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Collaborative Investigation in Infectious Diseases

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THE NUMBER of scientific publications has increased dramatically during the past few years. There is no doubt that it reflects, to some extent, increased activity in clinical and laboratory study of medical problems; nevertheless, it is likely that many investigators undertake studies which have only a limited importance because of the limited number of observations that are made.

Collaborative studies can be an answer to this problem and are particularly meaningful in microbiology and infectious diseases where the multicentric distribution of cases can compensate for local epidemiologic factors. These considerations were the basis for the development of collaborative groups for the study of infectious diseases in cancer patients under the auspices of the European Organization for Research on Treatment of Cancer (E.O.R.T.C.). The importance of the co-operative studies by these groups has been underlined recently by Waldvogel in the microbiology literature [1]. It seems useful to stress the activities of these groups for the oncologists as well.

In 1973, a symposium was held in Brussels on optimal antimicrobial therapy in patients with cancer. To that symposium investigators participated from Europe and from the United States as well. It appeared clearly that each of the studies which were presented involved only small numbers of patients and that, if meaningful results were to be obtained, the need for a co-operative study was obvious [2]. At the same time, the importance of infectious diseases in cancer patients was stressed. It was clear to many participants that effective supportive care during cancer chemotherapy, with a special emphasis on the prevention and management of infectious diseases, would be an essential step for further improvement in overall results of cancer therapy. Another meeting was organized at the Institut Jules Bordet one year later, and at that time, it resulted in the organization of a co-operative group within the framework of the E.O.R.T.C. The group was entitled as the E.O.R.T.C. International Antimicrobial Therapy Project. It was different from the other co-operative groups of the E.O.R.T.C. in the sense that investigators from both Europe and the United States were co-operating to the same protocol.

The first protocol prepared by the Group was a comparative study of three antibiotic regimens as empirical treatment of febrile granulocytopenic patients with cancer. The idea of treating febrile granulocytopenic patients without waiting for bacteriologic results was presented by Schimpff and his co-workers in 1971 [3]. Since, then, it has become clear that this approach represents a major improvement in the management of sepsis in neutropenic patients.

We choose to investigate the following combinations; carbenicillin plus cephalothin, carbenicillin plus gentamicin and cephalothin plus gentamicin. The choice of double antibiotic combinations was made on the assumption that none of the antibiotics, used alone, would have an adequate antimicrobial spectrum for the likely pathogens encountered as causes of severe infections in granulocytopenic patients. In addition, we were interested in investigating the possible role of synergistic action between antibiotics as it can be demonstrated *in vitro*. We also investigated the question whether a specific combination of antibiotics might be more adequate in treating specific infection defined from the microbiological point of view.

This co-operative study was terminated in

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1977 and published in 1978 in the *Journal of Infectious Diseases* [4]. It demonstrated that a co-operative group was able to achieve a major investigation. There were about 15 centers participating in that investigation, each contributing a variable number of cases. The total study examined the results of 625 trials of antibiotics in the treatment of suspected or confirmed infections in patients with leukemia or cancer who all were granulocytopenic (neutrophil count less than 1000/μl. The cases could be retrospectively subdivided into five groups: absence of possible infections (70 and 20% respectively); clinically documented infections (20%); and microbiologically documented infections with or without bacteremia (21 and 22% respectively). Four organisms: *Staphylococcus aureus*, *Klebsiella* species, *Escherichia coli* and *Pseudomonas aeruginosa* were responsible for the great majority of the infections. A first conclusion was that any empirical regimen for therapy of febrile neutropenic patients should have an adequate coverage for these four types of pathogenic organisms. The overall success rate for each of the three randomized treatment schedules, carbenicillin plus gentamicin, carbenicillin plus cephalothin and cephalothin plus gentamicin, was 70%, although the percentage was lower in patients with bacteremia. In patients with a neutrophil count of less than 500/μl, which did not increase during therapy, carbenicillin plus gentamicin appeared to give the best results. Clinical improvement was observed in 27 out of 44 (62%) patients. The two other regimens, cephalothin plus gentamicin and carbenicillin plus cephalothin seemed to be less effective under these conditions; the respective rates of favorable results were 44 and 39%.

A few additional remarks should be made at this point. A few patients presented septicemias caused by organisms resistant to both carbenicillin and cephalothin. All these patients died very soon after the initiation of therapy. Therefore, the combination of carbenicillin plus cephalothin would not be suitable as empirical therapy in hospitals where a large number of Gram-negative bacteria are resistant to both these antibiotics.

The study also demonstrated inability of antibiotics to provide protection against newly acquired infections in the continuously agranulocytopenic patients. In the patients who remained granulocytopenic, the rate of superinfection was in the range of 20%, whether therapy was prolonged or not. On the other hand, in patients whose granulocyte count increased during therapy, there was a definite relationship between the incidence of superinfection and the duration of therapy with antibiotics. These data suggest that prolongation of antibiotic therapy in patients whose granulocyte count returned to the normal is unnecessary and potentially harmful.

Finally, the co-operative study drew attention to the potential toxicity of the cephalothin–gentamicin combination, a finding that has stimulated considerable debate and experimentation since then. Cephalothin plus gentamicin was associated with an increased rate of nephrotoxicity, especially in patients who were older (over 60 yr) and in the patients who had an abnormal serum creatinine level at the time of therapy. Since then, cephalothin plus gentamicin has been found nephrotoxic in other controlled trials [5].

Since then, the E.O.R.T.C. International Antimicrobial Therapy Project Group has initiated two other major co-operative studies. The first is a co-operative trial of empirical antibiotic treatment and early granulocyte transfusion in febrile neutropenic patients. In that study, we were comparing a combination of amikacin and carbenicillin vs amikacin, carbenicillin and cefazolin. In addition, patients with a poor prognosis, as determined by criteria which are based on findings from the first co-operative trial [4], were randomized to receive or to not receive early, empirical therapy with granulocyte transfusions. So far, the number of patients is still too small for evaluation. There is no difference, so far, between these two antibiotic regimens as far as efficacy and nephrotoxicity are concerned. It means that a combination of a cephalosporin with an aminoglycoside is not necessarily nephrotoxic, provided excessive doses of the cephalosporin are avoided. However, the negative results, as far as efficacy is concerned, do not mean necessarily that the triple combination might not be more useful than carbenicillin plus amikacin in difficult situations such as *Klebsiella* infections.

The second clinical study, which is presently being undertaken by the Group, is relative to the possible effectiveness of cotrimoxazole in preventing bacterial infections in neutropenic patients. In that protocol, neutropenic patients are treated at random with cotrimoxazole or placebo, possibly in addition to other decontamining procedures, if used in the institutions participating to the protocol.

The study will eventually examine the results in four groups of neutropenic patients

who will receive placebo, cotrimoxazole, placebo plus a standard decontamination procedure, or cotrimoxazole plus a standard decontamination procedure. So far, the results obtained by our co-operative group do not show any difference in the incidence of infections between the patients who received the placebo and those treated with cotrimoxazole. About 150 patients have been reviewed so far; however, it is necessary to increase this number before drawing definite conclusions.

Finally, the group will soon start a large clinical investigation, in order to compare three double drug combinations, in which newer antibiotics such as cefotaxim and azlocillin will be used. In addition, it will investigate two other points of importance. The first question will relate to the duration of therapy in patients who respond to empirical antimicrobial therapy but remain neutropenic. There are some indications, in the literature, which suggest that prolonged therapy might be useful in these patients [6]; however, the risk of superinfection might also increase with prolonged therapy and therefore, data obtained in many patients are needed. The second question is whether patients who remained febrile and neutropenic, in spite of empirical antimicrobial therapy, and in whom no pathogenic bacteria could have been isolated might be improved by early empirical antifungal therapy with amphotericin B.

A second research to which another E.O.R.T.C. co-operative group (the E.O.R.T.C. Gnotobiotic Group) has contributed during recent years is the study of protective isolation and antimicrobial decontamination in neutropenic cancer patients. Cases with acute leukemia were randomly allocated to :(1) strict protective isolation (plastic isolation systems or laminar air flow rooms) complemented by a non-absorbable antibiotic regimen; (2) the same strict isolation without antibiotics only and (3) routine hospital ward care. It has been considered that treating patients with non-absorbable antibiotics, without strict isolation was not indicated here because of the risk of selecting resistant strains and disseminating them in the hospital environment. The results showed a significant reduction in the microbial colonization with the two first regimens. However, similar numbers of severe infections occurred in all three groups. However, when pulmonary infections only were considered, a statistically significant difference could be found between the patients treated with routine hospital care and those isolated with or without intestinal decontamination [7]. These results are an important part of the information which is now available in that field, after a decade of intensive investigation on the value of protective environment (PE) and non-absorbable prophylactic antibodies (PA) in neutropenic patients. Most of the studies which addressed themselves to that question indicate there is a reduced frequency of infection in patients who are treated with PE and PA. In all seven studies, this advantage of PEPA could be found. The PA were found to be as good as PEPA in reducing the infections in patients with acute nonlymphocytic leukemia in two studies and less effective than PEPA in three others. In two studies, PA were not found more effective than standard care and in three studies, PA were found be more effective than standard care. Thus, one cannot make any clear statement about the efficacy of PA as compared to PEPA or controls. On the other hand, that PE might as effective as PEPA is suggested by two investigations, including the one performed by the E.O.R.T.C. Group.

That strict isolation and non-absorbable antibiotics can reduce the frequency of infection in neutropenic patients should be accepted. Whether these these preventive measures really increase the rate of remission of the leukemia and whether the patients who undergo these prophylactic measures will survive longer, remains to be seen. However, data in the literature suggest that there might be an effect from the use of PEPA as far as the outcome of acute non lymphocytic leukemia is concerned [8]. Moreover, when an adequate therapy for the underlying malignancy is available, protective environment definitely improves the survival rate [9].

The results presented by the E.O.R.T.C. co-operative groups have shown conclusively that co-operative research in the field of infectious diseases is possible and that it can achieve significant results. Clearly, most of the answers to the questions which have been discussed here, could not have been obtained, in a reasonable period of time, by single investigators. This is not to say that any investigation should be conducted on a co-operative basis: it is clear that basic clinical research should be conducted on small number of patients in academic institutions which can provide the necessary intellectual and technological basis. On the other hand, some investigations can only be conducted with the participation of many centers. There is an-

other aspect in co-operative investigations which cannot be underestimated. Collaborative work allows close contacts between investigators from various origins and with different backgrounds. It necessarily goes with exchange of ideas and experiences.

In addition, collaborative studies impose attention to the quality of routine clinical care of patients. In that way, the participation in collaborative trials, which requires the observation of strict protocols, improves the quality of the day to day care of the patients.

Finally, it has been our experience that international co-operation can do much for improved understanding, mutual appreciation and friendship between investigators from various countries and even, if that would be the only result, it might already be a major successful achievement.

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