CHAPTER 5

DISCUSSION

This was a randomized placebo controlled study investigating the effectiveness of garlic in reducing the incidence of infection among chemotherapy induced neutropenic AML patients.

Garlic has been used as a folk medicine for thousands of years. Its therapeutic efficacy has been studied extensively in recent decades. The antihyperlipidemic effect of garlic has already been proven clinically. Animal experiments are being undertaken to investigate the efficacy of garlic to inhibit the growth of certain tumor cells. However the dosage used in animal tests are rather high and impractical in human. Therefore there has been no clinical trial on cancer prophylaxis of garlic.

As mentioned in the literature review, garlic has been proven to have bactericidal effect both by in vitro experiment and animal tests. However, there has been no standard dosage or preparation of garlic that should be used clinically. Previous studies have used aged garlic water extract, garlic powder, oil extract and so on. It was reported that garlic juice had a bacterial inhibitory effect about 100 times stronger than other extracts of garlic[28]. Su GL et al[29] also proved the strongest in vitro fungal inhibitory effect of garlic juice, compared to garlic oil, alcohol extract etc. In the present study, aqueous garlic extract (AGE) was used, the preparation of AGE was similar to that of garlic juice described by Su Guilan et al. Preparation of garlic

juice or AGE is relatively easy and can be performed by the patients or their family members. This will reduce the cost.

Reports in China have used 30-40 grams of raw garlic daily for adult, 6-9 grams for children with pulmonary fungal infection[20, 21]. In the present study, a maximal tolerable dose of 30 grams of raw garlic was decided by a pilot study. This was similar to the reported dosage.

Only AML patients who were not infected, undergoing remission induction, reinduction and post-remission consolidation chemotherapy were included in this study. This have somewhat reduced the generalizability of the results. However, it was probably responsible for allowing us to see a treatment effect.

5.1   Unprocessed Procedure

Surveillance culture for the bacteria colonizing the GI tract, oropharynx and skin had been originally proposed to guide the administration of empirical antibiotics to patients with infection. Later however, this was found not available at the central laboratory of my hospital because of the lack of personnel and its excessive cost. If surveillance culture had been performed in the present study, it would have helped explain more clearly whether garlic could serve the purpose of GI decontamination.

Although surveillance culture was widely used in studies investigating the effectiveness of antibiotics in providing GI decontamination, it was found by de Jong PJ et al[30] that surveillance cultures were of limited use in predicting infection or identifying causative organisms of fever in neutropenic patients receiving selective intestinal decontamination. However surveillance cultures were useful in monitoring the effect of microbial suppression. Therefore the inability of performing bacterial

surveillance cultures in the present study did not influence the outcome of those infected patients in whom the infection could not be documented either biologically or clinically, namely the selection and modification of empirical antibiotics.

5.2   The Therapeutic Outcomes

The total incidence of infection in the present study was 63.2%. Different hospitals in China reported incidences of infection between 56-90%[31, 32, 33]. Infection is associated with the duration of neutropenia. The incidences of infection were 57.89% and 68.42% in garlic and placebo recipients respectively. There was no significant difference between the two groups. However, the power of this study was very low. Considering the original estimated incidences of infection of 80% in AML patients without antibiotic prophylaxis and a reduction in this proportion to 50% in patients receiving garlic prophylaxis, a total of 64 patients, with 32 in each group were needed to prove the difference. With the sample size of 19 each group in the present study, the power was rather low, 46%. If we consider the incidences of the infection in the present study represent the true incidences in the population, the power of the present study was extremely low. Two-hundred seventy seven patients for each group are needed to find a significant difference between the proportions of 57.89% and 68.42%.

Only 1 patient died in this study and the cause of death was pulmonary aspergillosis. The diagnosis was based on clinical, radiological and microbiological findings. Because of the small number of patients included in this study and most patients recruited were in postremission consolidation which usually had a less severe

infection, no conclusion could be drawn from the infection related death in the present study.

The total days of fever in this study were 4.05±1.07 days and 6.47±1.33 days in garlic and placebo recipients respectively, similar to those reported by Ward TT et al[34]. The total days of antibiotics given to patients were 7.26±1.27 and 10.42±1.92 days for garlic and placebo recipients respectively, much less than the 18.9 days reported by Ward TT et al. This is probably due to the difference in included patients and intensity of chemotherapy between the present study and that of Ward TT et al. In the present study, most recruited patients were AML in complete remission, unlike in other studies, in which most patients were with active leukemia. Patients in complete remission had a higher potential for bone marrow recovery after chemotherapy than patients not in complete remission. The relatively short neutropenic period in the present study may count for the short duration of antibiotics given to patients.

Among the infected patients, 6 out of 12 in garlic recipients had their infection effectively controlled by simply using piparacillin plus amikacin (Table 4.5), compared to 3/13 in placebo recipients. Third generation cephalosporin or imipenem were required in 8 patients in the placebo group, while 4 garlic recipients required them. The cost of piparacillin in China is about 0.25 US dollar per gram, in comparison to that of cefatazidime, about 25 US dollars per gram. Although there was no statistically significant difference between the two groups in the types of antibiotics used, an economic study is needed to investigate the reduction in the cost of antibiotics brought by garlic.

Was the selection of antibiotics in this study biased by the inability to blind the doctors and patients from identifying which patient was receiving garlic? This did not seem possible. In this study, the fact of using placebo control was kept confidential to all the staff and patients. Therefore neither the doctors nor the patients knew which drug was the study or control drug, although they might have identified that one of them contained garlic. Physicians were not biased when selecting antibiotics for the patients by not knowing whether patients were taking active drug for prophylaxis. Before the start of this study, detailed guidelines for empirical antibiotics were provided to the physicians. All the staff participating in the study used these guidelines for antibiotic selection or modification.

The incidence of septicemia was 1/19 (5.26%, 95% CI: 0.13%, 26.23%) and 4/19 (21.05%, 95% CI: 6.05%, 45.56%) in garlic and placebo recipients respectively (Table 4.6). There was no significant difference between the two groups (p=0.34, Fisher's exact test). The incidences of documented infection were 5/19 (26.32%, 95% CI: 9.15%, 51.20%) and 10/19 (52.63%, 95% CI: 28.86%, 75.55%) in garlic and placebo recipients respectively. Like most of the previous studies of antibiotic prophylaxis, the effect of garlic in reducing the documented infections was offset by the increasing numbers of unexplained fever or possible infection (6/19 and 3/19 in garlic and placebo recipients respectively).

The clinical implication of unexplained fever is not yet clear. Jones GR et al suggested that discontinuation of antibiotics was safe in febrile episodes without documented infections before neutropenia resolved in patients with high potential for bone marrow recovery[35]. De Marie S et al[36] also reported that empirical parenteral

antibacterial therapy could be safely withheld or discontinued early in neutropenic patients who were receiving quinolone prophylaxis and had unexplained fevers. These findings suggest that some unexplained fever might not be associated with infection, or it could have resulted from increased absorption of such pyrogenic substances as endotoxin through gut epithelia surfaces damaged by cytotoxic therapy[37]. In the present study, it was found that patients with undocumented infection had a shorter duration of fever and antibiotic requirement. Further work is needed to investigate the outcomes of patients with unexplained fever and to differentiate infectious unexplained fevers from those of noninfectious origin.

Fungal colonization of the rectum was significantly reduced in garlic recipients. Unlike the studies of TMP/SMZ or quinolones, all of which found increased fungal colonization in the study groups[34, 38], ingestion of garlic significantly reduced the fungal colonization. This is probably attributable to the antifungal activity of garlic. Clinical application of garlic in treating pulmonary fungal diseases, cryptococcal meningitis, topical application for treatment of skin fungal infection already proved this effect of garlic[21, 22, 23, 26].

Although fungal colonization was suggested to be a predictor of invasive fungal disease[39] and associated with fungal infection[40], only 2 patients in the present study were proven to have fungal infection, 1 in garlic and 1 in placebo recipients. This was probably due to lack of appropriate instrument for diagnosing fungal infection. The diagnosis of fungal infection was very difficult. In a postmortem study of patients with hematological malignancy, only 2 of the 29 patients with systemic fungal infection had been diagnosed before the patients died[41]. Another report of

autopsied cases of hematologic malignancy also showed a relatively increased incidence of fungal infection as the cause of death in recent years[42].

Although more patients in control group seemed to require the addition of antifungal medication, there was no significant difference between garlic and placebo recipients in the proportions of patients to whom fluconazole was added.

All patients treated by antifungal medication were among those with fungal colonizations. Doctors seemed to be influenced by the results of fungal colonization to decide the addition of antifungal medication. However this was not the case for most patients in the present study. In my hospital, the results of fungal culture went back to the ward one week after the sample had been submitted to the laboratories. Therefore most decisions of addition of antifungal medication was made on the basis of the clinical situation of the patients and the antibiotic guidelines.

5.3 The Side Effect of Garlic

Generally speaking, garlic had no major side effects except the unappealing order. Gastric irritation had been reported from patients taking garlic. In the present study of taking 30 grams of raw garlic per day, no vomiting was reported from the patient. Nausea was complained by similar proportions of patients in each group. Therefore the nausea in this study may not be associated with garlic. For patients suffering from acute leukemia, there may be many reasons for nausea, e.g. chemotherapy, antibiotics, depression etc.

Twelve of garlic recipients experienced heart burn and 2 dropped out because of this. Garlic, onion and some other plants can cause an uncomfortable heart burn, the mechanism of which is not clear. It was reported that heart burn induced by garlic

could be alleviated by taking oil or vitamin B1 at the same time of taking garlic. In the present study, taking AGE along with meals also helped to alleviate this side effect. As a result, AGE equivalent to 30 grams of raw garlic was well tolerated by most patients. Nausea was only mild. Interestingly, 6 patients in the control group also complained of mild heart burn. No possible explanations could be made for these patients except a psychological effect.

There was no bleeding associated death in the present study. Garlic and placebo recipients received similar amount of platelet and packed red blood cell transfusions. Therefore garlic ingestion was not associated with an increased bleeding tendency.

No definite method is available for measuring the bleeding tendency. Studies comparing different cancer chemotherapy regimens used whether transfusion of platelets was need, how much platelet transfusions were needed or deaths caused by hemorrhage to describe the severity of bleeding. Therefore in the present study, the tendency of garlic to cause excess bleeding was measured by the platelet and red blood cell transfusions needed by the patients.

Although garlic has been reported to have antiplatelet and fibrinolytic activities[43, 44, 45], there has been no definite clinical report of garlic induced bleeding, except a case report suspecting the postoperative bleeding of a patient attributable to the garlic preparation the patient had been taking for years[46]. The present study did not find any bleeding associated with garlic. No excess bleeding was reported in a study in China of the bone marrow transplantation recipients receiving intravenous garlic infusion for protection against CMV infection[25].

5.4   Assessing Instrument

The criteria for diagnosis of infection was the major instrument used in the present study. There is no unified standard for diagnosing infection. Hughes WT et al[5] suggested all fever patients with neutrophil counts of $< 0.5 \times 10^9/L$ and those with counts of $0.5-1.0 \times 10^9/L$ in whom a decrease could be expected should be assumed to have a potentially life-threatening bacterial infection and treated with broad-spectrum antibiotics promptly by the intravenous route and in maximal therapeutic dosages. Other studies took fever episodes as infection and divided the fever episodes to bacteriologically, clinically documented infections and fever of unknown origins (excluding fever associated with noninfectious causes such as blood transfusion, administration of antileukemic therapy, or the administration of other drugs)[34, 38, 47]. However, some of the unexplained fevers might not be associated with infection[36, 37]. In the present study, infection was defined as fever episode plus bacteriologically or clinically documented infection, or unexplained fever with a neutrophil count of $< 0.5 \times 10^9/L$. Therefore patients with unexplained fever were classified as infected if their neutrophil count was $< 0.5 \times 10^9/L$. They were observed closely if the neutrophil count was $\geq 0.5 \times 10^9/L$. Among patients with fever, 21 patients met with the criteria of infection at the onset of fever, 4 met with the criteria on the 2nd or 3rd day of fever, 4 did not meet with the criteria. Of these last 4 patients, 3 were garlic recipients, 1 was placebo recipient. Defervescence occurred within two days. All patients in the present study responded well to antibiotics except the one who died of pulmonary aspergillosis. No death or serious complications were associated with the delay in the

initiation of empirical antibiotics in the 4 patients not meeting with the criteria of infection at the onset of fever.

Two recent publications in China about the infection of hospitalized leukemic patients reported much lower incidences of infection, 28-33.14% in AML patients[48, 49]. One reason for the low incidences of infection may be the less intensive chemotherapy regimen applied in many hospitals in China. Another reason is they only considered those patients with documented infection as infected. Therefore, establishing a unified standard for the diagnosis of infection is very important to protect patients against fatal infections, to reduce the cost of antibiotics given unnecessarily to patients without infection. The criteria for diagnosing infection in the present study seemed appropriate in our setting. Since the number of study subjects were rather small in this study and most of the included patients were in complete remission, these criteria should be applied with caution.

5.5 Clinical Implication

Infection is a serious problem among patients suffering from malignant diseases. The frequency of febrile neutropenic episodes among patients with acute leukemia undergoing chemotherapy has led investigators to test the potential of oral antimicrobial agents as an adjunct to other infection prevention techniques. TMP/SMZ was initially reported to decrease the occurrence of bacterial infection[17]. Although clinical trials have shown a decrease of gram-negative bacterial infection, the occurrence of episodes of fever, the need for therapeutic antibiotics and the survival of patients have not been changed. In addition, TMP/SMZ had been reported to increase fungal colonization, prolong marrow suppression, accompanied with an

increasing incidence of antimicrobial resistance. Therefore TMP/SMZ chemoprophylaxis is not recommended by some authors[18, 34, 50]. Another selection of antimicrobial chemoprophylaxis is quinolone. The cumulative experience with quinolone chemoprophylaxis has been sufficiently encouraging for it to become perhaps a standard of care for patients with leukemia and recipients of bone marrow transplantation. In 1996, a meta-analysis including 19 randomized clinical trials, 2112 patients proved that prophylaxis with fluroquinolones significantly reduced the frequency of gram-negative bacteremia, without affecting the frequency of gram-positive bacteremia and infection related mortality, addition of gram-positive prophylaxis to fluroquinolone prophylaxis significantly reduced the frequency of gram-positive bacteremia without affecting the incidence of fever related morbidity[51]. But quinolone prophylaxis is also associated with increased fungal colonization. In China, quinolones are widely used both in the community and in hospitals for treatment of all kinds of infections or possible infections, because quinolones have a wide antibacterial spectrum and the cost is relatively low. Therefore the occurrence and spread of quinolone resistant bacteria is highly possible.

The results of the present study showed that garlic could not lower the incidence of overall febrile episodes. This is similar to the results of studies of antimicrobial chemoprophylaxis. However, the incidence of septicemia was lower in garlic recipients, although the difference between the two treatment groups was not statistically significant. The major benefit of garlic over the previous studied antibiotis was that it significantly decreased the fungal colonization of AML patients. This distinct characteristic of garlic will probably recognize itself as the most

appropriate agent for infection prophylaxis in the future. Based on the results of the present study, we recommend garlic for infection prophylaxis in chemotherapy induced neutropenic patients.

To the author's knowledge, there have been no trials of using garlic for infection prophylaxis in patients undergoing chemotherapy. Although an overall protection against all febrile episodes was not demonstrated in this study, garlic worth more studies on its efficacy in infection prophylaxis. It should be noted that garlic is only a natural plant. Therefore its therapeutic effect can not be very strong. The antilipidemic effect of garlic had not been proven until a meta-analysis was performed by Silagy et al[52] who finally concluded that garlic had antilipidemic activity. More studies are needed before a final conclusion can be made on whether garlic is suitable for the purpose of infection prophylaxis. Since garlic is inexpensive, non-toxic, easily accessible, it can now be recommended for clinical use, based on the finding in the present study that garlic decreased fungal colonization. Physicians interested in using garlic for infection prophylaxis should notice that until now no drug has been proven effective in preventing the overall incidence of infectious febrile episodes. Therefore the initiation of empirical antibiotics should not be delayed in patients taking garlic. Since infection in neutropenic patients is often fatal, efforts should be made to identify the source and the pathogen of infection and to make appropriate modifications of antibiotics according to the bacteriological studies.

5.6   Other possible approaches

Although this study seemed to show a favorable outcome toward garlic, we can not rule out the possibility that this was a random error. Therefore, it is quite
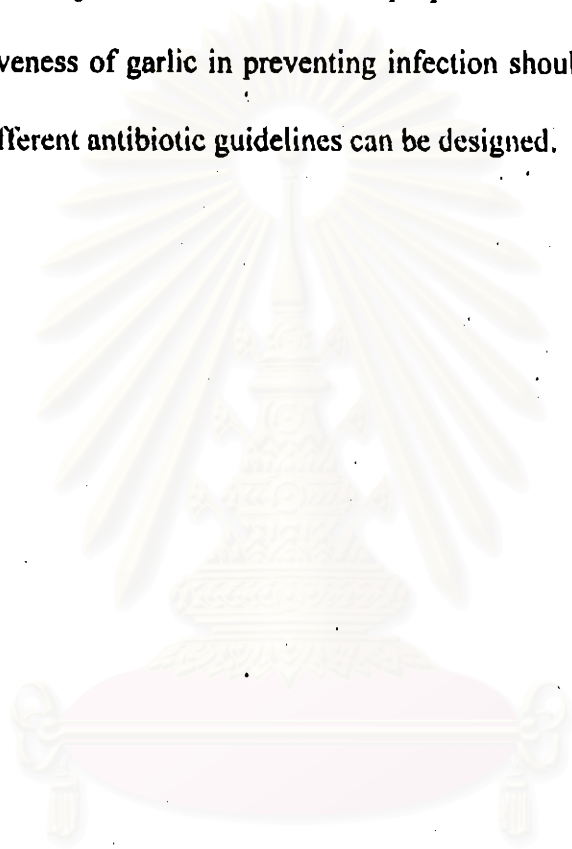
possible that garlic can not decrease the incidence of infection. One possibility is that garlic is like all the previously tested oral antibiotics, which did not decrease the overall incidence of infection. Another possibility is garlic could not eliminate the microorganisms that colonize the GI tract. The present study can not make this point clear since fecal bacterial surveillance culture was not performed. However, this is not quite likely since we found in the present study that garlic decreased the number of fungi from the rectal swab cultures. Therefore, studies with larger sample sizes are needed to prove whether garlic is better than placebo in reducing the incidence of infection.

Except from observing the proportion of infection in garlic and placebo recipients, there are some other possible ways to carry out the study. One method is to measure the time period before the onset of infection. Then by using survival analysis, it can be analyzed whether garlic can delay the occurrence of infection.

Another possible approach is to use garlic for a prolonged period, from the start of the first course of chemotherapy till the end of the last course of chemotherapy. Then the total episodes of fever can be compared between the study and control groups. The major problem with this kind of study design is the compliance of patients. It is difficult to ask patients to take garlic juice continuously for 6 to 8 months. Some patients may be lost to follow up if the study period is too long.

A third possible way is to change the antibiotic guidelines. Based on the results of the present study, garlic recipients seemed to require less expensive antibiotics. Therefore different antibiotics can probably be used for garlic and placebo

recipients who are febrile. An economic study can be performed to see whether garlic will reduce the cost of antibiotics. However, a study like should be carefully designed. Since infection is often fatal in neutropenic patients, serious complications may occur if infected patients did not receive proper antibiotics. More information about the effectiveness of garlic in preventing infection should be available before a study of using different antibiotic guidelines can be designed.