse to chemotherapy and adverse outcome is far stronger than that between response and favorable outcome (11). This discrepancy is mirrored by positive correlations of chemotherapy response with adverse survival prognosticators, such as, in the case of breast cancer, lack of hormone receptor expression, aggressive tumor pathologic grade, and high mitotic rate (12, 13). Similarly, tumors that respond rapidly to cytotoxic drugs often also relapse rapidly (14). Moreover, despite the ability of neoadjuvant therapy to permit direct assessment of tumor response and thereby optimize drug "activity" (15), there is as yet no clinical context in which this approach is proven to enhance overall survival beyond that achievable with conventional ("blind") adjuvant therapy alone (16).

A central debate in modern oncology thus concerns whether tumor response is better regarded as a primary treatment end point—more aggressive pursuit of which should produce commensurate survival enhancements—or as a secondary phenotype [e.g., reflecting cell cycle control integrity (17, 18) or genome stability (19, 20)] that is little affected by treatment intensification beyond a certain level. The latter view is theoretically consistent with the "saturable target" or E_{max} paradigm of cytotoxic drug action (21) in which the efficiency of cell kill varies with the proportion of cells containing a critical level of drug target [e.g., topoisomerases (22) and nucleotide synthases (23)], and is empirically supported by the

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equivalent survival benefits of “adequate” and dose-escalated adjuvant breast cancer chemotherapies (24). An opposing model proposes that each cytotoxic treatment eliminates a logarithmic mass of cells in proportion to drug concentration (25), thus favoring a dose escalation (log cell kill) therapeutic strategy (26). For space-limited *in vivo* systems such as epithelial cancers, however, the clinical phase of tumor growth may be accompanied by compensatory growth retardation due to Gompertzian constraints such as density-dependent arrest or oxygenation/pH demands (27). This revised kinetic model teaches that cell cycle arrest is a major cause of cytotoxic drug resistance (Fig. 1; ref. 28).

Tumor Dormancy

Chemoresistance due to transient cell cycle arrest may be reduced by increasing the frequency of cytotoxic drug administration (29, 30). An analogous therapeutic opportunity relates to tumor dormancy [i.e., prolonged cancer cell survival in the absence of DNA replication (31), such as may often occur in micrometastatic locations (32)], which is likewise implicated as a reversible mechanism of resistance to adjuvant cytotoxic drugs (33, 34). Evidence supporting the validity of the dormancy concept has come from clinical timings of tumor recurrences (35) and growth rates (36). Tumor cell dormancy has been pathogenetically linked to either micrometastatic deposition of solitary tumor cells (37), which lack the micro-environmental architecture or local humoral milieu required for clonal proliferation (38), or to suppression of tumor angiogenesis in micrometastatic sites (39), leading to a hypovascular state associated with increased tumor cell apoptosis (40). The possibility is thus raised that suppression of dormancy may reactivate tumor cells and up-regulate vascularity (41), at the same time sensitizing micrometastases

to cytotoxic drug killing. Such events could be triggered by surgical removal of primary tumors (42), consistent with evidence that tumors left *in situ* maintain the dormancy of micrometastases (43).

A complementary viewpoint involves considering dormancy not as a problematic source of chemoresistance but as a positive therapeutic end point (44). Most of what is known about medical induction of tumor dormancy concerns hormone-inhibitory (“cytostatic”) interventions (45); dormancy can be induced in tumors by hormone withdrawal (46) and can in turn be abolished by hormone replenishment (47, 48). Concurrent hormone blockade fails to enhance chemotherapy efficacy in patients—notwithstanding tumor heterogeneity *in vivo*, which might be expected to favor an additive benefit—whereas *in vitro* studies confirm antagonism of cytotoxic killing by prior hormonal inhibition (49, 50). These findings caution that therapeutic induction of dormancy should not coincide with the timing of cytotoxic therapy; if the two modalities are combined, however, it is the hormonal component that determines the durability of tumor response and hence the survival benefit (51), emphasizing the likely future importance of dormancy-inducing therapeutics (52, 53). Cytotoxic therapy seems capable of inducing sustained dormancy in breast cancer (54), but it remains unclear whether hormonal suppression or paracrine loop disruption (55) contributes to this. Cancer vaccines likewise have the potential to maintain dormancy, presumably via immune-mediated mechanisms (56, 57).

Metastasis and Metastasis Suppression

Biological processes that abolish dormancy may promote metastatic progression (58). Such prometastatic processes are not confined to mitogenic cascades such as the Ras/Raf/

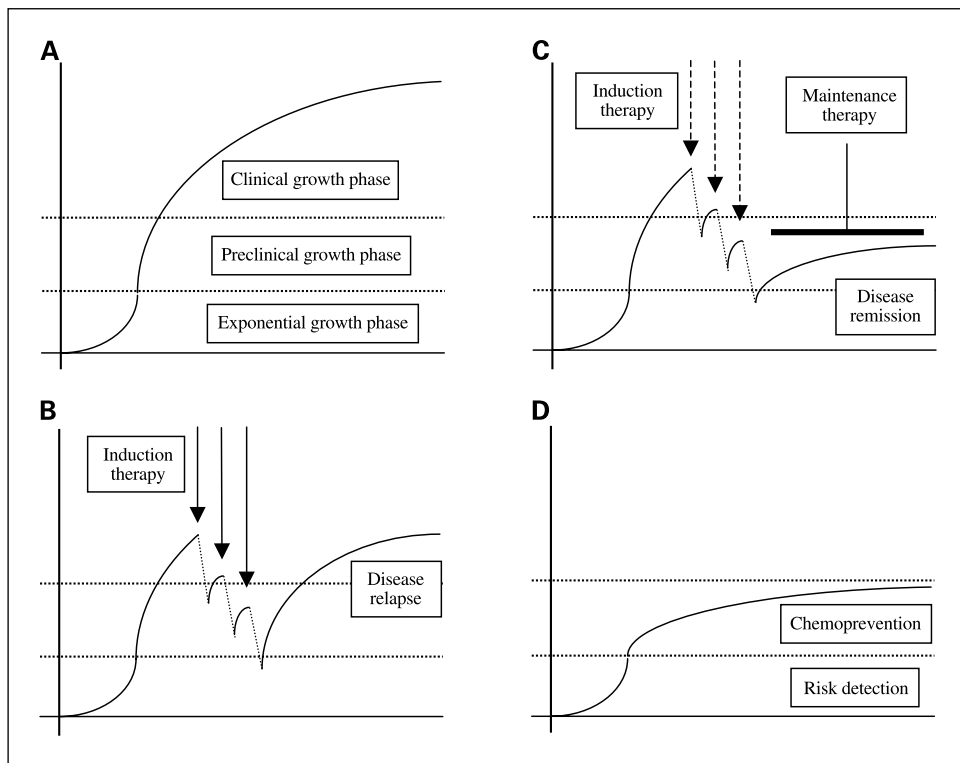
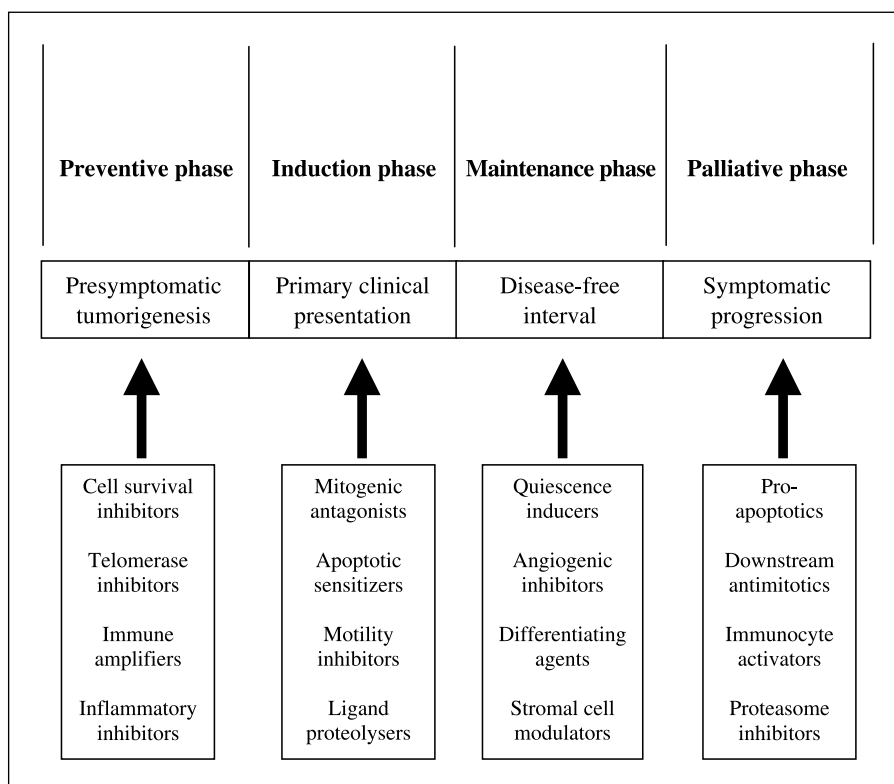


Fig. 1. Varying patterns of cancer growth. *A*, natural history of untreated cancer. Note that the exponential growth phase is not maintained, and that later growth induces its own growth retardation as a Gompertz function. *B*, effect of conventional induction therapy on cancer growth and recurrence; the reduction of tumor mass achieved with each cycle is modeled to be logarithmic. *C*, potential effect of “smart maintenance” adjuvant therapy on postinduction cancer regrowth kinetics, showing an increase in disease-free survival due to a postulated dormancy-inducing effect. *D*, potential efficacy of chemopreventive interventions in high-risk populations.

Fig. 2. Model illustrating how distinct functional groups of anticancer drugs may be sequentially prescribed in the future, depending on the clinical scenario; it is plausible that cytotoxic drugs may come to be reserved for the palliative phase of certain neoplasms, with noncytotoxic drugs dominating early treatment.



extracellular signal-regulated kinase (ERK) pathway, a traditional target of anticancer drugs, but include nonproliferative mechanisms such as angiogenesis, chemotaxis, intercellular adhesion, and extracellular proteolysis. These metastasis-modifying processes may be influenced by noncytotoxic drugs such as retinoids, protease inhibitors, differentiating agents, chemokine antagonists, kinase blockers, adhesion modifiers, anti-inflammatories, anticoagulants, and bisphosphonates.

The survival benefits of adjuvant cytotoxic therapy imply a metastasis-suppressive effect, yet the evidence that such benefits derive from direct tumor cytotoxicity remains incomplete. For example, fluoropyrimidine drugs have long been a central component of both colorectal cancer (5-fluorouracil/leucovorin) and breast cancer (cyclophosphamide, methotrexate, and fluorouracil (CMF); fluorouracil, doxorubicin, and cyclophosphamide (FAC) adjuvant protocols (59), yet the ability of 5-fluorouracil to induce responses in advanced colorectal (60, 61) and breast cancer (62) seems minor compared with many other agents. Similarly, expression of thymidylate synthase (the target of 5-fluorouracil; ref. 63) varies directly with survival benefit in the adjuvant setting (64) but inversely with response in the palliative setting (65). These discrepancies are consistent with evidence that fluoropyrimidines exert some of their survival benefits via metastasis-blocking pathways (66) rather than via tumor cell kill alone.

Crucial progress towards the rational development of antimetastatic drug therapy has been achieved with the identification of metastasis suppressors (67), a heterogeneous family of genes including *Nm23*, *KISS1* (metastin), *RHOVD12*, *KAI1*, *BRMS1*, *Mkk4*, *CRSP3*, *VDUP1*, *TIMP-2*, and *RKIP*. Many of these genes are expressed during embryonic development (68), implying wild-type functions relating to pattern forma-

tion and stability. Consistent with this, the encoded gene products mainly inhibit metastasis in adult somatic tissues not by tumor cell killing but by modulation of cell signaling (69, 70). Because expression levels of such genes may be reduced not only in secondary (71) but also in primary tumors (72), restoration of gene expression could be used as a surrogate end point in neoadjuvant and metastatic studies for identifying anticancer drugs capable of prolonging survival in the adjuvant maintenance setting.

Adjuvant Drug Strategies: Induction versus Maintenance

There exists a subset of solid tumors in which response induction is of greater curative importance than maintenance therapy (e.g., germ cell tumors; ref. 73), although such tumors tend to be characterized by intact p53-dependent signaling pathways and hence by high apoptotic susceptibility and genomic stability (74). For the common carcinoma with its numerous genetic defects and paracrine growth interactions, optimal adjuvant therapy seems more likely to comprise not only cytotoxic induction drugs but also noncytotoxic (and hence, perhaps, nonpalliative or "inactive") metastasis-suppressive maintenance drugs such as histone deacetylase inhibitors (75), nuclear factor κ B inhibitors (76), metalloprotease modifiers (77), or growth factor antagonists (Fig. 2; ref. 78). Furthermore, the most abundant cancer cell substrates dephosphorylated by tyrosine kinase inhibitors seem to be those mediating tumor cell motility rather than proliferation (79). Strict reliance on response and toxicity end points may thus fail to detect well-tolerated target-specific drug effects pertinent to patient survival (80).

New clinical and preclinical (including animal model) approaches are needed to address this deficiency (81). The development of targeted clinical trials, in which only those patients predicted to benefit from an intervention are eligible (82), represents a key step in reducing clinical trial sizes (83) and hence in facilitating more rational innovation in adjuvant studies. To this end, therapeutic benefit can now be reliably predicted by a variety of tumor-associated molecular aberrations including overexpression of estrogen receptor/progesterone receptor (84) and c-Kit/CD117 (85), amplification of *ErbB2* (86), mutation of *EGFR* (87), and promoter methylation of *O⁶-MGMT* (88).

For noncytotoxic interventions that lack such well-defined targets, a short-term method for assessing therapeutic induction of dormancy would be invaluable for clinical research. The best candidate at present seems to be computed tomography-positron emission tomography (CT-PET) scanning, which is capable of noninvasively separating drug signal-inhibitory effects (via reduction of [¹⁸F]fluorodeoxyglucose-positron emission tomography uptake) and cytoreductive potency (via computed tomography tumor size reduction; ref. 89). Another promising approach involves

phosphoproteomic and/or phosphoantibody assessment of cell signaling in sampled tumors (90).

Conclusion

Adjuvant is where the action is—or, at least, where it should be. The inability of a drug to palliate late disease may not imply lack of benefit when used in early disease to inhibit metastasis; survival enhancements may prove to be better achieved by noncytotoxic maintenance treatments than by more “active” cytotoxic induction therapies. Indeed, different categories of anticancer drugs seem likely to vary in efficacy depending on whether they are used for prevention, induction, sensitization, maintenance, or ablation.

When it comes to cancer therapy, smarter is better than stronger—and the smarter the therapy, the stronger the potential for patient benefit (91). The lesson of the last century is that cancer cannot be simply battered into submission by radical medical or surgical assaults. The thrills of the chemotherapeutic battle tend to be short-lived; to win the war, it may prove smarter to refocus our efforts on keeping the beast asleep.

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