CHAPTER 4

RESULTS

For the following analysis and data presentation, p value less than 0.05 was considered being statistically significant. All continuous data are expressed as means +/- SEMs. STATA program was used to analyze the data.

4.1 Patients Accounting

A total of 84 patients were screened during May 1997 to February 1998. Twenty-seven was excluded because they had already been included in this study once and should not be included again. Three were excluded because they were over 60. Fourteen patients were excluded because they were already infected on admission. Two patients were excluded because they refused to give written informed consent. Thirty-eight patients were included in the study, with 19 in the study group and 19 in control group.

Three patients dropped out during the study, 2 in the study group at the second and third week of the study period, 1 in the control group at the third week of study. The drop-outs in the study group were because of heart burning. The drop-out in the control group did not give a reason. Since they were not discharged, all of them were followed till the end of the study. Their data were included in the analysis, based on intention-to-treat analysis.

4.2 Analysis of the 38 Eligible Patients

4.2.1 Baseline Data

Table 4.1 Demographic Data of Eligible Patients

	Garlic* n=19	Placebo* n=19
Stratification		
Newly diagnosed	3	3
Relapsed	1	1
Consolidation	15	15
Age (years)	33.47±2.55 (28.12, 38.83)	31.05±2.33 (26.17, 35.94)
Sex (M/F)	12/7	10/9
FAB subtypes		
M1	8	5
M2	3	8
M3	3	3
M4	3	2
M5	2	1
Performance Status		
0	14	13
1	4	4
2	1	2
3-4	0	0
Hb (g/L)	109.58±5.86 (92.28, 121.88)	106.52±6.17 (93.55, 119.49)
WBC ($X10^9$/L)	5.24±0.62 (3.93, 6.55)	6.12±0.59 (4.89, 7.36)
Platelet ($X10^9$/L)	121.95±15.75 (88.86, 155.03)	122.53±14.36 (93.36, 152.70)
Duration of sickness (days)	215.37±45.76 (119.24, 311.50)	267.89±44.76 (173.86, 361.93)
Severe bone marrow suppression (days)	9.63±0.70 (8.16, 11.11)	9.42±0.76 (7.81, 11.02)
Bone marrow recover period (days)	17.42±1.52 (14.21, 20.63)	15.68±0.98 (13.62, 17.75)
Complete Remission	2/4 (7%, 93%)	3/4 (19%, 99%)

* The number in the parenthesis is the 95% confidence interval

Each treatment group had 19 patients, 3 newly diagnosed for induction chemotherapy, 1 relapsed for reinduction and 15 in post-remission consolidation.

The demographic data of the study subjects were listed in Table 4.1. There was no significant difference between the two groups in age, sex, duration of sickness,

performance status, FAB subtypes, hemoglobin, white blood cell and platelet count at recruitment. At the end of the study, there was no difference between the two groups in severe bone marrow suppression, bone marrow recovery period and complete remission rates.

4.2.2 Therapeutic Results

Primary outcome

According to the operational definition of infection, a total of 24 patients were infected, with 11 in the study group and 13 in the control group. Among the infected patients, 21 met the criteria of infection at the onset of fever, 4 met the criteria on the second or third day of fever. Among the non-infected patients, 3 in the study group and 1 in the control group experienced one episode of fever each lasting 1-2 days. They were observed without being given antibiotics, because they did not meet the criteria for infection. Their temperature became normal within 2 days. Therefore they were counted as non-infected.

The incidence of infection was 57.89% (95% CI: 33.50%, 79.75%) and 68.42% (95% CI: 43.45%, 87.42%) respectively in the study and control groups. By using Fisher's exact test, it could be calculated that there was no significant difference between the two groups.

Table 4.2 Treatment Result

	Garlic	Placebo	Total
Infection	11	13	24
Non-infection	8	6	14
Total	19	19	38

Fisher's exact test: p=0.369 (one-tailed)

The 95% confidence interval of the difference in the proportions of infection between the 2 groups were between -41.02% and 19.96%. This included 0. Therefore there was no significant difference between the two groups in the incidence of infection.

Subgroup analysis within each stratum also showed no significant difference between the study and control groups in the incidence of infection.

Table 4.3 Infections in Patients under Induction and Reinduction Chemotherapy

	Garlic	Placebo	Total
Infection	3	4	7
Non-infection	1	0	1
Total	4	4	8

Fisher's exact test p=0.500 (one-tailed)

Table 4.4 Infections in Patients under Consolidation Chemotherapy

	Garlic	Placebo	Total
Infection	8	9	17
Non-infection	7	6	13
Total	15	15	30

Fisher's exact test: p=0.500 (one-tailed)

Secondary outcomes

Infection related death

One patient in study group died of pulmonary aspergilosis 42 days after induction chemotherapy. No patients in the control group died. There was no

significant difference between the two groups in the infection related death, p=1 (Fisher's exact test).

Total days of fever

Thirteen patients in the study group experienced 15 episodes of fever. As mentioned in the primary outcome section, 2 patients with one episode each unsatisfied the criteria of infection and were therefore excluded from the analysis of infection. Since no other explanation could be found for the fever, these 2 episodes were included in the analysis of the total days of fever. One patient had two episodes of fever associated with the transfusion of blood product and these two episodes were not included in the analysis of the total days of fever.

In the control group, 14 patients experienced 16 episodes of fever. One patient had an episode of unexplained fever not meeting the criteria for infection . Therefore this patient was not counted as infected but the fever was included in the analysis of the total days of fever. One episode was associated to blood transfusion and another to chemotherapy for the underlying disease. These episodes were not included in the analysis of total days of fever.

The total days of fever were 4.05±1.07 (95% CI: 1.81, 6.30) and 6.47±1.33 (95% CI: 3.68, 9.26) in the study and control groups respectively. There was no significant difference between the two groups, p=0.164 (two-tailed t-test). The 95% CI of the difference was -5.88, 1.03.

Subgroup analysis showed that among patients undergoing induction and reinduction chemotherapy, the total days of fever were 9.5±3.12 and 13.5±2.96 respectively in the study and control subgroups (p=0.388, two-tail t-test). Among

patients undergoing consolidation chemotherapy, the total days of fever were 2.6± 0.77 and 4.6±1.08 respectively (p=0.143, two-tailed t-test). There was no significant difference between the study and control groups.

The total days of antibiotics given to patients

The total days of antibiotics given to patients were 7.26±1.77 (95% CI 3.54, 10.99) days and 10.42±1.92 (95% CI: 6.39, 14.45) days respectively for the study and control groups. There was no significant difference between the two groups (p=0.234, two-tailed t-test). The 95% CI of the difference was between -8.46 and 2.1.

Among patients undergoing induction and reinduction chemotherapy, the total days of antibiotics were 15±5.31 and 20.25±2.29 days respectively (p=0.399, two-tailed t-test). These numbers were 5.2±1.44 and 7.8±1.83 days respectively in patients undergoing consolidation chemotherapy (p=0.274, two-tailed t-test).

The types of antibiotics were recorded as the antibiotics used since last modification. In the study group, 6 patients were treated by piperacillin plus amikacin, 3 treated with third generation cephalosporin plus amikacin, 1 treated with imipenem/cilastatin plus amikacin, 1 treated with ciprofloxacin plus amikacin. In the control group, 3 patients were treated with piperacillin plus amikacin, 6 with amikacin plus third generation cephalosporin, 2 with imipenem/cilastatin plus amikacin, 1 with ciprofloxacin plus amikacin, 1 with vancomycin. Though it seemed that more patients in the study group had their infection controlled by simply using piparacillin plus amikacin, there was no significant difference between the study and control groups in the types of antibiotics used (p=0.561, Fisher's exact test).

Table 4.5 Types of Antibiotics

Antibiotics	Garlic		Placebo	
	Induction and reinduction	Consolidation	Induction and reinduction	Consolidation
Piparacillin+ amikacin	0	6	0	3
3rd generation cephalosporin + amikacin	2	1	2	5
Imipenem/cilastatin + amikacin	1	0	2	0
Ciprofloxacin + amikacin	0	1	0	1
Vancomycin	0	0	0	1

Modification of antibiotics was not required in 5 patients (45.45%) in the study group and 4 (30.77%) in the control group. Five (45.45%) and 4 (30.77%) patients in the study and control groups respectively had their antibiotics modified once. One (9.09%) patient in the study group and 5 (38.46%) in the control group had their antibiotics modified 2 times. There was no significant difference between the two groups in antibiotics modification (p=0.30, Fisher's exact test). Infected patients in the study group had their antibiotics modified by 0.64±0.20 times, while those in the control group had their antibiotics modified by 1.08±0.24 times. There was no significant difference between the two groups (p=0.183, two-tailed t-test, 95% CI of the difference: -1.11, 0.224). The majority of antibiotic modification was a change from antipseudomonal penicillin to third generation cephalosporin and addition of fluconazole, a few were a change from third generation cephalosporin to imipenem/cilastatin.

Categories of infection

Table 4.6 Categories of Infection

Infection	Group	
	Garlic	Placebo
Septicemia	1(5.26%)	4(21.05%)
Other bacteriologically documented infection	1(5.26%)	1(5.26%)
Clinically documented infection	3(15.79%)	5(26.32%)
Unexplained fever	6(31.58%)	3(15.79%)
Total	11(57.89%)	13(68.42%)

In the study group, the infected patients included 1 Escherichia coli septicemia, 1 pulmonary aspergillosis (died), 1 with infection of the injection site, 1 mucositis, 1 acute gastroenteritis, 6 without symptoms or signs of any sites of infection.

In the control group, the infected patients included 4 septicemias (1 Staphylococcus aureus combined with maxillary aspergillus sinusitis, 1 Staphylococcus epidermidis, 1 Pseudomonas aeruginosa, 1 Escherichia coli), 1 urinary tract infection caused by Escherichia coli, 1 pleuritis combined with herpes zoster, 2 pneumonia, 2 mucositis, 3 without symptoms or signs of any sites of infection. There was no significant difference between garlic and placebo recipients in the types of infection (p=0.404, Fisher's exact test).

Fungal colonization

Oropharyngeal and rectal swab cultures were performed 4 times for each patient. The first time was on admission, and then once a week. On admission, fungal culture was positive in 3 patients in the oropharynx, 1 in the study group, 2 in

the control group. The greatest majority of fungal colonization was acquired during hospitalization. Totally, fungal colonization was positive in 28/38 (73.68%) patients, with 12/19 (63.16%) in the study group and 16/19 (84.21%) in the control group. However the difference in the proportions of patients with fungal colonization between the two groups was not statistically significant. The 95% CI of the difference was between -48.24% and 6.14%. The number of positive fungal cultures per patient (including both the oropharyngeal and the rectal surveillance cultures) was 1.21±0.31 (95% CI: 0.58, 1.84) in the study group and 2.32±0.32 (95% CI: 1.65, 2.98) in the control group. There was significant difference between the two groups in the number of fungal colonization (p=0.0159, two-tailed Student's t-test). The 95% CI of the difference was between -1.99 and -0.22. Patients receiving garlic had significantly less fungal colonization than patients receiving placebo.

In the oropharynx, the numbers of positive fungal cultures per patient were 0.63±0.21 (95% CI: 0.20, 1.06) in garlic recipients, 1±0.23 (95% CI: 0.52, 1.48) in placebo recipients. There was no significant difference between the two groups (p=0.239, two-tailed t-test).

In the rectum, the numbers of positive fungal cultures were 0.58±0.18 (95% CI: 0.21, 0.95) in garlic recipients, 1.32±0.19 (95% CI: 0.92, 1.17) in placebo recipients. There was significant difference between the two groups (p=0.007, two-tailed t-test, 95% CI of the difference: -1.26, -0.21).

A total of 67 strains of colonizing fungi were identified, including 40 (59.7%) Candida species, 21 (31.3%) Aspergillus species and 6 (9%) Mucorales species.

Fungal infection was confirmed in only two patients, 1 pulmonary aspergilosis

in the study group, 1 aspergilosis of maxillary sinus in the control group. There was no association between fungal colonization and proved fungal infection.

Addition of antifungal medication

According to the antibiotic guidelines, antifungal medication was added to 2 (10.53%, 95% CI: 1.3%, 33.1%) patients in the study group, 6 (31.58%, 95% CI: 12.6%, 56.6%) patients in the control group. There was no significant difference between the two groups (p=0.232, Fisher's exact test). Since amphotericin B was not available in my hospital at the study period, only intravenous fluconazole was used.

Although addition of antifungal medication was not limited to patients with fungal colonization, fluconazole was added to none of the patients without fungal colonization.

4.2.3 Side Effects of Garlic

Nausea

Seven patients (36.84%, 95% CI: 16.3%, 61.6%) in the study group and 9 (47.37%, 95% CI: 24.4%, 71.1%) patients in the control group complained of mild nausea, there was no significant difference between the two groups (p=0.511, Chi-square test). No vomiting was reported except 1 patient with acute gastroenteritis.

Heart burn

Twelve (63.16%, 95% CI: 38.4%, 83.7%) patients in the study group and 6 (31.58%, 95% CI: 12.6%, 56.6%) patients in the control group complained of heart burn. The heart burn could be well tolerated by all patients except 2 in the study group who dropped out. Chi-square test showed a p value of 0.051. The 95% CI of the difference was between 1.46% and 67.70%.

Transfusion of blood products

Patients in the study group received 6.32±2.78 (95% CI: 0.49, 12.15) units of platelets and 1.05±0.47 (95% CI: 0.07, 2.04) units of packed red blood cells. Patients in the control group received 11.79±4.32 (95% CI: 4.82, 18.75) units of platelets and 2.63±0.77 (95% CI: 1.02, 4.24) units of packed red blood cells. There was no significant difference between the two groups in platelet or red blood cell transfusions ($p=0.21$ for platelet transfusion, $p=0.087$ for red blood cell transfusion, two-tailed Student's t-tests).