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Randomized Comparison of Cooked and Noncooked Diets in Patients Undergoing Remission Induction Therapy for Acute Myeloid Leukemia

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ABSTRACT

Purpose
A neutropenic diet is often used to prevent infection in patients with acute myeloid leukemia (AML). Although such a diet potentially entails inconvenience, its value is uncertain.

Patients and Methods
One hundred fifty-three patients admitted to a high-efficiency particulate air–filtered room (protected environment [PE]) to receive induction therapy for newly diagnosed AML were randomly assigned to a diet containing no raw fruits or vegetables (cooked diet) or to a diet containing fresh fruit and fresh vegetables (raw diet). Stratification was based on the patients' early risk of mortality (ERM) score. All patients received antibacterial and antifungal prophylaxis and remained on study until they were discharged from the PE. The outcomes of principal interest were major infection (pneumonia, bacteremia, or fungemia) and death; if the true probability of either event was 20% on the cooked arm and 40% on the raw arm, then the probability that the cooked arm would be selected as superior was 83%.

Results
Seventy-eight patients were randomly assigned to the cooked arm, and 75 were assigned to the raw arm. The two groups were similar with respect to age, ERM, chemotherapy received, and days at risk. Twenty-nine percent of patients in the cooked group and 35% of patients in the raw group developed a major infection ($P = .60$). Time to major infection and survival time were similar in the two groups. Fever of unknown origin occurred in 51% of the cooked group and 36% of the raw group.

Conclusion
In patients treated in a PE, a neutropenic diet did not prevent major infection or death.

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INTRODUCTION

It is well known that neutropenia predisposes patients to infection.[1] It is similarly established that foods, particularly fresh fruits and vegetables, contain *Escherichia coli*, *Pseudomonas aeruginosa*, and other Gram-negative bacilli that can cause life-threatening sepsis and pneumonia.[2,3] These two facts have led to the use of the neutropenic diet. After querying 400 hospitals associated with the Association of Community Cancer Centers, Smith and Besser[4] reported that 78% of the 156 responding hospitals used such a diet, typically once neutropenia ($< 1,000$ or $1,500/\mu L$) was documented. A wide range of dietary exclusions fell under the rubric of a neutropenic diet. However, 98% of such diets restricted fresh vegetables, and 93% restricted fresh fruits and juices.

Despite the routine use of a neutropenic diet, there seems to be little evidence of its benefit.[5] In contrast, data exist that demonstrate that at least some patients would prefer not to be limited to a neutropenic diet. Specifically, DeMille et al[6] found that 30% of the 23 outpatients participating in a study of the effect of this diet on infection rate were not compliant with the mandates of the diet. Infection rates were similar in compliant and noncompliant patients. A small trial (19 patients total) in children (median age, 4 to 5 years) found no difference in rates of febrile neutropenia according to whether patients were randomly assigned to a US Food and Drug Administration–approved food safety diet or a diet that, in addition, did not allow raw fruits and vegetables, take-out food, or fast food.[7] Similarly a small randomized trial (total of 20 patients, 15 with acute myeloid leukemia [AML])

found no differences in gut colonization or infection according to whether a normal hospital diet or a low bacterial diet was used.[8] In each of these trials, it was unclear whether the different dietary groups were at equal underlying risk of infection.

To assess whether the benefits of a neutropenic diet justify its inconvenience, we performed a larger trial that randomly assigned patients with untreated AML or high-risk myelodysplastic syndrome (MDS) who were about to receive chemotherapy in high-efficiency particulate air–filtered rooms (protected environment [PE]) to either a diet that contained fruits and vegetables only if cooked, as per standard practice of The University of Texas M. D. Anderson Cancer Center, or to a diet that permitted fresh (ie, raw) fruits and vegetables.

PATIENTS AND METHODS

Patients admitted to the PE were eligible provided that, at the time of random assignment, they had neither pneumonia nor bacteremia and were about to receive remission induction therapy on an ongoing Leukemia Department protocol for AML or high-risk MDS (10% to 19% blasts in marrow or blood). Two hundred six patients were eligible. Fifty-three of the patients (26%) preferred to conform to the hospital's policy of eating a diet containing no raw fruits and vegetables. The remaining 153 patients consented to be randomly assigned to either the hospital's diet of eating no raw fruits or vegetables or a diet containing fresh fruits and vegetables. The Leukemia Department Data Management Office performed the random assignment using the patients' early risk of mortality (ERM) score[9] as a stratification factor. The ERM incorporates pretreatment values for performance status, bilirubin, age, albumin, fibrinogen, absolute neutrophil count, hemoglobin, and creatinine to estimate the probability of death within 4 weeks after initiation of chemotherapy. The 604 patients admitted to the PE from 2000 to 2004 had a median ERM score of 0.17 (corresponding to 17% probability of death in the 28 days after beginning chemotherapy), leading us to stratify patients according to whether their ERM was greater or less than this value. Patients randomly assigned to the diet allowing fresh fruits and vegetables were encouraged to eat at least one of these daily, with the fruits and vegetables washed with cold water for 30 seconds before eaten. Compliance with the assigned diet was facilitated by placing notices of this diet on patients' charts and by use of diaries in which patients recorded what they ate each day. All patients remained on the correct diet while on study, although some did not eat a fresh fruit or vegetable every day as suggested.

All patients had central lines placed and received prophylaxis with levo-floxacin, valacyclovir, and depending on protocol, itraconazole, voriconazole, or a lipid preparation of amphotericin B. If fever of unknown origin (FUO) or pneumonia occurred, patients received intravenous ceftazidime or equivalent; if fever did not resolve, antifungal coverage was broadened. Patients remained on study until they were discharged from the PE to the outpatient setting, usually after return of the neutrophil count to more than 500/μL or after 6 weeks in patients in whom neutrophil recovery was delayed. Granulocyte colony-stimulating factor was used only when there was a delay (eg, 6 weeks in neutrophil recovery or after a major infection developed), and its use was equally infrequent in the cooked and raw diet groups.

The principal outcomes of interest were major infection (pneumonia, bacteremia, or fungemia, or pneumonia accompanied by bacteremia or fungemia) and death; we also noted the rates of minor infections and FUO. The principal comparison was between the group randomly assigned to eat only cooked food and the group randomly assigned to eat fresh fruits and vegetables; these groups are hereafter referred to as cooked and raw, respectively. To allow the reader to evaluate whether the patients randomly assigned to the cooked group were representative, we also report the incidences in the non-randomized group (ate only cooked food). A diagnosis of pneumonia required a compatible chest x-ray or computed tomography scan. Bronchoalveolar lavage to isolate a causative organism was performed if no resolution had occurred after 3 to 5 days. A diagnosis of bacteremia as a result of frequent contaminants such as coagulase-negative *Staphylococcus* required two positive blood cultures.

The statistical design was the Bayesian multiple outcome design of Thall et al[10] as extended by Thall and Sung.[11] The outcomes monitored were major infection and death. Specifically, if after every 20 patients were randomly assigned, the probability was more than 0.995 that the incidence of death or major infection was greater in either the raw or cooked arm, then the study would stop. Otherwise, 188 patients would be randomly assigned, with 94 patients on each arm. If the true probability of major infection was 20% on the cooked arm and 40% on the raw arm, then the probability that the cooked arm would be selected as superior at the end of the trial was 83%; this is analogous to a power of 83% using a more traditional design.[12] In contrast, if the true probability of major infection was 30% on both arms, then the probability that an arm would be selected as superior was 0.07, corresponding to $P = .07$ in more traditional designs.[12]

We used the χ^2 or Kruskal-Wallis test to compare various pretreatment characteristics; number of days on study and number of days with neutrophil counts less than 500/μL and less than 100/μL; and rates of diarrhea, mucositis, and infection in the cooked, raw, and nonrandomized groups. Time to major infection and time to death in the cooked and raw groups were compared using the log-rank test. We performed approximately 40 tests of statistical significance. Although a standard Bonferroni correction, which would regard a P value as significant if less than approximately .001 (0.05/40), is perhaps overly conservative given the related nature of many of the tests (eg, patients with any infection, patients with any infection or FUO), we would certainly advise regarding any $P > .01$ with caution. The M. D. Anderson Cancer Center Institutional Review Board approved this study, which was conducted in accordance with the Declaration of Helsinki.
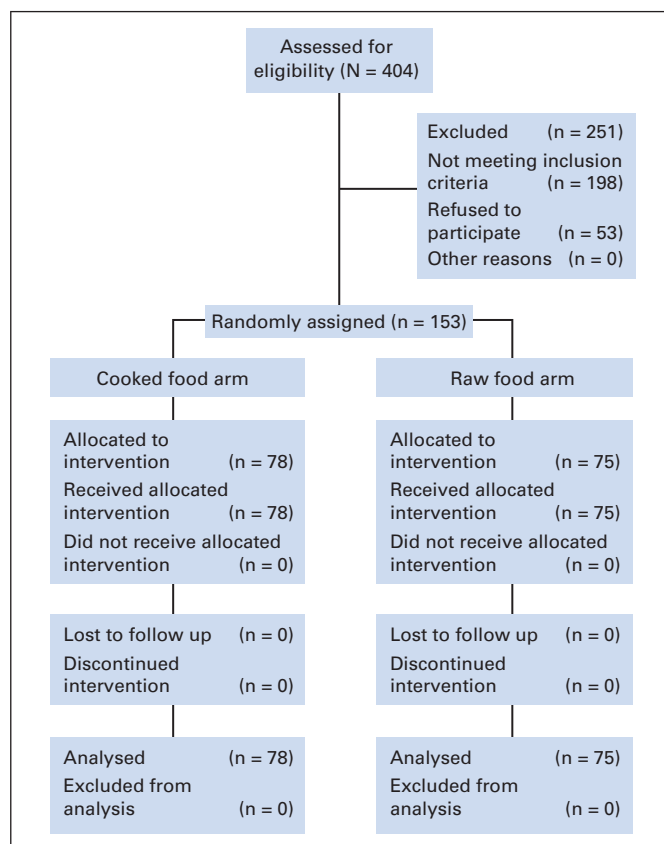

Fig 1. Flow of patients admitted to protected environment.

RESULTS

Seventy-eight patients were randomly assigned to the cooked arm, and 75 were assigned to the raw arm; 53 patients chose not to be randomly assigned, thus eating only cooked food (Fig 1). The three groups were similar with respect to age and ERM score (Table 1). Patients in the cooked and raw groups received prophylaxis with voriconazole more often than non–randomly assigned patients, of note because we have reported that such prophylaxis is more effective than itraconazole or lipid amphotericin B in preventing fungal infection[13]; however, similar proportions of patients in the cooked and raw groups received voriconazole (Table 1). Patients in the cooked group were more likely than those in the raw group to receive cytarabine, but the two groups were equally likely to receive high-dose therapy of any kind as opposed to targeted therapy (eg, decitabine; Table 1). Patients were on study (ie, at risk) for 24 to 25 days in each group. Fifty-three percent of patients in the cooked group and 57% of patients in the raw group had an antecedent hematologic disorder. The number of days spent with neutrophil counts less than $500/\mu L$ and less than $100/\mu L$ were similar in the cooked and raw groups (median of 20 and 21 days at $< 500/\mu L$ in the cooked and raw groups, respectively; $P = .77$; and median of 15 and 16 days at $< 100/\mu L$ in the cooked and raw groups, respectively; $P = .53$). Twenty-eight patients in both the cooked and raw groups had lost weight (a median of 5 lb in each group) when they came off study. The incidence of grade 3 to 4 mucositis or diarrhea was similar in the cooked and raw groups (10% and 16%, respectively; $P = .34$), further suggesting that the anti-AML therapies were equitoxic in the two groups. Grade 3 to 4 diarrhea or mucositis was seen in only one of the 36 cooked or raw group patients not administered cytarabine compared with 19 of the 117 cooked or raw group patients administered cytarabine.

Major Infection

Twenty-nine percent and 35% of patients in the cooked and raw groups, respectively, developed a major infection ($P = .60$; Table 2). An exact 95% CI for the true difference in rates is -11% to 21%. The rate of major infection in the nonrandomized group (36%) was similar to the rate in the randomized cooked group. Time to development of a major infection was likewise similar in the three groups (Fig 2). Excluding coagulase-negative *Staphylococcus* and α-hemolytic *Streptococcus*, the rates of major infection were 27% in the cooked group and 24% in the raw group ($P = .71$); when excluding patients administered monotherapy with clofarabine or VNP40101M (Cloretazine; Vion Pharmaceuticals, New Haven, CT), major infections occurred in 22 (31%) of 72 and 21 (34%) of 61 patients in the cooked and raw groups, respectively ($P = .71$).

Bearing in mind the multiple tests of statistical significance, the incidence of pneumonia was higher in the cooked group, whereas the

	Patients Randomly Assigned to No Fresh Fruits and Vegetables (cooked diet; n = 78)		Patients Randomly Assigned to Fresh Fruits and Vegetables (raw diet; n = 75)		Patients Not Randomly Assigned (preferred cooked diet; n = 53)		
Characteristic	No.	%	No.	%	No.	%	P
Age, years							.62
Median	64		63		66		
Range	17-88		47-84		49-81		
ERM score							
25th percentile	0.05		0.05		0.05		.98
Median	0.11		0.14		0.12		
75th percentile	0.25		0.26		0.32		
Disease							.63
AML	75		69		51		
MDS	3		6		2		
Voriconazole prophylaxis	14	18	8	11	0		.005*
Chemotherapy							
With cytarabine	65	83	52	69	40	75	.13†
Idarubicin + cytarabine ± tipifarnib	32		24		21		
Clofarabine + cytarabine	20		18		16		
Fludarabine + cytarabine	10		9		3		
Without cytarabine	13	17	23	31	13	25	
Clofarabine	3		11		2		
VNP40101M	4		8		8		
High dose	70	90	70	93	50	94	.64
Targeted	8	10	5	7	3	6	
No. of days on study							.27
Median	24		24		24		
Range	10-47		6-42		8-45		

Table 1. Patient Characteristics

Abbreviations: ERM, early risk of mortality; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.
*$P = .25$ for comparison of cooked v raw groups.
†$P = .06$ for comparison of cooked v raw groups.

Table 2. Incidence of Infection or FUO

Infection and FUO	Patients Randomly Assigned to No Fresh Fruits and Vegetables (cooked diet; n = 78)		Patients Randomly Assigned to Fresh Fruits and Vegetables (raw diet; n = 75)		P (cooked v raw)	Patients Not Randomly Assigned (preferred cooked diet; n = 53)	
	No.	%	No.	%		No.	%
Patients with any major infection	23	29	26	35	.60	19	36
Patients with pneumonia	12	15	4	5	.06	12	23
Patients with bacteremia or fungemia	7	9	17	23	.03	4	8
Patients with pneumonia accompanied by bacteremia or fungemia	4	5	5	7	.74	3	6
Patients with any minor infection	5	6	4	5	.99	4	8
Patients with FUO	40	51	27	36	.07	22	42
Patients with either major or minor infection	28	36	30	40	.62	23	43
Patients with infection or FUO	68	87	57	76	.09	45	85

Abbreviation: FUO, fever of unknown origin.

incidence of bacteremia was higher in the raw group. With either type of infection, the nonrandomized group bore more resemblance to the cooked group than the raw group. In only one of the 28 patients with pneumonia unaccompanied by bacteremia or fungemia was an organism recovered (*Aspergillus* species in a patient in the cooked group), and there were only three other documented fungal infections (one in each of the cooked, raw, and nonrandomized groups; Table 3). Organisms resident in the gut (*E coli*, *Enterococcus*, *Candida albicans*, *Enterobacter*, *Pseudomonas*, and *Klebsiella*) were cultured from blood in 6% of the cooked group and 15% of the raw group ($P = .12$; exact 95% CI, −.04 to .23).

Death

There was no suggestion that patients randomly assigned to the cooked group lived longer than those assigned to the raw group (Fig 3). Survival in all three groups was as expected in newly diagnosed AML or MDS patients, as were complete response rates (56% in
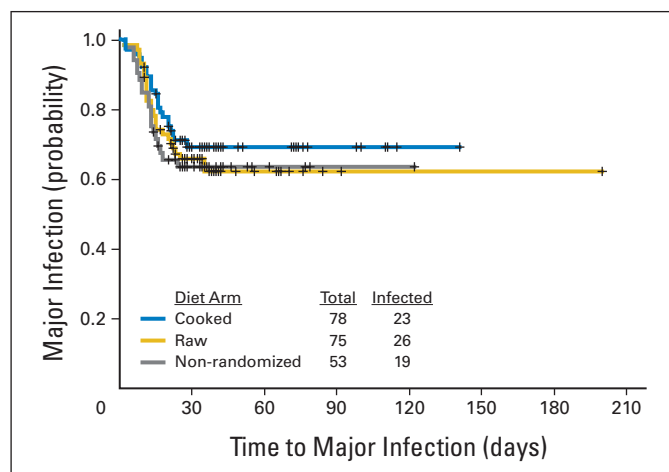
cooked group, 61% in raw group, and 64% in patients not randomly assigned).

Minor Infection and FUO

Minor infections were observed in less than 10% of patients in all three groups. FUO was more common in the cooked group than the raw group. As typically occurs in treatment of AML or high-risk MDS, the great majority of patients had either an infection or an FUO (87% in cooked group, 76% in raw group, and 85% in patients not randomly assigned; Table 2).

Table 3. Isolated Organisms

Organism	No. of Patients		
	Cooked Group	Raw Group	Nonrandomized Group
Pneumonia			
Aspergillus	1	—	—
Unknown	11	4	12
Bacteremia/fungemia ± pneumonia			
Escherichia coli	2	3	—
Enterococcus	2	5*	1
Staphylococcus aureus	1	—	—
Coagulase-negative *Staphylococcus*	1	3	1
α-Hemolytic *Streptococcus*	1	5	—
Enterobacter	—	1	1
Neisseria	1	—	—
Pseudomonas	—	1	1
Klebsiella	—	1	1
Stomatococcus	—	—	1
Flavimonas	1	—	—
Scedosporium	—	—	1
Alcaligenes xylosoxidans	1	—	—
Candida albicans	1	—	—
Corynebacterium	—	1	—
Roseomonas	—	1	—
Capnocytophaga	—	1	—
Fusarium	—	1*	—

*One patient had both *Enterococcus* and *Fusarium*.

Fig 2. Probability of major infection in cooked, raw, and nonrandomized groups; the nonrandomized group ate only cooked food (log-rank test, $P = .50$ for three-way comparison and $P = .44$ for comparison of cooked and raw groups).
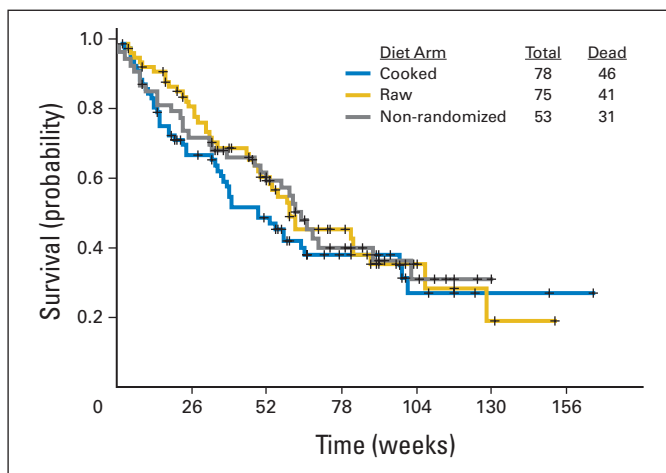
Fig 3. Probability of death in cooked, raw, and nonrandomized groups (log-rank test, *P* = .32 for three-way comparison and *P* = .36 for comparison of cooked and raw groups).

organisms not resident in the gut; the presence of such organisms would not be expected to be influenced by cooking of fruits and vegetables. Furthermore, the incidence of FUO and, hence, of potentially false-negative bacteremias was higher in the cooked group.

A major question is the extent to which our results can be generalized. This question arises because 26% of patients who were eligible for random assignment declined to be randomly assigned (preferring to eat only cooked food). The observation that results in nonrandomized patients were similar to those in patients randomly assigned to a cooked diet gives us some confidence that our results are not a function of selection bias. It may also be difficult to generalize our results to patients treated outside a PE or to patients not administered, as were our patients, antifungal prophylaxis with itraconazole, voriconazole, or lipid amphotericin. Nonetheless, at the least, our results suggest that a randomized trial similar to ours but conducted outside a PE would be appropriate. This is particularly the case as induction therapy changes in older patients to emphasize targeted rather than intensive therapy.

DISCUSSION

Our results suggest that there is little to be gained from use of a neutropenic diet in patients undergoing remission induction therapy for newly diagnosed AML or high-risk MDS. In particular, rates of major infection and death, the two major end points, were similar regardless of whether patients were randomly assigned to eat a cooked or raw diet. The exact 95% CI for the difference in rates of major infection suggests that a difference of no more than 10% is as plausible as no difference because 0 and 0.10 are equidistant from the midpoint of the CI (0.05), whereas the probability of survival was slightly higher in the raw group, making it unlikely that death would in fact have been more frequent in this group than the cooked group had more patients been entered. Although the incidence of bacteremia was higher in the raw group, a substantial part of this difference reflected isolation of

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