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Infections in Acute Leukemia: A Retrospective Study of 148 Patients

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To study the nature, offending organisms, consequence, and prognostic factors of infection in acute leukemia, we reviewed the cases of 148 patients admitted to the internal medicine service at Seoul National University Hospital between December 1980 and June 1984.

The findings are summarized as follows : (1) The total number of infections was 143, 54% of which occurred after anti-cancer chemotherapy (induction ; 28%, maintenance ; 14%, reinduction : 10%, consolidation ; 2%). Fifty-one percent responded to therapy, and 24% expired due to infection (13%) or other causes (11%). (2) Sixty-four percent of the infections occurred during a granulocytopenic episode ($<500/mm^3$), whereas 36% occurred in the absence of granulocytopenia. When induction, reinduction or consolidation chemotherapy was instituted, infection occurred in 85% of the cases in which granulocytopenia had developed ($n=59$) and in 50% of the cases in which granulocytopenia had not developed ($n=14$). (3) Microbiologically documented infection, clinically documented infection and, possible infection accounted for 19%, 47%, and 34% of the total infection episodes, respectively, and in microbiologically or clinically documented infection ($n=95$), mortality due to infection was 19%, compared to 2% in possible infection ($n=48$), which was significantly lower ($P<.005$). Gram negative and positive bacteria accounted for 71.4% and 25.0% of the microbiologically documented infection, respectively, and Pseudomonas species, E. coli, and Staphylococcus aureus were the most common pathogens. Pharyngitis was the most common type of infection to be followed by skin and soft tissue infection, pneumonia and primary septicemia, etc. (4) Eighty-eight and two tenths percent of the patients with bone marrow recovery responded to therapy, a percentage significantly higher than 46.5% for those whose bone marrow function was not restored ($P<.005$).

Key Words : *Infections, leukemia*

INTRODUCTION

Although the prognosis of acute leukemia has improved with the advent of new regimens of anti-cancer chemotherapy, the importance of supportive care against the complications of modern chemotherapy, e.g., bone marrow depression, has become increasingly emphasized. To be specific, the prevention, early detection, and treatment of various infectious complications subsequent to granulocytopenia are the mainstays in determining the outcome of treatment,[1-3] and, therefore, studies regarding the administration of new combinations of chemotherapeutic agents,[4-7] and antifungal agents,[8-9] and selective transfusion of granulocyte,[10-13] etc., are being carried out by many investigators.

Infection, occurring in granulocytopenia is known to be characterized by the absence of normal local inflammatory reactions and systemic

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signs of infection; rapid systemic dissemination, yielding grave results; [1-3] and high fever as a sole clue to the infection in some cases, which is quite different from ordinary infections.[1-2] In view of this, studies related to the clinical aspects of infection occurring in granulocytopenia are considered to be needed since it is believed that their findings wil supply guidelines for the management of acute leukemia, especially when anti-cancer chemotherapy is being given. Domestically, reports of such studies have been scarce.

The present study was carried out to compile data on the subject, encluding data on the general characteristics of infections occurring in acute leukemia, their course and response to therapy.

MATERIALS AND METHODS

The subjects were 148 patients admitted to Seoul National University Hospital between December 1980 and June 1984 because of acute leukemia or a blast crisis of chronic myelogenous leukemia. They were comprised of 93 cases of acute myelogenous leukemia, 37 cases of acute lymphocytic leukemia, 7 cases of acute unclassified leukemia and 11 cases of blast crisis. The male to female ratio was 1.8:1, and the range of ages was 14-72.

An infection was defined as either a single elevation of oral temperature above 38.5°C, or elevations of oral temperature over 38.0° on two occasions within 24 hrs when the temperature was taken at intervals of 4 hrs or more, in the apparent absence of any exogenous causes of fever such as a transfusion.[8] The cases with objective evidences of infections, such as an abscess, were also included even if the temperature criteria had not been fulfilled.

Infection was classified as (1) microbiologically documented infection if infection could be proven microbiologically from reliable specimens (excluding throat swab, open pus, sputum, etc.) with reliable methods, and the results were reliable (excluding single culture of staphylococcus epidermidis and urine culture of colony counts below 10^5/ml, etc.); (2) clinically doclumented infection if there were objective signs of infection with an identifiable site of infection in spite of lack of microbiological proof of presence of an etiologic agent; (3) possible infection if an infection did not belong to either (1) or (2).[14] Response to therapy was defined as stabilization of oral temperature at 37.0°C or below accompanied by the disappearance of the local inflammatory lesion. Granulocytopenia and bone marrow recovery were defined as peripheral neutrophil count of below 500/mm^3, and a rise in neutrophil count to over 500/mm^3, from granulocytopenia.

As microbiological studies, boood cultures were done three or more times at an interval of 30 min, in addition to cultures of specimens from suspected lesions, followed by the administration of appropriate antibiotics. If no response to antibiotic therapy was observed in 72 hrs, granulocyte transfusion or administration of antifungal agents was done with repeat cultures, if necessary. A complete blood count with differential was also done at the beginning of the infection and repeated at intervals of 1-3 days up to the time of recovery from infection.

The t-test, x^2-test and ANOVA were used for statistical analyses; a p-value below .05 was considered arbitrarily as statistically significant.

RESULT

1. The Incidence of Infection in Acute Leukemia and its Relation to Anti-cancer Chemotherapy

Of the 148 patients hospitalized for over 72 hrs due to acute leukemia or blast crisis of chronic myelogenous leukemia, infection developed at least once in 110 patients. The total number of infections was 143, and 77 (54%) of them were considered to be related to anti-cancer chemotherapy, whereas the remaining 66 (46%) were not.

Of the 77 infection episodes related to anti-cancer chemotherapy, 40 (28%) developed after induction chemotherapy and 20 (14%) after maintenance chemotherapy; 14 (10%) after reinduction chemotherapy, and 3 cases (2%) after consolidation chemotherapy (Table 1).

As to outcomes, 73 patients (51%) recovered from the infection, 19 patients (13%) and 16 cases (11%) died of infection and of the other causes, respectively, and the results of the remainder were unknown.

2. The Relation between Peripheral Neutrophil Count and Infection

Of the 143 infection episodes, 92 (64%) had granulocytopenia when the infection occurred, with a peripheral neutrophil count of below 500/

mm^3, whereas, in the remaining 51 patients (36%), infection occurred in the absence of granulocytopenia. Of one hundred ten patients with infection, excluding cases of relapse, blast crisis and 3 or more granulocyte transfusions, 52 and 53% recovered from infection in the presence and absence of granulocytopenia, respectively. Of each group, 9 and 12% died of infection, 10 and 7% died of other causes, and 29 and 28% left the hospital against advice, yielding no difference between two groups. ($P > .1$) Meanwhile, granulocytopenia ($>500/mm^3$) developed in 59 (81%) of the 73 cases, with institution of induction, reinduction, or consolidation chemotherapy, and did not develop in the remaining 14 cases (19%). Infection developed in 50 cases (85%) of the former, an incidence of infection a significantly higher than that in the latter : 1 cases (50%) ($P < .05$).

3. The Time Relationship between the Denvelopment of Granulocytopenia and the Infection

Of the 47 cases of infection which developed in association with granulocytopenia following induction, reinduction, or consolidation chemotherapy, 20 cases (43%) developed either simultaneously or before the onset of the granulocytopenia, and the remainding 27 cases (57%) developed after the onset of the granulocytopenia. The range of time gaps between the onset of the infection and the granulolcytopenia was 6 to 16 days, with a median of 1.5 days. The sum of the number of days of granulocytopenia which developed in 52 patients after induction, reinduction or consolidation chemotherapy was 684 days (mean for each patient : 13 days).

The ratio of total febrile days/total granulocytopenic days was 0.62, and the mean duration of the febrile episode was 9 days.

4. Classification of Infection

Microbiologically documented infection accounted for 28 (19%) of the total 143 infection episodes, whereas clinically documented infection and possible infection accounted for 67 (47%) and 48 (34%) of the episodes, respectively.

Of the 28 infections documented microbiologically, gram negative and gram positive bacteria accounted for 20 (71.4%) and 7 (25.0%), respectively. Pseudomonas species were the most common pathogens (25.0% : Pseudomonas aerugenosa 21.4% and Pseudomonas fluorescence 3.6%), followed by E. coli (21.4%), Staphylococcus aureus (21.4%), Klebsiella pneumoniae (10.7%) and Alcaligenes species (7.1%), etc. (Table 2).

Offending microbes were cultured from blood (21 cases), urine (4 cases), pus (4 cases), and sputum (1 case : acid fast bacilli) amounting to a total of 30 cases of microbiological confirmations with 2 simultaneous cultures from (1) blood and urine and (2) blood and pus.

With regard to type of infection, primary septicemia accounted for 11.6% of the total 95 cases of documented infection, microbiologically as well as clinically, whereas pharyngitis, skin, and soft tissue infection, pneumonia, and rectal abscess accounted for 37%, 16%, 12%, and 9%, respectively (Table 3).

Comparing the outcome of infection confirmed either microbiologically or clinically ($n=95$) with that of possible infections ($n=48$), the ratio of controlled infection was 52% in the case of the former and 50% in the case of the latter, with no

Table 1. Classification of Infection in Acute Leukemia in Relation to Chemotherapy

Chemotherapy related	77
Induction	40
Maintenance	20
Reinduction	14
Consolidation	3
Non-Chemotherapy related	66
Total	143

Table 2. Microbiologically Documented Pathogens in Acute Leukemia

Pathogen	N	%
Gram (+)		
Staphylococcus aureus	6	21.4
Non-hemolytic Streptococcus	1	3.6
Gram (−)		
Pseudomonas aerugenosa	6	21.4
Pseudomonas fluorescence	1	3.6
Escherichia coli	6	21.4
Klebsiella pneumoniae	3	10.7
Alcaligenes species	2	7.1
Enterobacter agglomerans	1	3.6
Salmonella enteritidis	1	3.6
Mycobacterium tuberculosis	1	3.6
Total	28	100.0

significant difference between them (P>.1). There was no significant difference in the ratio of total deaths between the two groups, either (P>.1). But the ratio of deaths due to infection itself was significantly higher in documented infections (19% vs. 2%), whereas the ratio of deaths due to other causes was significantly higher in possible infection (21% vs. 6%) (P<.005,P<.005) (Table 4).

5. The Relationship between Bone Marrow Recovery and Control of Infection

Of the 60 cases of infection in granulocytopenia, excluding relapse, blast crisis, and those with 3 or more granulocyte transfusions, bone marrow function was restored in 17.

Infection was controlled until discharge in 88.2% of those in which bone marrow function was restored a significantly higher percentage than the 46.5% of those in which that function was not restored (P<.005) (Table 5).

Table 3. Types of Infection in Acute Leukemia

Type of infection	N	%
Primary septicemia	11	11.6
Pharyngitis	37	38.9
Skin & soft tissue infection	16	16.8
Pneumonia	12	12.6
Anal & rectal abscess	9	9.5
Urinary tract infection	4	4.2
Thrombophlebitis	1	1.1
Peritonitis	1	1.1
Pulmonary tuberculosis	1	1.1
Others	3	3.1
Total	95	100.0

Table 4. Outcome of Infection in Acute Leukemia

	Documented infection(%)	Probable infection(%)
Infection, controlled	49 (52)	24 (50)
Death, due to infection	18 (19)	1 (2)
Death, due to other causes	6 (6)	10 (21)
Outcome, unknown	22 (23)	13 (27)
Total	95 (100)	48 (100)

Table 5. Prognosis and Bone Marrow Recovery (χ^2=8.72, p.005)

	Controlled (%)	Not controlled (%)	Total
Marrow recovery (+)	15 (88.2)	2 (11.8)	17
Marrow recovery (−)	20 (46.5)	23 (53.5)	43
Total	35	25	60

6. Prognosis of Infection with Relation to Antibiotic Regimens

Carbenicillin and aminoglycoside were administered in 19 cases; Cephalothin, Carbenicilin, and Aminoglycoside in 14 cases; and Cephalothin + Aminoglycoside or their congeners were given in 31 cases for the initial 3 or more days, excluding the cases with relapse of leukemia, blast crisis, and those with 3 or more granulocyte transfusion. The ratios of controlled infection, uncontrolled infectioin (including change to another regimen), and unknown outcome were 31.6%, 31.6% and 36.8% in the cases managed with Carbenicillin and Aminoglycoside; 50.0%, 35.8% and 14.2% in those managed with Cephalothin, Carbenicillin, and Aminoglycoside; and 39.4%, 30.3% and 30.3 % in those managed with Cephalothin and Aminoglycoside. It seemed that the ratio of controlled infection was higher in those managed with the "Big Thre", although the difference was not significant statistically. (P>.1).

DISCUSSION

Although susceptibility to infection is known to increase when the peripheral neutrophil count is below 1,000/mm^3, clinically the case with a count below 500/mm^3 is at high risk. According to the report of the EORTC International Antimicrobial Therapy Project Group, the incidences of bacteremia were 19% and 13% in cases with a count below 100/mm^3 and 100-499/mm^3, respectively, compared to 8% in cases of 500-999/mm^3 [14]. The authors regarded a peripheral neutrophil count of below 500/mm^3 as granulocytopenia, using the criterion of Pizze et al.[8] However, our observation that infection occurred in 50% of the cases in which there was no granulocytopenia, despite induction, reinduction, and consolidation chemotherapy, suggests that susceptibility to infection increases substantially before the peripheral neutrophilcount reaches 500/mm^3. The incidence of infections's developing during granulocytopenia due to

induction chemotherapy, etc., in the present investigation (85%) is thought by Gurwith et al.[15] to be lower than 95% becauses they included infections under maintenance chemotherapy. Granulocytopenia due to maintenance chemotherapy is more likely to be overlooked if not complicated by infection, thus leading to an overestimation of the true incidence of infection. Our ratio of total febrile days/total granulocytopenic days, 0.62, was higher than the figure by Gurwith et al.[15] probably because they regarded the count below 1,000/mm^3 as granulocytopenia. Infections and possible infections, and the ratio of the former is reported to be around 60%, including around 20% of bacteremia.[14,16] Documented infection can also be subclassified into microbiologically documented one and clinically documented ones. Regarding the offending pathogens in microbiologically documented infections, it is generally held that gram negative bacteria account for the majority of cases, and staphylococcus has been playing an increasingly important role more recently.[14,16] The observations of this study, that Pseudomonas species, E. coil, and Staphylococcus aureus were the most common pathogens, and pharyngitis was the most common type of infection are similar to those of other investigators, although subsequent lists have differed slightly.[14,16] The observed difference between the mortality in documented infection and possible infection sugests that possible infection defined only by means of body temperature criteria may not always be true infection althought infection in granulocytopenia tends to manifest itself only in fever. This suggestion is also supported by the observations by Gurwith et al.[5,15] that possible infection had a better prognosis than documented infecions in which there had been persistent fever defeveresced despite the discontinuation of antibiotics. However, total mortality did not differ significantly because mortality due to other causes was higher in possible infection, which suggests that febrile episodes in possible infection may be related to causes other than infection, e.g., leukostasis.

Although various factors can influence prognosis of infection in leukemia, e.g., confirmation of infection and mentioned above, age, the presence or absence of initial shock, height of peak of fever episode, sensitivity of microbes to antibiotics, initial peripheral netrophil and platelet count,[1,14,18] the most conspicuous sign is bone marrow recovery. According to the EORTC International Antimicrobial Therapy Project Group,[14] infection was controlled in 88% of the cases with a rise in peripheral neutrophil count to over 100/mm^3, whereas it was controlled in only 22% of the cases in which there was no restoration of the count to over 100/mm^3. The authors also found significant difference in prognoses between the members of the group with recovered bone marrow function and those without recovery. No significant difference in prognosis was observed, however between the prognosis of patients with infections caused by microbes sensitive to 2 or more antibiotics used and those with infections caused by microbes sensitive to 1 or less antibiotics used, as well as no difference in prognosis with relation to the regimens of antibiotics in the present retrosepective study, in comparison with the report by the EORTC International Antimicrobial Therapy Project Group.

One of the gravest complications indigenous to the immunocompromised state is infection by fungus.[8,19,20,21] The incidences of infection or superinfection by fungus differ, according to reports, from below 5%[15] to over 50%.[16] We observed 15 cases of fungal infection includding 8 cases of superinfections in the total 143 infection episodes, but all of them were mucocutaneous candidiases which were not considered as causes of fever at all. The difference in outcome in regard to fungal infection is partly due to the technical difficulties involved in attempting to make a microbiological diagnosis of fungal infection, in addition to the problem intrinsic in designing a study, such as difference in materials and criteria for selection, etc. using the traditional methods of culture, it has been reported that candida can be isolated from blood in only 50% of the cases of candida bacteremia confirmed by autopsy or biopsy, and even in a lower percentage in case of Aspergillus.[20] Further research and an added number of technical improvements are needed for making more accurate diagnosis of fungal infection, althought it is claimed that recent application of radioimmunoassay; ELISA; and methods for the detection of fungal products, such as mannan; or specialized methods for the culturing of various fungi can heighten diagnostic accuracy.[19]

In summary, although infection developing in granulocytopenia, including acute leukemia,

differs from ordinary infection in many aspects, and is still one of the main causes of mortality, advances in the management of strict isolation, chemoprophylaxis against bacterial or fungal infection, improved diagnostic methods, the selective transfusion of granulocytes the provision of a ready supply of sterile food, and the judicious use of antibiotics will pave the way to the eventual solution of the problem in the future.[20,21]

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