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Perspectives in Cancer Research

Preoperative Chemotherapy for Operable Solid Tumours*

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Abstract—*Accumulating evidence suggests that most common solid tumours in man have latent metastases when clinically detected. Further evidence indicates that when the primary focus is resected, its micrometastases may become enhanced as a result of immunosuppression and other tumour-promoting factors at work in the perioperative period. In this favourable setting, the development of new metastases may also be facilitated from cells forced into the circulation during operative manipulations. It is suggested that the above events are important in the treatment outcome and that they may be prevented to some extent if treatment is first directed to the systemic component of these tumours; resections of the primary focus can be more advantageously done later. Results from experimental and clinical studies as well as many theoretical considerations support the potential value of this approach in the management of operable solid tumours.*

INTRODUCTION

MOST of our treatment failures in common solid tumours (S.T.) at an operable stage appear to be due to our current inability to control metastases present but latent at diagnosis. Although this is common clinical experience with intrinsically very aggressive neoplasms, e.g. of the lung, pancreas or stomach [1], it is not readily appreciated in tumours with longer range of survival, e.g. those of the breast or colon. For example, what clinically appears as 'localised' breast cancer is in fact systemic at the time of diagnosis with up to 90% of the patients ultimately dying as a result of dissemination [2–4]. The risk is probably life-long as it was recently demonstrated in a follow-up of many large reported series. Even in patients with stage I and II disease, an annual increment of death due to cancer of about 6% was observed 10–36 years after mastectomy [5]. Systemic spread is apparently also quite frequent in carcinoma of the urinary bladder at the time of cystectomy in all stages of the disease [6]. The same seems to be the case in the presumably less aggressive colorectal cancer; fewer than 50% of the patients with stage I disease (without lymph node metastases) will survive for five years [7] and early tumour dissemination is also invoked to explain the inability of locoregional treatment to control it [8]. The anastomosis was found to be the initial site of recurrence in only 1.5% of patients who underwent curative resection, the remaining relapsing into additional metastases regionally and/or systemically [9].

Another factor that could adversely influence treatment outcome is the possible enhancement of micrometastases resulting from the depression of host defences in the perioperative period. Contributing factors in this regard are the immunosuppression due to surgical injury, anaesthetic and other drugs and various other host factors which reduce cell-mediated immunity and increase tumour metastatic potential [10]; the perioperative changes in the coagulability of the blood which favour the development and growth of micrometastases [11]; and the circulating immunosuppressive peptides appearing shortly after major operations [12] which may also

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accelerate tumour growth. Indeed, experimentally, elimination of the primary lesion can enhance distant microscopic foci. In a number of tumour models, within hours from resection of the primary tumour, micrometastases begin to grow faster [13–16]. Whether or not this kinetic change is due to the tumour enhancing factors cited above or to other as yet unidentified mechanisms is not known, but its possible applicability to S.T. in man must arouse serious concern. Assuming that perioperative enhancement of micrometastases of human S.T. is possible, it would be reasonable to examine alternative courses of action, preventing such occurrence. Directing our initial treatment effort to the systemic component rather than the primary focus of S.T. represents such an alternative, the rationale for which is supported by many lines of evidence discussed below.

THEORETICAL ADVANTAGES OF PREOPERATIVE CHEMOTHERAPY

A number of arguments can be summoned in support of systemic therapy before operation and at the earliest possible time in the clinical course of any tumour: (a) The smaller the neoplastic focus, the greater the likelihood for its cells to divide more actively, be better oxygenated and less likely to accumulate metabolites capable of inhibiting the effects of chemotherapeutic agents [17]; at this stage, they are also more easily synchronizable [18] and presumably more vulnerable to chemotherapy [19]. (b) Tumour-elaborated substances, known to subvert host immune and other mechanisms of tumour destruction, e.g., the antigenic determinants shed from the tumour cell surface [20], moieties inhibiting macrophage function [21] or chemotaxis [22] and other factors, may be more effectively suppressed by preoperative systemic therapy. Entrenchment of micrometastases during perioperative immunosuppression may thus be prevented. (c) The spontaneous development of drug-resistant mutations in the tumour increases with time and may be as crucial to the chemotherapy of tumours as to that of microbial infections. It is therefore likely that initiation of chemotherapy simultaneously or even before the attack on the primary tumour will give a much better chance for cure [23]. (d) Cell variants destined to form metastases preexist in the primary tumour [24] and if forced into the circulation with intact potential, particularly in the favourable setting present in the perioperative period, they are likely to establish new micrometastases. Chemotherapy, however, will affect markedly clonogenic cells in the primary tumour [25] and limit this inherent risk of operations. (e) The delay of about one month from diagnosis to the beginning of postoperative adjuvant treatment currently practiced is likely to allow a substantial increase of the microscopic tumour burden of some common S.T. Assuming an average doubling time of 90 days at the time of diagnosis in e.g., breast or colon cancer [18], tumour burden will increase by about 30% before systemic treatment is begun. This of course may be an underestimate, with respect to fast-growing tumours which are also the most likely to have metastasised at the time of diagnosis. (f) Properly timed, preoperative chemotherapy can be exploited as an immunostimulating agent. After a short intensive chemotherapy course, immunity is depressed but gradually recovers in the second week and ultimately 'rebounds' to higher than the pretreatment levels of function where it is maintained for another week [26]. If operation is done during this period of heightened immunity, the suppressive effects of surgery on immunity and other host functions may be counteracted at least in part. We may conclude, therefore, that chemotherapy before operation appears to be advantageous not only to prevent enhancement of micrometastases and treat the systemic disease at the truly earliest point in its clinical course, but indeed for the initial management of the primary tumour itself. (g) Finally, the antitumour effect of chemotherapy may be directly assessed in most instances and an ineffective regimen can be withheld rapidly. This unique opportunity is lost if the primary tumour is initially resected so that the efficacy of systemic treatment becomes impossible to determine until relapses are documented.

EXPERIMENTAL SUPPORTING DATA

Brock [27] was the first, to my knowledge, to demonstrate the value of preoperative chemotherapy more than 20 years ago, using the transplantable Shay-chloroleukoma of the rat, a widely metastasizing tumour which is 100% lethal if untreated. Tumour excision was associated with a cure rate of 15%; 30 mg/kg of cyclophosphamide i.v. twice resulted in a cure rate of 28%. When the first cyclophosphamide injection was given 1 hr before operation and the second 24 hr after operation, 50% of the animals survived. If both doses of cyclophosphamide were given 8 and 7 days before operation, 90% of the

animals were cured. Subsequently, Karrer and coworkers [28], using a variety of treatment schedules in the Lewis lung tumour in BDF1 mice, showed a linear dose–response curve when chemotherapy was begun 2 days before amputation of the tumour-bearing extremity and it was continued every 5 days thereafter. This treatment schedule was the best of all combinations studied. Likewise, in the spontaneously metastasing adenocarcinoma in Fisher rats, which is 100% lethal if treated by surgery alone, it was shown that chemotherapy on the day of surgery or 10 days before surgery cured 70–80% of the animals [29]. In different sets of experiments with B16 melanoma in C57B1 mice, the same combination of a single course of chemotherapy preceding surgery increased survival from 38–43% in controls to 50.5–87.9% in treated animals [30]. Furthermore, in a mouse model with simulated metastases, Fisher and collaborators [31] observed an advantage in delaying the removal of the primary tumour in order to treat the 'metastatic' disease first, by various chemoimmunotherapy regimens.

Likewise, Schabel and his coworkers [32] recorded 63% cures in a transplanted metastasising murine model when adriamycin was given 12 days after implantation and operation was done on day 15. If adriamycin was given three days postoperatively, only 13% of the animals were cured. Schabel points out that metastatic tumour burden had three more days of growth than in the latter, and attributed the observed variations of cure rates to differences in size of tumour burdens; thus he indirectly quantitated the importance of early systemic treatment in the prevention of metastatic disease growth. In other as yet unpublished experiments in BDF1 mice implanted with Lewis lung tumour, methyl CCNU given intraperitoneally on day 7 and surgery on day 8 resulted in 90% cures whereas surgery on day 7 and methyl CCNU on day 8 yielded 50% cures. The same treatment sequence in the same model, applied after the seventh post implantation day, was less successful but again more effective than post-surgery chemotherapy [33]. Most recently, the importance of treating micrometastatic disease at the earliest possible time was again demonstrated in the B16 melanoma transplanted in C57BC/6 mice. A single dose of cyclophosphamide given when the tumour just becomes palpable on the eighth postimplantation day, followed by amputation up to one week later, cured 80% of the animals. Delay of only one day in the cyclophosphamide treatment decreased the cure rate to 26%. There were no long-term survivors by either chemotherapy or amputation alone given on the ninth day [34].

CORROBORATING CLINICAL EVIDENCE

Nissen-Meyer and collaborators from 10 Scandinavian hospitals used a 6-day course of cyclophosphamide intravenously (30 mg/kg, with 2400 mg maximal dose) to alternate patients, beginning on the day of mastectomy; radiotherapy followed on all patients. In only one hospital (a radiotherapy clinic), chemotherapy was given 2–4 weeks later, to referred patients for radiotherapy after wound healing. The group receiving cyclophosphamide had a small but statistically significant reduction of recurrence rate and equally significant increase in survival sustained up to 12 years [35]. Improvement was equal in premenopausal and postmenopausal patients. There was one notable exception in patients whose chemotherapy was delayed for 2–4 weeks in the radiotherapy clinic. No benefit was demonstrated in these patients indicating that an effective agent may become impotent if its administration is delayed even for a few weeks after operation. A similar observation was made in a large-scale collaborative study in the U.S. where thiotepa was given during mastectomy and the first two postoperative days. Whereas early differences between treated and untreated patients were not observed, in a re-evaluation of results 10 years later, patients with four or more positive nodes given chemotherapy had a 20% higher survival than their controls, but this benefit was restricted to premenopausal women [36]. However, the same drug given to patients with gastric cancer in the perioperative period showed no survival benefit at any time [37]. Both the above studies in breast cancer are important in suggesting that at least in that tumour the perioperative period may indeed be most appropriate for the initiation of adjuvant therapy. On the basis of the evidence previously cited, the good and long-lasting results of these two studies can be explained as follows: acceleration of tumour growth postoperatively [13–16] renders micrometastases more vulnerable to chemotherapy [19], which given during this period may have a greater and more lasting impact on the systemic expression of the disease. Thus, both preoperative and intraoperative systemic treat-

ment may yield maximal protection and best ultimate results.

In a number of other clinical studies, usually not prospective, chemotherapy before operation was given in a variety of common solid tumours, e.g., stomach [38, 39], lung [40], breast [41, 42] and particularly of the head and neck [43–47]. In other neoplasms of children and adults [48–53], chemotherapy given before surgery was also effective. Although all these studies usually concerned patients with advanced tumours, their results were consistently encouraging and as a rule better than expected if chemotherapy were to be given after operation. Indeed, in most, operation was not even possible or feasible before chemotherapy. A consistent feature of these studies is that wound complications or other chemotherapy-related problems were not observed. This has been also our own experience with the use of preoperative chemotherapy in a variety of gastrointestinal [54] and other tumours. It is therefore logical to conclude that if chemotherapy followed by operation is a more effective sequence that its reverse for advanced tumours with dismal prognosis, it must be even more successful for neoplasms in a less advanced stage.

DISCUSSION

The systemic nature of S.T. is likely to remain a problematic feature in the management of these neoplasms until more effective means of detection and treatment of latent microscopic disease are discovered. The traditional perception of the majority of common S.T. as localised diseases has so far dictated their initial management by operation. This conviction continues to prevail among clinicians despite the compelling evidence indicating that S.T. in man are in fact systemic diseases in disguise. However, if S.T. are conceptually accepted primarily as systemic problems, chemotherapy at the earliest possible point in time would be entirely justified and indeed the more logical course to pursue.

Although on the theoretical grounds presented,chemotherapy must be more effective if given before operation than in the reverse order, to what extent this is so, after how many courses, etc., remains conjectural. In actuality, it is possible that preoperative chemotherapy may curtail growth of existing and new micrometastases to a limited degree, or in a small subset of patients, so that continuation of treatment during and after operation is imperative. Even in this case, however, treatment would begin against an overall microscopic tumour burden smaller than that logically expected to be present if adjuvant therapy is delayed for a few weeks after operation. At any rate, the combination of preoperative and postoperative chemotherapy is more likely than the latter alone to reduce the overall microscopic mass below the critical volume which is necessary for tumour regrowth. In this setting, host immune mechanisms either alone or aided by stimulating agents could become more efficient in extirpating remaining subclinical disease.

This proposal is easily testable and if improvement of end-results is indeed demonstrated, the overall amount of cytotoxic agents necessary in each case may be diminished along with their cost, toxicity and other adverse effects. In addition, if systemic treatment affects the size and curability of the primary tumour, the study of operations progressively more conservative of form and function will become further justified. Ultimately, fewer drugs combined with less incapacitating operations may reduce morbidity, improve the quality of life and save a greater number of patients from cancer.

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