Reduction of Toxicity in Cancer Chemotherapy

Seymour Perry
National Cancer Institute, Bethesda, Maryland 20014

SUMMARY

In this paper, the present status of the supportive care of patients undergoing cancer chemotherapy has been reviewed. Myelosuppression with thrombocytopenia and leukopenia are of particular significance. Fortunately there are measures which can be utilized to ameliorate these effects and the complications to which they give rise without compromising antitumor therapy.

In simple terms, toxicity as a consequence of antitumor therapy is a reflection of the fact that most cytotoxic agents currently in use affect normal as well as neoplastic cells, and in general these agents have a low therapeutic index. True selective cell toxicity has thus far been difficult to achieve although the agents currently in use are of value because, if administered in the proper dose and schedule, they will destroy tumor cells more rapidly than normal cells. As far as is known, neoplastic cells synthesize DNA and divide in essentially the same way as their normal counterparts. In fact, cell cycle times are not too dissimilar although the proportion of cells in active proliferation and nonproliferation may be different. Toxicity and recovery from toxicity would then be dependent upon the distribution of normal and neoplastic cells in these pools. Theoretically, then, scheduling of drug administration is an important factor contributing to toxicity, but this will be dealt with in other portions of this symposium. The tissues in the body most frequently affected by cytotoxic agents are the bone marrow and gastrointestinal tract. These organs have high rates of renewal so that agents exerting their effects on DNA synthesis or on mitosis will encounter relatively large numbers of susceptible cells. Fortunately the high renewal rate also means that, once the offending agent is eliminated, the repair process is quite rapid.

Hair is another tissue which is frequently affected in patients receiving antitumor therapy, but obviously this is a problem only from the cosmetic standpoint. However, the effects on the hair follicle are of interest from a theoretical standpoint since the cells in the germinative cell population of the hair matrix have an extremely high rate of mitosis (53). Thus, growing scalp hair may be lost after cytotoxic chemotherapy, but resting hair in the axillae and pubis is spared because the mitotic rate in the folicles in these areas is relatively low.

As indicated above, the most frequent serious problems in toxicity encountered in patients receiving antitumor therapy relate to the gastrointestinal mucosa and bone marrow. These effects often limit the use of an agent and frequently preclude the administration of drugs in amounts or frequency necessary to achieve optimal tumor cell kill. There are many complications of cancer chemotherapy, including nausea, vomiting, diarrhea, constipation, chemical cystitis, muscle weakness, hepatotoxicity, alopecia, peripheral neuropathy, and urate nephropathy. These will not be discussed here. In many cases, the complications can be managed only if therapy is stopped or the dose reduced. In other instances, relatively simple measures may be employed to reduce toxicity without compromising treatment. In this paper, some of the more important technics for the protection of patients undergoing cancer therapy will be reviewed along with measures for the prevention of complications.

BONE MARROW SUPPRESSION

Thrombocytopenia

Leukopenia and thrombocytopenia associated with bone marrow suppression, with subsequent infection and hemorrhage respectively, are two of the most serious complications of cancer chemotherapy. Bone marrow replacement is a difficult procedure and the results have generally been disappointing. However, the replacement of individual blood constituents is much more practical and feasible. The use of blood transfusions for the treatment of patients with hemorrhage due to thrombocytopenia was first reported in 1910 (18). Subsequently, technics were developed to separate platelets, but the effectiveness of platelet transfusions remained speculative until their value was clearly demonstrated in irradiated animals in 1951 by Dillard et al. (15). However, it was only when plastic tubing and containers for the collection of platelets were developed that the clinical effort for the improvement of methods to separate, preserve, and transfuse was given great impetus. Intensive transfusions with platelets are now generally recognized to be valuable in preventing or controlling hemorrhage resulting from thrombocytopenia in a variety of clinical situations (16, 22, 27, 33, 36).

In acute leukemia, there is a rough inverse relationship between the height of the platelet count and the incidence of hemorrhage. Serious hemorrhage is infrequent in patients with platelet counts above 20,000–50,000 per cu mm (28). Accordingly, in many institutions, platelet transfusions are now given routinely to patients whose platelet counts fall below this level. This prophylactic program appears to be
Fever and infection have deleterious effects on both.

Platelets are transfused as fresh whole blood, platelet-rich plasma (PRP), or platelet concentrates (PC). Fresh whole blood should be used only if the clinical situation requires replacement of red blood cells and plasma as well as platelets, but even in such situations, supplementation with additional platelets is usually necessary. PRP is easily prepared, but PC are used more commonly because multiple transfusions are usually necessary and large volumes may overload the cardiovascular system.

Acid-citrate-dextrose (ACD) is the anticoagulant of choice in the preparation of PC even though persistent platelet aggregation due to the release of adenosine diphosphate (ADP) may occur. Acidification of the medium used to resuspend platelets prevents ADP-induced clumping and after transfusion results in better in vivo survival of the platelets (1). This has been substantiated by clinical experience (23, 48) so that it is preferable to acidify the plasma for the preparation of PC. Acidified platelet concentrates are approximately 50% more effective than ordinary concentrates (48) and 80–90% as effective as PRP (23).

Since the intravascular survival time of platelets is relatively short, transfusions must be frequent and multiple. With PC, the platelets from four to eight units (500 ml/unit) of blood should be administered to a 30-kg child. Proportionately larger quantities must be given to an adult. Storage has a deleterious effect on platelets, and ultrastructural changes occur within a relatively short period after procurement. This may result in diminished recovery and shortened survival in vivo. Accordingly, separated platelets should be transfused promptly, at least within 6 hours after collection. Platelet-rich plasma prepared from a unit of fresh whole blood from a normal donor will yield approximately 10^11 platelets. When these are transfused to a thrombocytopenic patient with acute leukemia, the average platelet increment will be 12,000–14,000/cu mm/sq m with an average recovery of 30% one hour after transfusion (24). Fever and infection have deleterious effects on both recovery of platelets and their survival in the circulation.

Although, as indicated above, platelet transfusions have been used clinically for years, the problem of incompatibility has not been adequately studied, and this remains an important problem both in terms of complications for the recipient and in wasting of valuable material. Presumably, this is less of a consideration in patients receiving immunosuppressive therapy. Recent studies at the National Cancer Institute indicate that typing for HL-A antigens may be of value for the selection of compatible platelet donors (30). Patients with aplastic anemia who had become refractory to platelets from random donors were well maintained on less than 25% of the number of units previously required. If these observations are confirmed, they will have important implications for the platelet supply problem. Unfortunately, at the present time it appears that a program to type donors and recipients will be a large and expensive undertaking. However, the problem of histocompatibility in replacement therapy of patients with cancer is extremely important and deserves a great deal of effort.

There are also problems associated with the procurement of platelets. If platelets are obtained locally, donor availability is often erratic and the procedure for platelet separation is tedious and time consuming. Approximately 20 years ago, Tullis et al. (51) introduced the first device specifically designed for separation of blood into its component parts on an in vivo basis. It has never gained wide acceptance probably because of the complex procedures required in its operation. Recently, the bowls have been modified so that they can be operated in commonly available refrigerated centrifuges (52). The operation is essentially a batch-type process in that, for separation of cellular elements, the blood flow must be interrupted at intervals. Platelet recovery approximates 50–60% with minimal white blood cell contamination (50).

Recently, another device, the NCI-IBM Cell Separator, has been developed at the National Cancer Institute (8, 25). As in contrast to the instrument just mentioned, this device is capable of operating at rates up to 200 ml per minute although 40 ml per minute is the usual rate employed. Most of the emphasis in this program thus far has been on granulocyte procurement. However, preliminary studies indicate that the Cell Separator will be useful for the preparation of PC on a continuous flow basis. Hopefully, these or similar instruments will make it possible to collect large numbers of platelets with less effort and more efficiently than the plasmapheresis technique now employed.

Some institutions do not have their own platelet procurement programs but obtain platelet concentrates by contract from local blood banks. The packed red blood cells which are left are usually wasted because of the general resistance by the medical profession to the use of packed red cells or platelet-poor whole blood. It has been repeatedly pointed out that in most clinical circumstances the separate use of the constituents of the blood is not only more efficient and a better utilization of a valuable commodity but is much safer (20, 21).

These then are some of the obstacles to greater and more widespread use of platelet transfusions. Since many institutions are unable or unwilling for practical reasons to establish their own platelet procurement units, it would appear that the use of platelets would be greatly enhanced if they could be stored and preserved and then distributed from centrally located blood banks on request. A number of methods for cryopreservation of platelets have been described, but freezing in liquid nitrogen (−195°C) in a combination of dimethylsulfoxide and dextrose is used most commonly. When thawed and transfused the in vivo yield of platelets preserved in this manner is 10–50% compared to the recovery of fresh platelets (16, 17). Unfortunately, the transfusion of platelets frozen in dimethylsulfoxide is associated with a number of undesirable side effects, including nausea and vomiting, local venospasm, and an undesirable odor. Large doses of dimethylsulfoxide in animals have produced pathologic eye changes, particularly cataracts. It is obvious that an intensive effort is needed to improve the technic of platelet preservation before the widespread use of platelets will become feasible.
Leukopenia

While the use of platelet transfusions has quite clearly resulted in a decrease in the incidence of hemorrhage and death due to bleeding in thrombocytopenic individuals, infection associated with severe granulocytopenia has become the single most important cause of death in patients with acute leukemia (32, 54), being responsible for 70% of all deaths. In spite of antibiotics, septicemias due to Gram negative organisms, particularly those due to Pseudomonas, have become increasingly frequent along with secondary fungal infections. During 6000 admissions of patients with malignancy to the National Cancer Institute between 1955 and 1966, there were 789 episodes of septicemia (A. A. Levitan, personal communication). From 1955 to 1958 S. aureus was the most frequent cause of septicemia (26% of all cases with a mortality of 43%). The incidence of septicemia due to Pseudomonas was 16% with a mortality rate of 80%. While the incidence of and mortality due to S. aureus has markedly decreased because of penicillinase-resistant antibiotics, Pseudomonas has become the most common cause of septicemia (15%) with a mortality of 65%. Infections of all types increase both with duration of disease and with prolonged use of chemotherapeutic agents, presumably due to progressive deleterious effects on marrow function. There does not seem to be any relationship between globulin levels and frequency of infection (54), but the incidence of infection increases with decreasing granulocyte levels in the peripheral blood (5). The critical level appears to be 1500 granulocytes per cu mm; above this the incidence of infection bears no relationship to the white blood count.

Sepsis in adults with acute leukemia who fail to go into remission is a particularly serious problem. Two papers can be cited to illustrate the gravity of this problem. Burke et al. (10) recently reported the results of a study in which combination therapy with cytosine arabinoside, vincristine, and prednisone was employed in 19 patients with acute leukemia. Eight patients, four with acute lymphocytic and four with acute myelocytic leukemia, achieved complete remissions. In the remaining 11 patients (none with lymphocytic leukemia) there were 10 deaths, 8 due to sepsis including 5 due to Pseudomonas species. Similarly, sepsis may not infrequently limit the usefulness of a new agent. In 61 patients with acute leukemia treated with daunomycin, there were 30 complete remissions (4). However, at the same time among the remaining 31 patients, there were 19 instances of fatal marrow aplasias.

These are only two examples, but it is obvious that in spite of modern antibiotics, myelosuppression with leukopenia following by fatal sepsis is a major problem in cancer therapy. It is impossible to say, of course, what the incidence of remission would be if this complication could be controlled, but certainly the results would be better than at present. Since antibiotics have been far from completely effective, then replacement therapy with granulocytes should be considered.

Replacement therapy with erythrocytes has been a recognized procedure for years, and, although the use of platelet transfusions is relatively new, their role is fairly well established. However, white blood cell replacement is another matter. The feasibility of leukocyte transfusions was demonstrated many years ago by Brecher et al. (7). These workers transfused homologous leukocytes into dogs rendered aplastic with X-irradiation and showed that the donor leukocytes migrated to sites of infection and were functional. Unfortunately, in contrast to red cell and platelet replacement, clinical application of this observation is beset with several problems. The major obstacle to the evaluation of white blood cell transfusions in clinical medicine has been the difficulty in obtaining adequate numbers of granulocytes from normal donors. The technic of plasmapheresis permits the procurement of adequate numbers of platelets from normal donors. However, the relatively small numbers of granulocytes in normal blood and the difficulty in separating these cells because of overlapping densities (R. L. Greenfield and S. Perry, unpublished observations) make it impractical to obtain adequate quantities of granulocytes from normal individuals for replacement therapy. Yankee et al. (57) used dextran sedimentation to isolate leukocytes from normal blood buffy coats, and following transfusion, white blood increments compared favorably at the same dose level with leukocytes obtained from donors with chronic myelocytic leukemia (CML). However, it was estimated that approximately 40 units of normal whole blood would have to be processed in order to obtain sufficient leukocytes to achieve the same increment (1000 per cu mm) resulting from the transfusion of leukocytes from one unit of CML blood. Accordingly, patients with CML and high white blood counts have been utilized as donors (26, 46). Leukocytes are obtained by standard plasmapheresis technic, with the red blood cells and plasma being returned to the donor. For obvious reasons, transfusions of CML cells have been administered only to patients with acute leukemia or other life-limiting diseases, but whether CML leukocytes are comparable to normal leukocytes in combating infection is questionable (47). Reactions, particularly fever and chills, are common following leukocyte transfusions and, occasionally, are quite severe, resulting in sternal constriction, tachycardia, sweating, dyspnea, tachypnea, pallor, and cyanosis. Transient sequestration of infused leukocytes in the lungs has been demonstrated recently in vitro labeling of the cells with 51Cr followed by body surface monitoring (19) and may, in part, explain the respiratory symptoms.

Freireich et al. (26) transfused a group of leukopenic individuals, predominantly patients with acute leukemia, with a median of 5.8 X 1010 CML granulocytes and band cells. The median recovery one hour post transfusion was 5% (range, 0–36%) with an increment of 1000 leukocytes per cu mm. Peripheral white blood counts in recipients returned to pretransfusion levels by 48 hours. Even though the patients had received antibiotics, there was strong suggestive evidence that, in febrile individuals, lysis of fever was often related to the transfusions. The results in patients with sepsis due to Gram negative organisms, particularly those with Pseudomonas septicemia, appeared especially striking. The proportion of all patients responding seemed to correlate with the dose of leukocytes administered, 1 X 1011 per sq m or more being most effective. Myeloid grafts are not uncommon in transfused patients receiving intensive cytotoxic chemotherapy, and persistence of the Ph1 chromosome has been detected in bone marrow aspirates (26). This has frequently been accompanied...
by increases in peripheral blood counts, apparently due to production of leukocytes and/or erythrocytes by the donor graft. Subsequently, symptoms may appear which are similar to the secondary syndrome in allogenic marrow grafting in man, and it has been postulated that remissions induced by leukocyte transfusions may be related to this phenomenon (46).

As indicated above, white blood transfusions in the supportive care of patients have not achieved wide acceptance. Physicians may not have access to suitable donors, or the facilities for plasmapheresis may not be available, and there is still a reluctance by some clinicians to use CML transfusions even in life-limiting clinical situations. In addition, the reported beneficial results have been questioned since control studies have not been reported. Unfortunately, such studies are difficult to design and carry out because of the clinical setting of patients acutely ill with sepsis. The erratic availability of suitable donors would also add to the problems in implementing the study. In this connection, it should also be pointed out that very large quantities of white blood cells are theoretically necessary even for partial replacement. Except for the spleen, there are probably no significant platelet pools in the body so that transfused platelets are utilized very efficiently. On the other hand, there are large pools of granulocytes which are not reflected in the white blood count unless some technic for granulocyte mobilization is employed (41). Hence, when white blood cells are transfused, many of the cells may be "lost" into these pools and not readily available. In the patients with leukemia both the spleen and bone marrow are responsible for trapping, if only temporarily, large numbers of leukocytes from the circulation (19, 40). Hence, following the transfusion of homologous granulocytes, it is not surprising that recovery and survival in the circulation is poor. Results are even less satisfactory if granulocyte stores have been depleted as a consequence of cytotoxic therapy, and production has been impaired and utilization increased due to infection and fever.

The problem of granulocyte procurement may soon be resolved in view of the recent development of the NCI-IBM Cell Separator (8, 25). Studies in dogs utilizing this device have demonstrated that large numbers of leukocytes can be obtained which by all criteria appear to be undamaged (9). It has now been used for granulocyte procurement from both normal donors (R. G. Graw, Jr., R. Eisel, C. D. Buckner, and S. Perry, unpublished observations) and from patients with CML (8). The median collection of white blood cells per centrifugation (average duration 195 minutes) was $1.1 \times 10^{10}$ from normal donors and $2.6 \times 10^{11}$ from CML donors with mature granulocytes constituting 55% of the normal white cells and 60% of the CML cells. Upon transfusion into patients with bone marrow hypoplasia and severe leukopenia, the recovery of white blood cells and granulocytes was approximately 3% respectively with the CML cells in contrast to 19% and 15% respectively when normal cells were used (R. G. Graw, Jr., and S. Perry, unpublished observations). These preliminary observations suggest that normal granulocytes can now be obtained from individual normal donors in adequate quantities for the supportive care of leukopenic individuals.

The NCI-IBM Cell Separator has also been utilized to transfer immunity to patients with malignancy. Curtis et al. (14) collected peripheral blood leukocytes from donors immunized to a specific antigen and after transfusion could demonstrate that the antigen had been successfully transferred in 28% of the recipients. Although untreated patients with acute leukemia and most other neoplasms show little or no disturbances in serum immunoglobulins and delayed hypersensitivity, and respond fairly well to antigenic stimulation, cytotoxic therapy often results in impairment of the immune mechanisms. This is another area where replacement therapy or protection technics need to be developed, and this demonstration in the use of immunocompetent lymphocytes may be a first step.

Since it appears that the supply of fresh granulocytes will always be a problem, there is a great need for an efficient technic for granulocyte preservation. In contrast to lymphocyte preservation, granulocyte preservation has not been successfully achieved. Rapid freezing to $-196^\circ$C utilizing 10% or 15% dimethylsulfoxide reduces the number of cells capable of phagocytosis after thawing to approximately 3% of the fresh cells (11). There is evidence that labilization of lysosomal membranes by the freezing process may be responsible for the poor recovery of granulocytes (R. Yankee, personal communication). An intensified effort is needed therefore to develop new technics of cell preservation which would permit, as suggested above for platelets, the storage and distribution of granulocytes on demand.

**PATIENT PROTECTION AND ISOLATION**

**Plastic Isolators**

The patient in a hospital undergoing therapy with cytotoxic and immunosuppressive therapy is at risk to infection by a large variety of organisms, both endogenous and exogenous from the unusual environment in which he finds himself. The hazards of acquiring infection in a hospital environment were, of course, recognized many years ago and led to the institution of aseptic technics and to the establishment of "pest" houses, sanitariums, isolation wards, isolation for individual cases, and other procedures to decrease cross-infection. These were attempts to limit the spread of infection and to protect the patient.

It is of some interest that infection rates in hospitals at the present time are no better than they were before 1940 and are still about 1–5% (56). The actual incidence of infections acquired in the hospital has never been clearly defined, but in a recent study (38) at a university hospital approximately one-third of the clinically apparent infections were due to cross-infection and two-thirds of these were caused by Gram negative organisms. It would seem logical, therefore, to utilize technics to protect the patient at risk to infection from his environment and to reduce his endogenous microbial burden.

Isolation technics for germ-free animals were first developed near the end of the last century, and there have been a great many studies of animals in germ-free environments in this context. It is now possible to limit the spread of infection by constructing "negative" pressure rooms in which air is filtered to a high degree of sterility and this air is introduced into the room. The patient is then protected from the environmental infections by living in this air-free environment. This technic may prove useful in patients at risk to infection with the usual amount of aseptic precautions (7, 23).

It is of some interest that infection rates in hospitals at the present time are no better than they were before 1940 and are still about 1–5% (56). The actual incidence of infections acquired in the hospital has never been clearly defined, but in a recent study (38) at a university hospital approximately one-third of the clinically apparent infections were due to cross-infection and two-thirds of these were caused by Gram negative organisms. It would seem logical, therefore, to utilize technics to protect the patient at risk to infection from his environment and to reduce his endogenous microbial burden.

Isolation technics for germ-free animals were first developed near the end of the last century, and there have been a great many studies of animals in germ-free environments in this context.
bacterial flora is associated with increased resistance to the toxic effects of myelosuppressive agents and radiation (29, 43, 55). In addition, for most therapeutic agents the dose response curve experimentally is very steep for both tumor and host cells (49). For example, a two-fold increase in dose of an agent may destroy ten-fold as many neoplastic cells. In man, the same general relationship appears to hold in terms of tumor regression, proportion of patients responding, and toxicity.

Clinical interest in isolators did not really begin until after Reyniers and Trexler in 1943 reported their technic of rearing germ-free animals (43). With the development of plastics technology, a variety of plastic isolators appeared and are now being utilized for the treatment of burn patients (31) and for surgical patients (35). These were followed by studies of the isolation technic for the protection of patients undergoing cancer chemotherapy (44, 45). The unit (Life Island®, Matthews Research Corp., Alexandria, Va.) employed provides a sterile environment and consists of a modified hospital bed completely enclosed by an airtight canopy. Air enters the enclosure through high-efficiency filters that remove almost all organisms and may be varied to yield 2 to 6 exchanges per hour. Plastic gauntlets with attached rubber gloves are used to gain access to the patient. All material entering the unit, including personal belongings, reading material, and linens, are sterilized. Items are passed into or removed from the isolator via two ultraviolet locks. Food is also sterilized, but recent studies with thoroughly cooked selected foods suggest that this approach can accomplish the same result. Before entry, the patient is subjected to an intensive regimen consisting of skin scrubs, antibiotic ointments, and nonabsorbable oral antibiotics, designed to reduce skin and alimentary tract organisms to a minimum. These preliminary studies, confirmed by other investigators (6), demonstrate the feasibility of maintaining patients in a sterile environment for a relatively long period of time while they are undergoing intensive antitumor therapy. The prophylactic program to reduce endogenous flora is successful in that 60% of the aerobic, 74% of the anaerobic, and 49% of the fungal stool cultures are sterile and cultures from other sites are also sterile in the majority of instances.

Approximately 30 patients with a variety of neoplasms have now been treated in the isolator units at the National Cancer Institute. A control study has not yet been done, but are based on the severity of observed granulocytopenia (5), there appeared to be a 60% reduction in the incidence of infection. Bodey et al. (6), using essentially the same technic, have had a similar experience. It is difficult to compare the toxicity associated with the chemotherapy in these patients with that seen under ordinary circumstances, but it is our impression that the toxic manifestations are somewhat milder. In addition, it appeared that the patients tolerated more intensive chemotherapy than would have been possible ordinarily (6). Whether this will result in a greater incidence of remission, duration of remission, or length of survival remains to be determined. In general, patients treated in the isolator were individuals with a poor prognosis, but the results of therapy were encouraging both in terms of tumor regression and survival.

Although the initial reports of patients undergoing cancer chemotherapy in a protected environment appear promising, it is important to realize that no control studies have yet been done. The management of patients in this environment is a large and expensive undertaking, and thus far it has been difficult to carry out comparative studies. However, until these are done, the role of this kind of patient isolation in cancer chemotherapy remains unclear.

Laminar Air Flow Rooms, Permanent

Even though the preliminary studies utilizing the plastic isolator appear promising, there are a number of problems which render the technic difficult for patients, physicians, and other health science personnel to accept. These include psychologic effects on the patient and the unusual physical efforts required on the part of nurses and others in managing seriously ill patients. In an effort to circumvent these problems and make existence in a sterile environment more acceptable to all concerned, laminar air flow rooms are being developed and evaluated. The advances in the creation of dust-free rooms for the assembly of space capsules and instruments for use in space exploration (2) are now being utilized.

Vertical laminar air flow rooms have been used in research laboratories (13) and in operating rooms (12). Recently, the technics of horizontal laminar air flow for patients have been developed by Michaelson et al. (39) at the University of Minnesota School of Public Health under contract for the National Cancer Institute. Two laminar air flow rooms similar in design have been installed at the M. D. Anderson Hospital, Houston, and the initial results with patients appear promising. It is of interest that “clean air” rooms have been utilized for the treatment of patients with cancer in both England and France (3, 34, 37) for some time with very promising results.

Laminar Air Flow Rooms, Portable

Following the demonstration of the practicability of laminar air flow for creating a sterile room environment, the National Cancer Institute undertook the development of portable laminar flow units by contract with Litton Industries, Applied Science Division, Minneapolis. The underlying reason for this program was the realization that many institutions, even though recognizing the value of patient protection for a variety of clinical situations, would be reluctant to expend large sums of money for renovations entailed in the installation of permanent units. These would also result in the loss of valuable and expensive hospital floor space. The effort to design portable laminar flow isolators is proceeding very well, and it is anticipated that the first portable units will soon be available for testing at the National Cancer Institute. These units are designed for quick erection in an ordinary hospital room and are self contained. They can be quickly dismantled and easily stored. The projected cost will be quite reasonable and far below the present cost of the permanent type installations, thus making it possible for most large institutions to acquire one or more of the units for use and evaluation not.
only for cancer patients but for other individuals at high risk to infection.

In this paper, the protective and preventive measures in cancer chemotherapy have been reviewed. There has been no attempt to discuss all of the complications, such as the cystitis and alopecia, associated with the administration of cyclophosphamide, primarily because preventive measures may be unknown or cessation of therapy may be the only way to handle the problem. Nor has there been any attempt to discuss delayed effects, such as the adrenal insufficiency syndrome and pulmonary fibrosis described after prolonged therapy with busulfan. These are usually rather infrequent and generally not amenable to any measures short of stopping the drug.

REFERENCES


Reduction of Toxicity in Cancer Chemotherapy

Seymour Perry


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/29/12/2319

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.