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*Sounding Board*

# After Goldie–Coldman—Where Now?

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FOR MANY YEARS, cancer treatment protocols have conformed to the principle that small tumours were more sensitive to chemotherapy [1]. Progress towards earlier diagnosis, surgical debulking and adjuvant chemotherapy followed from this concept. A parallel was made with radiation therapy where achievable doses could be argued to be most effective in eradicating tumour cells where the tumour volume was small, with a critical diameter of 2 cm or less [2]. A number of assumptions underly these calculations, including that the clonogenic fraction is greater for smaller tumours. It has, however, never been proven clinically that the detection of tumours at a smaller size improves chemosensitivity, nor that the gain in survival is greater than the lead time achieved by earlier diagnosis.

Residual disease after surgical debulking of a tumour may differ from a tumour of similar volume in growth fraction, kinetics, blood supply and invasiveness. The evidence that the intervention contributes to improved prognosis as a result of enhanced chemoresponsiveness, rather than a change in prognostic category as a result of the feasibility of the procedure, comes from studies on tumours with a low metastatic potential and moderate chemosensitivity [3], and has not been confirmed in a randomized study. The gain in survival from adjuvant therapy is principally in exquisitely chemosensitive tumours such as osteogenic sarcoma and nephroblastoma, whereas, in a moderately chemosensitive disease like breast cancer, the benefit is confined to a proportion of pre-menopausal women, a population who frequently have rapidly growing disease and may be assumed to have a high growth fraction. It may be inappropriate to generalize from physical approaches at disease control in slowly growing tumours, and biochemical attack in rapidly growing malignancies, to all solid tumours.

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The concept that small bulk was better also accorded with the log cell kill hypothesis of Skipper [4] who proposed that a constant proportion of cells, rather than a fixed number, were killed with each dose of therapy. These studies were based on experiments in tissue culture monolayers and in sensitive animal tumours with a high growth fraction and may not be relevant to the majority of solid tumours. A limiting factor is the inability to identify the clonogenic cell component in solid tumours. A small tumour is more curable by virtue of having fewer cells from which to initiate regrowth following treatment, but it does not necessarily hold that the smaller tumour would be more sensitive as defined by log cell kill per dose equivalent. Curability should be quite clearly distinguished from sensitivity in this context.

In 1977 a further extension of the kinetic theory was developed by Norton and Simon [5], and was based on Gompertzian growth kinetics, in which the growth rate is smallest for very small and very large tumours. They proposed that the growth-inhibiting effect of a treatment is proportional to the growth rate of an untreated tumour, which reaches a peak at an intermediate tumour volume. Experimental validation was provided of the hypothesis that the volume removed by a cycle of chemotherapy is proportional to the growth fraction multiplied by the total tumour volume, and this model could explain why very large as well as some small tumours fail to respond to treatment. Their analysis provided the theoretical basis of late intensification approaches in acute myelogenous leukaemia [6], non-Hodgkin's lymphoma [7] and small cell lung cancer [8].

In the 1970s advances in supportive care made modest dose escalation feasible, and this was enhanced by the development of dose-limiting organ rescue (e.g. bone marrow) or specific drug antagonism (e.g. folinic acid). Despite promising animal

data and preliminary clinical studies, the improvement in outcome has been confined to the most chemosensitive tumours such as childhood cancers, and the haematological malignancies [9–11]. The approach worked where there was a steep dose–response relationship for human cancer, and the ability to escalate dose without severe non-haematological toxicity. A 3 to 5-fold dose escalation was feasible with the alkylating agents, but severe organ toxicity has restricted wider use of dose escalation of other agents including cisplatin and etoposide. More recently, the rate of administration of dose equivalents has been shown to be important in determining outcome in breast cancer, ovarian cancer and Hodgkin's disease [12–14]. The aim of these approaches was to achieve a rapid reduction of the critical tumour volume below which regrowth did not take place, before cumulative toxicity prevented further treatment.

These theoretical models ignored certain fundamental properties of tumours in man. Firstly they failed to take account of adaptive changes in the cancer cells as a result of treatment. Resistance to drugs was regarded as a static concept with either a biochemical or kinetic basis, with a low incidence at presentation of around 1% [9], and leading to progressive selection of resistant cells. Thus a tumour could appear to be sensitive, as judged by clinical response over several cycles, and yet relapse by repopulation from resistant clones. Secondly, they ignored the quantitative and qualitative changes in the normal tissues in response to treatment [15], including the possibility of tumour–stroma interactions [16]. Many of the strategies were developed for the haematological malignancies where the marrow was the legitimate target for drug cytotoxicity, while in solid tumours the bone marrow was viewed as an inconvenient obstruction to the administration of a curative dose. In reality there is a dynamic interplay between the two which is perturbed for therapeutic gain by drug activity. Thirdly, they incompletely took account of the pharmacology of the drugs, with the alkylating agents being invoked to support mechanisms parallel to radiobiological concepts including dose escalation [17], and methotrexate being the paradigm for a cell cycle dependent drug which could induce resistance by gene amplification [18]. The full significance of drug activation, transport and detoxification was not yet perceived as clinically relevant.

Goldie and Coldman [19] proposed a mathematical model for drug treatment based on the random spontaneous development of mutant cells resistant to chemotherapy. The probability of cure would then be inversely related to the mutation rate per cell generation, and diminish with increasing size of the tumour: the effect of combination chemotherapy with non-cross-resistant drugs would be mathematically equivalent to a reduction in the rate of mutation to resistance. Evidence was accumulating at the time for a genetic basis for phenotypes resistant to drugs such as methotrexate and hydroxyurea [20], and they proposed that alternating chemotherapy with non-cross-resistant combinations would improve on sequential regimes by minimizing the chance for the early development of acquired resistance. Greater cell heterogeneity could explain the phenotypic variation in initial response [21], while the emerging concepts of pleiotropic drug resistance [22] provided a unifying hypothesis for acquired changes.

While the model appeared to explain the relationships between tumour size and response, as well as those between the requirement for early treatment and the clinical expression of drug resistance, there were a number of questionable assumptions in its derivation. It has been shown that the phenotypic expression of resistance can be overcome by dose escalation both in the laboratory [23] and in the clinic [11], while the model predicts mutation rate should be independent of dose [24]. The association between early institution of treatment and curability has been shown for rapidly growing tumours such as osteogenic sarcoma and testicular germ cell tumours, but repopulation during the delay is a more likely explanation of treatment failure than alteration in mutation rates [25]. Of the many studies recently initiated employing alternating regimens, only one has shown superiority over a sequential approach [26]. The existence of drug combinations which are truly non-cross-resistant in the clinical setting may be questioned, but it is in relation to their concepts of drug resistance mechanisms and control of cell proliferation that the Goldie–Coldman hypothesis requires modification.

Resistance is an adaptive phenomenon, involving a range of homeostatic responses on behalf of the normal and neoplastic tissues leading to a change in their relative proliferation rates. These changes occur over variable time periods following drug exposure, and some may show dose dependence. The initial response may be an attempt at detoxification either through metabolic inactivation of the drugs, or protection of critical sites from free-radical attack while later responses may be at the epigenetic or genetic level, including alterations in repair mechanisms, salvage pathways, drug efflux or interference with signal transduction [27]. Selection pressure under certain tissue culture conditions may give prominence to one mechanism, and explain the disparity between clinical phenotype and experimental models. Somatic mutation is only one component in the host cell defence against cytotoxic drug attack.

In recent correspondence [28], Goldie has moderated the claims for the clinical applications of the model to relating curability to the rapidity of cytoreduction and enhancing the curative potential of

chemotherapy by employing drugs in combination: these principles have been clear for many years, although they can now be applied with a greater margin of safety. The validity of the model is supported on the grounds that it predicts well for the mathematical probability of outcome, even if the single point mutation theory of resistance from which it was derived is now largely untenable. However, a model that is right for the wrong reasons does no more than impart a false scientific basis to one aspect of clinical empiricism. The Goldie–Coldman hypothesis has stimulated intense discussion and contributed to the development of more aggressive and effective approaches in a small range of sensitive tumours, but it is now time for it to be laid to rest.

What is required is a return to the component parts of the problem of treatment failure, and an acceptance of the fact that while certain general principles may hold, there may be as yet no unifying strategy which has emerged. Goldie–Coldman failed because of an invalid assumption on the nature of human tumour drug resistance, based on *in vitro* experiments and animal tumour models. The traditional morphological categories of tumours are in the process of being refined to take account of biochemical resistance. Similarly, ploidy analyses and tumour doubling times based on BrdU incorporation [29] may help to provide a more rational basis for kinetic approaches. However, the interaction of drugs with growth factors and the resultant effect on signal transduction and proliferation may render the distinction between kinetic and biochemical resistance somewhat arbitrary [30, 31]. Chemosensitivity assays, provided they comprise representative cells under relevant growth conditions, may give a qualitative measure of response [32].

Advantage should be taken of dose dependence where it can be demonstrated, while being cautious that overuse of dose escalation may be counter productive especially in combination where the relative contributions of the individual components are difficult to establish. Excessive normal tissue toxicity may lead to poor results in patients with low performance status or compromised organ function even when employing an approach that is fundamentally correct for the tumour type. This tactical error is commonly seen in patient selection for phase II studies, and is insufficiently appreciated in the phase III situation [33]. Cell cycle dependence of the drugs, rational use of putative mechanism of action, and an awareness of cumulative pharmacokinetic effects with increasing number of cycles are all factors which require consideration in protocol design.

New models should take into account concepts of growth inhibition and feed-back control of proliferation [16, 31], as well as the cytotoxic effects which have been the traditional goals of cancer chemotherapy. The parallel with drug screening and early development is clear: while a number of useful agents have been found from the leukaemic screens, no agent has been shown to be broadly active against solid tumours [34], and this self-perpetuating system may for many years have been a barrier to progress. In the same way the use of drugs in cancer treatment, and their integration with agents such as radiation [25] or biological response modifiers need to be reconsidered in the context of a more individual strategy for each cancer.

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