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Outcomes for newly diagnosed patients with acute myeloid leukemia dosed on actual or adjusted body weight

Whitney M. Bray¹, Cory Bivona², Michelle Rockey², Dave Henry³, Dennis Grauer³, Sunil Abhyankar⁴, Omar Aljitawi⁴, Siddhartha Ganguly⁴, Joseph McGuirk⁴, Anurag Singh⁴, and Tara L. Lin⁴

Whitney M. Bray: wbray@kumc.edu; Cory Bivona: cbivona@kumc.edu; Michelle Rockey: mrockey@kumc.edu; Dave Henry: dhenry@kumc.edu; Dennis Grauer: dgrauer@kumc.edu; Sunil Abhyankar: sabhyankar@kumc.edu; Omar Aljitawi: oaljitawi@kumc.edu; Siddhartha Ganguly: sganguly@kumc.edu; Joseph McGuirk: jmcguirk@kumc.edu; Anurag Singh: asingh3@kumc.edu; Tara L. Lin: tlin@kumc.edu

¹Department of Pharmacy, The University of Kansas Hospital Cancer Center Pharmacy, 2330 Shawnee Mission Parkway, Mail Stop 5022, Westwood, KS 66205, USA

²Department of Pharmacy, University of Kansas School of Pharmacy, The University of Kansas Hospital Cancer Center Pharmacy, 2330 Shawnee Mission Parkway, Mail Stop 5022, Westwood, KS 66205, USA

³University of Kansas School of Pharmacy, The University of Kansas Hospital, 3901 Rainbow Blvd, Mail Stop 4047, Kansas City, KS 66160, USA

⁴University of Kansas School of Medicine, The University of Kansas Cancer Center, 2330 Shawnee Mission Parkway, Mail Stop 5003, Westwood, KS 66205, USA

Abstract

Purpose—Data from solid tumor malignancies suggest that actual body weight (ABW) dosing improves overall outcomes. There is the potential to compromise efficacy when chemotherapy dosages are reduced, but the impact of dose adjustment on clinical response and toxicity in hematologic malignancies is unknown. The purpose of this study was to evaluate the outcomes of utilizing a percent of ABW for acute myeloid leukemia (AML) induction chemotherapy dosing.

Methods—This retrospective, single-center study included 146 patients who received 7 + 3 induction (cytarabine and anthracycline) for treatment of AML. Study design evaluated the relationship between percentage of ABW dosing and complete response (CR) rates in patients newly diagnosed with AML.

Results—Percentage of ABW dosing did not influence CR rates in patients undergoing induction chemotherapy for AML ($p = 0.83$); nor did it influence rate of death at 30 days or relapse at 6 months ($p = 0.94$). When comparing patients dosed at 90–100 % of ABW compared to <90 % ABW, CR rates were not significantly different in patients classified as poor risk ($p = 0.907$). All favorable risk category patients obtained CR.

Correspondence to: Whitney M. Bray, wbray@kumc.edu.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Conclusions—Preemptive dose reductions for obesity did not influence CR rates for patients with AML undergoing induction chemotherapy and did not influence the composite endpoint of death at 30 days or disease relapse at 6 months.

Keywords

Acute myeloid leukemia; Obesity; Induction chemotherapy; Actual body weight; Adjusted body weight

Introduction

Determining the dose of chemotherapy requires evaluation of each individual patient. For most conventional chemotherapy drugs, body surface area (BSA) is calculated to determine dosing in cancer patients. In obese adult cancer patients, physicians may modify dosing to limit the potential for toxicity by utilizing an adjusted or ideal body weight (IBW) or capping the BSA. Several studies have evaluated the use of actual body weight (ABW) in obese solid tumor cancer patients, and there was no increased risk of adverse events in obese compared to non-obese patients [1–3]. Meyerhardt et al. [1] examined the influence of body mass index (BMI) on adjuvant chemotherapy treatment-related toxicities of 1688 patients with stages II and III rectal cancer following primary surgical treatment. The patients were randomized into 5-fluorouracil-based treatment arms, dosed per protocol (using ABW), and the results concluded that obese patients had lower rates of grade 3/4 leukopenia ($p = 0.04$), neutropenia ($p = 0.003$), and stomatitis ($p = 0.03$) compared to normal weight patients.

There is the potential to compromise outcomes when chemotherapy dosages are reduced as a result of using adjusted body weight (AdjBW) in obese patients. Colleoni et al. [2] examined the relationship between BMI, dose reductions, and outcomes in 2140 pre-menopausal, node-positive breast cancer patients treated with adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil. Obese patients were more likely to receive lower chemotherapy doses ($<85\%$ of expected dose) for their first treatment ($p < 0.0001$). Dose reductions were associated with worse outcomes in the estrogen receptor-negative cohort (disease-free survival; $0.72 [0.56–0.94]$). Rosner et al. [3] evaluated outcomes of 1435 obese breast cancer patients treated in CALGB 8541 study (adjuvant cyclophosphamide, doxorubicin, and fluorouracil) and determined that patients who received $<95\%$ of the expected chemotherapy had worse failure-free survival rates. These observed inferior survival rates in obese patients treated with dose-reduced chemotherapy demonstrate the importance of dosing chemotherapy based on ABW in solid tumor malignancies.

The American Society of Clinical Oncology (ASCO) published clinical practice guidelines in 2012 to address appropriate chemotherapy dosing for obese adults. These guidelines recommend full body weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer, especially when the goal of treatment is cure [4]. While this guideline only addresses appropriate chemotherapy dosing in patients with solid tumors, there is currently no consensus regarding appropriate dosing in hematologic malignancies. Single institution retrospective reviews have consistently found safety in full body weight dosing in acute leukemia; however, no information regarding clinical outcomes comparing ABW and

AdjBW has been evaluated. Burhani et al. [5] evaluated the effect of BMI on outcomes in 89 patients receiving high-dose cytarabine and mitoxantrone for acute myeloid leukemia (AML) induction. Patients with normal BMI were more likely to respond to induction therapy (complete response (CR) rates: normal weight 77 %, overweight 55 %, obese 68 %), but there was no significant difference in rates of relapse. Wenzell et al. [6] also evaluated the efficacy and safety of dosing AML induction chemotherapy based on ABW. This study examined 247 patients with AML receiving an anthracycline and cytarabine-based induction chemotherapy and determined complete remission rates were similar among the three BMI groups (normal—69.1 %, overweight—79 %, obese—76.5 %, $p = 0.321$). Based on small, single-center studies, dosing with ABW appears to be safe and data from solid tumors suggest that ABW dosing improves overall outcomes; however, there is no data examining clinical outcomes comparing AdjBW versus ABW strategy.

The National Comprehensive Care Network (NCCN) provides treatment recommendations for induction chemotherapy in patients diagnosed with AML [7]. The NCCN guidelines do not address whether ideal, actual, or adjusted body weight should be used to calculate chemotherapy doses in AML. Our current practice for selecting the chemotherapy dosing weight at the University of Kansas Hospital (UKH) is to determine the IBW of the patient. If ABW is >130 % of the IBW, then AdjBW is applied for dosage calculations. This study retrospectively reviewed the outcomes in patients with newly diagnosed with AML when using a percentage of ABW for dosing induction chemotherapy.

Methods

This was a retrospective, single-center study of patients receiving 7 + 3 induction at UKH for the treatment of AML between April 1, 2008, and April 30, 2013, with a minimum follow-up period of 6 months. Inclusion criteria were patients greater than, or equal to, 18 years of age with newly diagnosed AML receiving induction chemotherapy with cytarabine and daunorubicin, or idarubicin. Exclusion criteria included patients diagnosed with acute promyelocytic leukemia, acute lymphoblastic leukemia, relapsed AML, or chronic myelogenous leukemia in blast phase, patients who required empiric dose adjustments for induction chemotherapy for reasons other than obesity (i.e., prior anthracycline or low ejection fraction), patients who received an induction regimen other than 7 + 3 (such as 5 + 2 or hypomethylating agent), or patients weighing less than their IBW. Data were abstracted from the electronic medical record. Data related to demographic characteristics, disease profiles, risk classification, outcomes, and survival at 6 months were collected. AML risk categorization was characterized using the NCCN risk status model (cytogenetics and molecular abnormalities) and confounding variables such as previous diagnosis with myelodysplastic syndrome (MDS) or diagnosis of AML secondary to previous chemotherapy exposure. Data on the choice of initial anthracycline and dosing were also collected. CR was defined as bone marrow aspirate/biopsy with <5 % blasts, transfusion independence, absolute neutrophil count >1000 cells/mm³, and platelets $\geq 100,000$ cells/mm³.

Statistical analysis included Pearson Chi-square tests to examine the impact of percentage of ABW dosing and risk category on CR rates, 30-day mortality, and relapse rates at 6 months.

Two-tailed *t* tests were performed to determine whether there was an association between CR rates and BSA, and one-way ANOVA was included to compare mean percent ABW with AML risk categories. *p* value <0.05 was considered statistically significant. Logistic regression was performed to determine whether certain patient variables would independently predict ability to obtain CR.

Results

A total of 290 patients were initially identified as potential candidates for review. After applying the exclusion criteria, 146 newly diagnosed patients with AML were included in the study. A total of 144 patients were excluded for the reasons summarized in Table 1. Baseline demographic and clinical treatment characteristics are summarized in Table 2. Overall, patient median age was 57 years (range 19–83) and median BSA was 2.02 m² (range 1.4–2.99). The median percentage of ABW dosing was 95.5 % (range 59.3–100). Based on the World Health Organization (WHO) BMI classification, 65 (45 %) patients were obese, 50 (34 %) were overweight, and 31 (21 %) were normal weight [8]. According to the NCCN AML prognostic categories based on cytogenetics and molecular abnormalities, 17.8 % of patients had favorable risk, 23.3 % had intermediate risk, and 58.9 % had poor risk status [7]. Daunorubicin 90 mg/m² was used as the anthracycline in 7 + 3 induction regimen in 55.5 % of patients (*n* = 81) and idarubicin 12 mg/m² in 37.7 % of patients (*n* = 55). Thirty-nine (48 %) patients who received daunorubicin 90 mg/m² and 26 (47 %) patients who received idarubicin 12 mg/m² were dosed at 100 % ABW. Overall, 123 (83 %) patients obtained CR, 21 (17 %) relapsed within 6 months of induction, and 3 (2 %) died within 30 days of induction therapy (Fig. 1).

Dosing by percentage of ABW was divided into five dosing categories and compared to CR rates, death at 30 days and relapse at 6 months (Table 3). There was no relationship between percent dosing of ABW and CR (*p* = 0.833) or incidence of AML relapse at 6 months or death at 30 days (*p* = 0.940). There was no significant difference when comparing BSA and CR rates, as the mean BSA of patients who obtained CR or did not obtain CR was 2.02 m² (±0.307) and 2.1 m² (±0.264) (*p* = 0.276), respectively (Table 4). In the subgroup of patients who relapsed at 6 months or died within 30 days of induction, the mean BSA was similar when comparing those who obtained CR and those who did not ([2.03 m² (±0.295)]; [2.04 m² (±0.305)]; respectively, *p* = 0.845).

Pearson Chi-square analysis of three treatment groups (daunorubicin 90 mg/m², [daunorubicin 45 and 60 mg/m²] and idarubicin 12 mg/m²) found no significant relationship between any anthracycline drug or dose and achieving CR (*p* = 0.578). The CR rate when comparing any dose of daunorubicin with idarubicin was not significant (*p* = 0.435). Selection of either daunorubicin or idarubicin for induction therapy was not associated with increased risk of relapse at 6 months or death at 30 days (*p* = 0.976).

The logistic regression analysis found the only significant predictor of CR was risk category, when analyzing confounding variables such as age, gender, BSA, percentage dosing of ABW, white blood cell count at diagnosis, AML risk category, and choice of anthracycline (favorable risk; *p* = 0.002, intermediate risk; *p* = 0.015, poor risk; *p* = 0.071). Poor risk

status was associated with decreased CR rates when compared to favorable and intermediate risk status groups, as expected. Both favorable- and intermediate-risk groups were associated with increased CR rates ($p = 0.001$) compared to poor-risk AML. Chi-square testing was used to determine whether there was a difference in weight used for calculation of chemotherapy doses within each risk category (Table 5). Within each risk category, there was not a significant difference in the number of patients dosed $<90\%$ of their ABW and those dosed $90\text{--}100\%$ of their ABW ($p = 0.537$). The mean percent dosing of ABW for the favorable-, intermediate-, and poor-risk groups was $90.87\% (\pm 12.16)$, $86.08\% (\pm 12.92)$, and $89.15\% (\pm 12.18)$, respectively, which was not statistically significant ($p = 0.298$). Overall, the number of patients that obtained CR was similar among the patients dosed $90\text{--}100\%$ of ABW and $<90\%$ of ABW when stratifying the patients based on risk category (Fig. 2). Due to every patient obtaining CR in the favorable-risk group, a p value could not be calculated. In the intermediate-risk group, only one patient in each dosing weight classification did not obtain CR; therefore, the p value is not valid. The poor risk category did not show any relationship between percent dosing of ABW and CR ($p = 0.907$).

After induction, 42 patients received consolidation with chemotherapy alone and 78 patients proceeded to transplant. Twenty-four (57%) patients who proceeded to consolidation chemotherapy and 42 (54%) patients that proceeded to transplant were dosed using adjusted body weight during $7 + 3$ induction. Dosing information for consolidation chemotherapy and transplant was not collected in this study, but the current practice for selecting the chemotherapy dosing weight at UKH is to determine the IBW of the patient. If ABW is $>130\%$ of the IBW, then AdjBW is applied for dosage calculations. It is possible that patients dosed on AdjBW during induction also received consolidation or transplant chemotherapy based on AdjBW at UKH.

Discussion

With an increasing number of obese cancer patients being treated with chemotherapy, it is important to understand how dosing can affect efficacy and toxicity. Due to the increased body mass in obese patients, patients receive larger doses of chemotherapy with the potential for increased toxicity. Historically, due to these concerns, physicians often empirically dose-reduced based on ideal/adjusted body weight or even capped the dose of chemotherapy. A growing body of literature and recent ASCO guidelines suggest that dose reduction-based weight alone may actually result in decreased chemotherapy efficacy and outcomes in solid tumors. Data specific to leukemia are lacking, and our study was designed to provide some insight regarding chemotherapy dose and outcomes in AML.

Dose reductions due to obesity did not influence CR rates in our sample. Admittedly, the CR rate in our institution over this time period is higher than one would expect from historical controls and published clinical trial data. No patients in this analysis were treated on a clinical protocol, and all received standard $7 + 3$ induction. Given these better than expected CR rates from the entire patient cohort, it is difficult to extrapolate the data to a high-risk AML population whose CR rate would expectedly be lower. In deciding whether or not to treat obese patients based on ABW, there is concern that obese patients may receive higher doses of chemotherapy than necessary to require CR and incur additional toxicity. Wenzell

et al. determined there were no significant differences in toxicity among normal weight, overweight, and obese patients with AML receiving induction chemotherapy dosed on ABW [6]. Recent data in the ECOG 1900 study demonstrated benefit in rates of CR and survival for AML patients less than 60 years of age treated with daunorubicin at 90 mg/m² instead of 45 mg/m², suggesting that for at least some patients with AML, higher doses result in improved outcomes [9]. Many institutions, including our own, have adopted this as preferred daunorubicin dosing for AML induction. Another concern with empiric dose reductions with chemotherapy in obese patients is the risk of underdosing. A retrospective study by Lin et al. [10] evaluated previously untreated patients with AML induced with 7 + 3 and tried to determine whether dose reductions for obese patients affected CR rates. The Lin study defined obesity as greater than or equal to 130 % of IBW and of the 21 obese patients, 6 were dose adjusted for obesity and 4 (66.7 %) obtained a complete response, which is different from our study that described a higher CR rate (78–90 %) for all patients regardless of percent ABW dosing. Similar to our study, the Lin study completed a multivariate analysis controlling for history of prior malignancy, FLT3-ITD and NPM1 status, and cytogenetic risk and determined there was no significant difference in CR rates between obese and non-obese patients. We found that there were no significant differences in CR rates between the percent dosing of ABW groups in the entire study population and within each risk category, which is similar to the results produced by Wenzell et al. [6].

It is widely accepted that poor-risk cytogenetics are the most important predictor of relapse and survival in AML [7]. Similarly, our study found that poor-risk cytogenetics/molecular markers were the only significant predictor of CR despite considering other variables such as age, gender, BSA, percent dosing of ABW, white blood cell count at diagnosis, risk category, and choice of anthracycline. Although the majority of patients reviewed were classified as poor risk, there was no influence on rate of obtaining CR. Additional analysis and studies would be required to determine the long-term outcomes of poor-risk patients that received empiric chemotherapy dose reductions for obesity.

A limitation of this retrospective, single-center study design is the reduction in external validity. Since AML is a subset of hematologic malignancies, the results of this study are difficult to widely apply to other hematologic malignancies without further study. For instance, hematologic malignancies with higher cure rates from treatment with chemotherapy alone may show different outcomes for patients empirically dose-reduced due to overweight/obesity. There are also challenges in terms of generalizing our findings to all patients with AML given the heterogeneity of the disease and our institution's bias to pursue stem cell transplant versus chemotherapy for all intermediate- and high-risk patients. The patient population in this study may not accurately reflect the standard distribution of favorable-, intermediate-, and poor-risk AML as tertiary academic medical centers may accept more complicated patient cases compared to smaller hospitals. Importantly, the role of chemotherapy in curing AML varies by risk category, and there may be more importance in not underdosing those with favorable-risk disease and the best chance for cure with chemotherapy alone. Unfortunately, prognostic risk category is not often known at the time that induction chemotherapy is prescribed. The current chemotherapy dosing practices at UKH did not allow for the study design to include two comparator groups, and in future studies, it may be beneficial to prospectively accrue and randomize obese patients to receive

either full body weight dosing or adjusted body weight dosing. Alternatively, it may be beneficial to study the long-term outcomes of obese patients who received ABW dosing. Also, some patients may be more aggressively treated and given full body weight dosing despite weighing over 130 % of their IBW due to provider preference. A prospective study would be able to provide a standard weight-based dosing regimen to avoid the dosing variations between physicians. The follow-up period for this study was limited to at least 6 months, and a longer follow-up period would allow for the evaluation of long-term outcomes for patients who received dose reductions. In addition, analysis of outcomes for favorable-risk patients treated with chemotherapy alone may be most informative in determining the effects of empiric dose reduction for obese patients.

Conclusions

In our study, preemptive dose reductions for obesity did not influence CR rates for patients with AML undergoing induction chemotherapy and were not associated with increase in death at 30 days and relapse rates at 6 months. Recent data such as the E1900 study demonstrate the importance of dose intensity in younger patients with AML, and several studies have failed to demonstrate an increase in toxicities with ABW dosing in other malignancies [9]. Our data add to this literature and did not demonstrate any adverse outcome in CR rate with dose adjustment. Further studies are necessary to confirm the results of this study in larger AML cohorts as well as in other hematologic malignancies.

This study was reviewed and approved by the University of Kansas Hospital institutional review board and protocol review and monitoring committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Per the University of Kansas Hospital institutional review board, patient consent was not required due to the retrospective nature of this study.

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Fig. 1.

Percentage of patients who obtained complete remission, died prior to 30 days post-induction, and relapsed at 6 months. The number of patients who relapsed at 6 months is lower than the original 146 patients due to various patient and treatment-related factors (e.g., never obtained CR due to refractory AML, transferred to hospice within a few months of starting induction chemotherapy, or deceased before 6 months post-induction)

Fig. 2.

Number of patients who obtained CR dosed by 90–100 % of ABW or <90 % of ABW within each risk category. Due to every patient obtaining CR, a *p* value could not be calculated in the favorable-risk group. Only one patient in each dosing classification did not obtain CR in the intermediate-risk group; therefore, the *p* value is not valid. The poor risk category did not show any relationship between percent dosing of ABW and CR ($p = 0.907$). Poor-risk AML includes those with cytogenetic and molecular (FLT3 mutation) conferring poor prognosis

Table 1

Reasons for patient exclusion from study

Exclusion criteria	No. of patients excluded
ABW is less than IBW	25
Acute lymphocytic leukemia diagnosis	23
Acute promyelocytic leukemia diagnosis	25
Relapsed acute myeloid leukemia	16
Chronic myeloid leukemia in blast crisis	11
Induction with other regimen (5 + 2)	10
Did not complete 7 + 3 induction	9
Less than 18 years of age	9
Transferred care to other facility	8
Dose reduction due to cardiac dysfunction	5
Other types of leukemia and lymphoma	2
Electronic medical record test patient	1

Table 2

Patient demographics and treatment characteristics

Characteristics	All patients (<i>n</i> = 146)	CR (<i>n</i> = 123)	Refractory (<i>n</i> = 23)
Age (years)			
Median	57	56	58
Range	19–83	19–83	20–76
Male sex [no. (%)]	65 (44.5)	53 (43)	13 (57)
Body surface area (m ²)			
Median	2.02	2.01	2.12
Range	1.4–2.99	1.4–2.99	1.44–2.64
Percent dosing of ABW			
Median	95.5	95.3	92.9
Range	59.3–100	59.3–100	65.8–100
White blood cell count at diagnosis (cells/μL)			
Median	6.05	6.9	3.9
Range	0.3–241.6	0.6–241.6	0.3–69.4
Body mass index [no. (%)]			
Normal	31 (21)	27 (22)	4 (17)
Overweight	50 (34)	43 (35)	7 (30)
Obese	65 (45)	53 (43)	12 (53)
Comorbidities [no. (%)]			
Hypertension	65 (44.5)	54 (44)	11 (48)
Diabetes mellitus	25 (17.1)	21 (17)	4 (17)
Coronary artery disease	15 (10.3)	13 (11)	2 (9)
Liver dysfunction	0 (0)	0 (0)	0 (0)
Anthracycline [no. (%)]			
Daunorubicin 45 mg/m ²	1 (0.6)	1 (0.01)	0 (0)
Daunorubicin 60 mg/m ²	9 (6.2)	8 (7)	1 (4)
Daunorubicin 90 mg/m ²	81 (55.5)	66 (54)	15 (65)
Idarubicin 12 mg/m ²	55 (37.7)	48 (39)	7 (30)
NCCN risk category [no. (%)]			
Favorable	26 (17.8)	26 (21)	0 (0)
Intermediate	34 (23.3)	32 (26)	2 (9)
Poor	86 (58.9)	65 (53)	21 (91)

Table 3

Percent dosing of actual body weight and CR rates, relapse rates at 6 months, and death at 30 days

Dosing % ABW	CR (%) <i>n</i> = 123	<i>p</i>	Relapse rates at 6 months or death at 30 days (%) <i>n</i> = 48	<i>p</i>
100 % (<i>n</i> = 69)	59 (86 %)	0.833	22 (32 %)	0.940
90–99 % (<i>n</i> = 9)	7 (78 %)		4 (44 %)	
80–89 % (<i>n</i> = 21)	19 (90 %)		6 (29 %)	
70–79 % (<i>n</i> = 35)	28 (80 %)		12 (34 %)	
<70 % (<i>n</i> = 12)	10 (83 %)		4 (33 %)	

For statistical analysis, patients who relapsed prior to 6 months post-induction and patients deceased within 30 days of induction were combined into one category due to the minimal number of patients that died prior to 30 days of induction (*n* = 3). Cause of death at less than 30 days was septic shock for all three patients

Table 4

Mean BSA and CR rates, relapse rates at 6 months, and death at 30 days

	Mean BSA (m ²)	<i>p</i>
CR		
Yes (<i>n</i> = 123)	2.02 (±0.307)	0.276
No (<i>n</i> = 23)	2.1 (±0.264)	
Relapse rates at 6 months or death at 30 days (%)		
Yes (<i>n</i> = 48)	2.03 (±0.295)	0.845
No (<i>n</i> = 98)	2.04 (±0.305)	

Mean BSA of patients who obtained/did not obtain CR and patients who relapsed at 6 months or died within 30 days of starting induction therapy. To complete statistical analysis, the three patients who died within 30 days of starting induction therapy were combined with patients who relapsed at 6 months

Table 5

Percent dosing of actual body weight based on risk category

Risk category	90–100 % Dosing ABW	<90 % Dosing ABW	<i>p</i>
Favorable (<i>n</i> = 26)	16 (62 %)	10 (38 %)	0.537
Intermediate (<i>n</i> = 34)	16 (47 %)	18 (53 %)	
Poor (<i>n</i> = 86)	46 (53 %)	40 (47 %)	