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The Safety and Efficacy of Radiation Therapy with Concurrent Dexamethasone, Cyclophosphamide, Etoposide, and Cisplatin-Based Systemic Therapy for Multiple Myeloma

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Abstract

Little is known about the safety and efficacy of delivering radiation therapy (RT) with concurrent DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) chemotherapy in patients with multiple myeloma. In this study, DCEP plus RT was safe, with low rates of grade 3+ hematologic toxicity and grade 2+ RT-related events. It was also effective at alleviating pain at symptomatic sites of disease and producing a radiographic response on imaging.

Introduction: The concurrent delivery of radiation therapy (RT) with salvage chemotherapies in the management of relapsed and refractory multiple myeloma (MM) is an area of ongoing investigation. This study examined the safety and efficacy of palliative RT given in the setting of concurrent dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP).

Patients and Methods: Fifty-five patients with MM received RT to 64 different sites within three weeks of receiving DCEP from 2010 to 2020. A median dose of 20 Gray (range 8-32.5 Gy) was delivered in a median of 5 fractions (range 1-15). Patients received a median of 1 cycle (range 1-5) of DCEP. Rates of hematologic and RT toxicity were recorded along with pain, radiographic, and laboratory responses to treatment.

Results: RT was completed in 98% of patients. 21% of patients experienced RTOG grade 3+ hematologic toxicity before RT, which increased to 35% one-month post-RT ($P = .13$) before decreasing to 12% at 3 to 6 months ($P = .02$). The most common toxicity experienced was thrombocytopenia. Grade 1 to 2 non-hematologic RT-related toxicity was reported in 15% of patients while on treatment and fell to 6% one-month after completing RT. Pain resolved in 94% of patients with symptomatic lesions at baseline. Stable disease or better was observed in 34/39 (87%) of the targeted lesions on surveillance imaging.

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Disclosure

The authors have no conflicts of interest they wish to disclose.

Conclusion: RT administered concurrently with DCEP was well-tolerated by most of the patients in this series, with low rates of hematologic and RT-related toxicity. RT was also very effective, with the vast majority of patients demonstrating resolution of their pain and a significant response on follow-up imaging.

Keywords

Radiation therapy; Multiple myeloma; Salvage chemotherapy; Toxicity; Safety

Introduction

Multiple myeloma is a plasma cell neoplasm that accounts for approximately 1.5% of all cancers and up to 10% to 15% of hematological malignancies.[1,2] Despite recent advances in systemic therapy that have significantly improved survival outcomes, MM remains a largely incurable disease and its incidence continues to rise.[1,3] Even in well-selected patients who are able to tolerate aggressive maneuvers such as stem cell transplants, relapse often occurs within 4 to 5 years and most patients require sequential lines of therapy over the following years.[2] Unfortunately, these subsequent therapies are generally less effective, often resulting in a slow progression of disease over time. As standard treatment options become more limited, patients are forced to consider enrolling on clinical trials or preparing to undergo salvage high dose chemotherapy with stem cell rescue. However, patients who are not eligible for clinical trials or suitable for stem cell transplant have fewer, less effective options, including recycling previously used therapeutics or utilizing salvage therapies.[1,4,5] Identifying additional treatment options may be of even more importance for patients with extra-medullary disease, which has been noted in up to 70% of patients at autopsy and can be more resistant to traditional therapies.[6]

A commonly used chemotherapy regimen is DCEP, which may be used as a salvage regimen for disease control, as a mobilizing regimen for stem cell harvest or as a bridge to additional therapies, such as novel therapeutic agents and hematopoietic stem cell transplant (HSCT).[7,8] Dadacaridou et al were the first to report on the safety and efficacy of this regimen as a third-line therapy in 2007, demonstrating a response rate of 58.3% and a median response duration of 9 months.[5] Similar results were published by Park et al, who reported a therapeutic benefit from DCEP in 80.1% of patients in the salvage setting, including a response rate of 45.1%.[4] In addition to having success as a salvage chemotherapy option, DCEP has also been demonstrated to have utility as a bridge to additional therapies, such as novel therapeutic agents, HSCT and, more recently, CAR-T cell therapy.[9,10]

However, survival and progression outcomes after chemotherapy tell only part of the story for patients with MM. Unfortunately, the vast majority of patients with MM will develop symptomatic bone lesions that may cause significant morbidity, lead to the development of pathologic fractures, and even worsen survival outcomes.[11-13] Because of the progression of these painful sites of disease, radiation therapy (RT) is used as a local treatment in up to 40% of patients with a diagnosis of MM.[14] It has been demonstrated that even low doses of RT can lead to significant improvement, and even resolution, of pain in many MM patients with

lytic bone lesions.[15-17] Despite the apparent benefits of RT, treatment is only palliative in nature and systemic therapy remains the definitive form of therapy. Therefore, it is important to minimize or avoid breaks in systemic treatment whenever possible.[18]

Even though the benefits of DCEP and RT are both well-studied when given alone, there is limited evidence as to whether combining aggressive systemic therapies with RT is safe or effective in treating MM. Two small series examining RT with concurrent chemotherapy and/or novel agents have reported pain response rates of greater than 80% with acceptable rates of toxicity, while another study demonstrated the safety of RT when given concurrently with numerous biologic agents.[18-20] However, despite the important roles of both DCEP and RT, there remains a lack of available evidence supporting their use concurrently. Thus, in this study, we identified a large cohort of patients who underwent RT concurrently with or within one month of receiving a DCEP-based chemotherapy regimen. We report on the safety and efficacy of combining these two therapies in patients with relapsed or refractory MM.

Materials and Methods

We reviewed a large retrospective database of patients in the Mount Sinai Hospital system treated for MM from 2010 to 2020 and identified patients who received DCEP and were later treated with palliative RT within 1 month of completing chemotherapy. Additional regimens containing the agents of DCEP, such as VDPACE (bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) and VDCEP (bortezomib, dexamethasone, cyclophosphamide, etoposide, and cisplatin), were also included in the analysis. Chemotherapy details (including the number of cycles administered and whether additional agents were added to DCEP) and RT details (including dosage, number of fractions, and treatment volumes) were collected. Planning target volume (PTV) was defined as the target volume plus a set-up margin designed by the treating physician for patients treated with conformal techniques and by the volume encompassed by the 100% isodose line for patients treated with non-conformal RT techniques.

Charts were reviewed for clinical toxicity outcomes using the RTOG (Radiation Therapy Oncology Group) grading system while receiving RT, 1 month after completing RT, and 3 to 6 months after completing RT. Hematologic toxicity was also assessed using the RTOG grading system with laboratory data (absolute neutrophil count (ANC), calcium, creatinine, hematocrit, hemoglobin, platelets, and white blood cell count (WBC)) collected at baseline, 1-month post-RT and 3 to 6 months post-RT. Treatment efficacy was evaluated using pre- and post-RT pain assessment, response on follow-up imaging (including x-rays, computed tomography, magnetic resonance imaging, and/or positron emission tomography), and comparison of pre- and post-RT Myeloma protein (M protein), kappa light chain, lambda light chain, and calcium laboratory values. Survival outcomes are also reported.

Continuous patient, treatment and response related characteristics were summarized by median (range: [min–max]) while categorical variables were summarized by N (%). The method of Kaplan-Meier was used to estimate the median overall survival time. Linear mixed models of natural log transformed laboratory data were used to compare geometric

means of values over time at baseline, 1 month, and 3 to 6 months post-RT. Median kappa/lambda values at baseline were compared among categories of pain improvement at follow-up and among levels of radiographic response at follow-up, using a Kruskal-Wallis test. Hypothesis testing was two-sided and conducted at the 5% level of significance. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics are depicted in Table 1. A total of 55 patients were included in our analysis with a median follow-up of 59.8 months. The median age of the cohort was 66 years (range, 39-81). Thirty patients (55%) were men and 25 (45%) were women. A total of 64 sites were treated, and nine patients received RT to multiple sites concurrently or consecutively. Sites treated included the spine (31%), head and neck (25%), extremities (17%), thorax/chest (16%) and abdomen/pelvis (11%). The median radiation dose delivered was 20 Gray (Gy) (range 8-32.5 Gy) in five fractions (range 1-15). The median PTV treated was 523 cc (range 14.8-4298 cc). A median of six (range, 1-19) lines of prior systemic therapy were delivered prior to treatment with DCEP plus RT. The median number of consecutive DCEP cycles delivered at the time of RT was one (range 1-5), with 55% of patients having received one cycle and 45% of patients having received two or more. Fifty-six percent of patients received one or more additional chemotherapeutic agents in addition to DCEP, with 19 (35%) receiving a proteasome inhibitor, 10 (18%) receiving additional cytotoxic chemotherapy, and 3 (5%) receiving PD-1/PDL-1 inhibition. One of these patients received both proteasome inhibitor and cytotoxic chemotherapy. Of 29 patients with bony lesions in the spine or extremities, 7 (24%) received bisphosphonate therapy.

Ninety-eight percent of patients completed their planned course of RT. Rates of RTOG grade 3+ hematologic toxicity over time are shown in Table 2. Twenty-one percent of patients had grade 3+ toxicity at baseline. While this value increased to 35% one-month post-RT, it did not approach statistical significance ($P = .13$). The rate then decreased to 12% at 3 to 6 months after RT, which was significantly lower when compared to the 1-month time point (P = .01). Thrombocytopenia was the most common toxicity event at each time point but did not change significantly over time (absolute rate of 13% at baseline, 21% at 1 month after RT, and 11% at 3-6 months after RT, $P = .40$ for time-effect). No patients experienced a grade 3+ event related to ANC or WBC during the study period. On univariate analysis, the development of grade 3+ hematologic toxicity was not associated with PTV volume ($P = .98$).

No grade 3+ RT-related non-hematologic toxicities were observed in any patients. As shown in Table 3, rates of grade 1-2 RT-related toxicities were low during RT on-treatment visits (15%), with the most common cause being gastrointestinal distress (n = 3). One month after RT, only 3 patients (6%) were noted to have persistent toxicity from RT, with two patients suffering from persistent nausea and one developing skin erythema over the treated area.

Laboratory data assessing treatment toxicity at baseline, 1-month post-RT, and 3-6 months post-RT can be viewed in Table 4. ANC values decreased significantly from a baseline value of $3.76/mm^3$ prior to RT to $3.17mm^3$ at one-month post-RT and remained lower at the 3

to 6 months post-RT (2.30/mm^3; $P = .02$). Total WBC also decreased significantly from a baseline value of 5.6×10^9/L to 4.4×10^9/L at one-month post-RT and 4.2×10^9/L at 3 to 6 months post-RT ($P = .02$). Conversely, the hematocrit increased significantly with time from 28.25% at baseline to 31.65% at 3 to 6 months post-RT ($P = .02$). Creatinine, hemoglobin, and platelet values did not appear to change significantly from baseline after treatment (all $P > .05$).

The median overall survival for the cohort was 9.9 months. At the time of the analysis, 45 (82%) patients had died and 10 (18%) were still alive as of their last follow-up visit. Complete pain assessment at baseline and follow-up was available for 48 patients. Of these, 33 patients had painful symptoms at baseline, while 15 patients did not have pain at the time of treatment. At the time of the 1-month follow-up visit, 31/33 patients (94%) reported a significant improvement in their pain, while two experienced persistent discomfort. Of the 15 patients treated for reasons other than pain, 14 were treated to prevent loss of function in a critical organ and one was treated due to rapid disease progression at one site. Complete assessment of radiographic response to treatment at baseline and follow-up was available for 39 sites in 34 patients: 13% of sites exhibited progression, 26% demonstrated stable disease, 31% showed a partial response, and 31% experienced complete resolution of disease.

Laboratory values assessing treatment response can be seen in Table 5. The median M protein value at baseline was 1.01 mg/dL. This decreased to 0.44 mg/dL and 0.20 mg/dL at 1- and 3 to 6 months post-RT, respectively. The median kappa light chain value at baseline was 23.6 mg/dL. This decreased to 10.96 mg/dL at 1-month post-RT and then increased to 14.2 mg/dL at 3 to 6 months post-RT. However, these changes did not approach statistical significance ($P = .71$). Free lambda light chain ($P = .84$) and calcium ($P = .2$) also did not differ significantly over time.

Discussion

This study aimed to evaluate the tolerability and efficacy of delivering RT to patients with relapsed or refractory MM while undergoing salvage chemotherapy with DCEP. One of the biggest concerns regarding concurrent chemotherapy and radiation in patients with MM is the significant risk for bone marrow toxicity.[20] In addition to increasing the risk for treatment-related morbidity, reduced blood cell counts can also preclude patients from pursuing additional systemic therapies that may have a larger impact on treatment outcomes.[21] Our results suggest that RT with concurrent DCEP is safe, with a low risk for significant hematologic toxicity. Although the rate of grade 3+ events increased from 21% prior to treatment to 35% at the time of one-month follow-up, this result was not statistically significant. Additionally, the rate of toxicity decreased to 11% by the 3 to 6-month time point, suggesting that the potential increased risk is transient in nature. Thus, even if a fraction of patients requires a break from chemotherapy due hematologic toxicity, long delays in resuming treatment are unlikely. Of note, the primary cause of grade 3+ event at each time point was thrombocytopenia, although platelet counts and rates of grade 3+ thrombocytopenia did not change significantly over time. Finally, although ANC and WBC counts demonstrated a statistically significant reduction over the course of the study, there were no grade 3+ events related to either of these measures at either 1- or 3 to 6-monts

post-RT. While clinicians should continue to monitor patients treated with this regimen closely for the development of treatment-related hematologic toxicities, our data suggests that there is little risk to the bone marrow when delivering RT concurrently with DCEP and that chemotherapy can be safely continued during radiation treatments.

The possibility of increased non-hematologic toxicities associated with concurrent chemoradiation (CRT) is another concern when considering delivering RT in conjunction with salvage systemic therapies in MM. While the increased rates of toxicity are acceptable in a number of disease sites, such as the cancers of the lung or cervix, due to improved local control and OS, it is unclear whether the risk to benefit ratio is favorable in patients with MM.[22, 23] Our data suggests that the overall risk of toxicity associated with RT in this setting is low and that the degree of toxicity is relatively mild. We report no grade 3+ non-hematologic events while on treatment or at 1-month follow-up. Additionally, the rate of grade 1 to 2 events was just 15% while on treatment. The vast majority of these events resolved within one month of RT completion, with only 3 patients suffering from persistent toxicity at their first follow-up visit. The findings in this study are supported by the results of similar study by Matuschek et al, which reported no increase RT-related toxicity in patients with MM when treated with CRT and tolerable rates of adverse events.[24] This further supports the notion that DCEP need not be held while RT is being delivered to painful or bulky sites of disease.

In addition to having a favorable safety profile, concurrent treatment with RT and DCEP also appears to be very effective at reducing pain and producing a response on surveillance imaging. Of the 33 patients who reported pain prior to treatment and had at least one follow-up visit, 94% had a significant improvement in their symptoms. Radiographic response was also seen in the majority of patients, with 62% of irradiated lesions decreasing in size and an additional 26% remaining stable. Significant pain relief and radiographic response associated with RT for MM have been reported in a number of similar studies, which further support the use of CRT in this setting.[20, 25] Additionally, RT is an important intervention for patients who present with refractory disease requiring rapid tumor reduction and is associated with preventing the development of new fractures in irradiated bones as well as damage to vital organs.[26] Finally, M protein levels appeared to decrease over time after treatment, while kappa and lambda light chain levels did not vary significantly over time. Additional studies, with larger number of patients are needed to better understand the effect that RT with concurrent DCEP may have on these important biomarkers.

There are a number of limitations to this study due to the retrospective nature of the analysis. Thus, a number of biases that could have been introduced that may have skewed our results. Potential confounding variables include the use of additional salvage therapies that could have altered the toxicity profile and efficacy of the treatment, the extent of tumor burden within the bone marrow, and the site of the body that was irradiated. Because laboratory studies were not ordered for the purpose of this particular analysis, not all patients had a complete dataset at all three time points. Although non-hematologic toxicities, pain assessments, and radiographic findings were clearly and consistently documented in the medical record in the majority of cases, some patients were not assessable prior to and after

treatment for these outcomes. A prospective study evaluating the effects of concurrent RT and DCEP would address these issues more conclusively.

Conclusion

This retrospective demonstrated the safety and efficacy of RT with concurrent DCEP for patients with relapsed or refractory MM. Patients treated with this regimen experienced tolerable rates of grade 3+ hematologic toxicity. The majority of these events were due to thrombocytopenia. Although a statistically non-significant rise in grade 3+ hematologic events was noted within one month of completing RT, this finding completely resolved by 3-6 months. Additionally, no grade 3+ non-hematologic toxicities were reported and grade 1 to 2 toxicities were rare and transient. Finally, treatment with RT and DCEP appeared to be effective at reducing pain and improving radiographic findings in these patients.

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Clinical Practice Points

- DCEP is a frequently-used salvage chemotherapy option that can be used as a bridge to therapies such HSCT or CAR-T cell therapy. RT can be used concurrently with DCEP, without interruption of systemic therapy.
- The combination of DCEP plus RT resulted in low rates of Grade 3+ hematologic (21% prior to RT, 35% at 1-month and 12% at 3-6 months) and Grade 2+ RT-related (15% on treatment and 6% at 1-month) toxicities.
- The vast majority (94%) of patients with painful lesions experienced a significant reduction in their symptoms and post-RT imaging demonstrated a response in most cases (87%).

Table 1

Patient Characteristics, N = 55

Age at End of RT, Median [Min, Max]	66 [39, 81]
Gender	30 (55%)
Men	25 (45%)
Women	
RT Site (n = 64)	20 (31%)
Spine	16 (25%)
Head/Neck	11 (17%)
Extremities	10 (16%)
Thorax/Chest	7 (11%)
Abdomen/Pelvis	
RT Fractions, Median [Min, Max]	5[1, 15]
RT Dose, Median [Min, Max]	20 [8, 32.5]
PTV Volume, Median [Min, Max]	522.55 [14.8, 4297.9]
Previous Lines of Therapy Median [Min, Max]	6[1-19]
DCEP Cycles, Median [Min, Max]	1[1, 5]
DCEP Cycles	30 (55%)
1	15 (27%)
2	6 (11%)
3	2 (3.5%)
4	2 (3.5%)
5	
Additional Chemotherapy	24 (44%)
No	31 (56%)
Yes	19 (35%)
Proteasome inhibitor	10 (18%)
Cytotoxic chemotherapy	3 (5%)
PD-1/PDL- inhibitor	

Table 2

Grade 3+ Hematologic Toxicity Over Time

	Before RT[0]	1 Month Post RT[1]	3-6 Months Post RT[2]	*P*-value for Time Effect
WBC <2.0 × 10^9/L				Not Estimable
No	51 (96%)	46 (90%)	37 (100%)	
Yes	2 (4%)	5 (10%)	0 (0%)	
Unknown	2 (4%)	4 (7%)	18 (33%)	
Platelets <50 × 10^9/L				.3974[overall]
No	47 (87%)	41 (79%)	33 (89%)	.2358[1,0]
Yes	7 (13%)	11 (21%)	4 (11%)	.7552[2,0]
Unknown	1 (2%)	3 (5%)	18 (33%)	.1921[2,1]
Neutrophils <1 × 10^9/L				Not Estimable
No	52 (100%)	48 (100%)	33 (100%)	
Yes	0 (0%)	0 (0%)	0 (0%)	
Unknown	3 (5%)	7 (13%)	22 (40%)	
Hemoglobin <7.5 g/dL				Not Estimable
No	49 (91%)	47 (89%)	37 (100%)	
Yes	5 (9%)	6 (11%)	0 (0%)	
Unknown	1 (2%)	2 (4%)	18 (33%)	
Grade 3+ Hematologic Toxicity				.2165[overall]
No	41 (79%)	31 (65%)	29 (88%)	.1343[1,0]
Yes	11 (21%)	17 (35%)	4 (12%)	.5144[2,0]
Unknown	3 (5%)	7 (13%)	22 (40%)	.0139[2,1]

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Table 3

Grade 1-2 RT Toxicity and Pain at Follow-Up

Grade 1-2 RT Toxicity on Treatment, N (%)	
No	44 (85%)
Yes- add why	8 (15%)
Unknown	3 (5%)
Grade 1-2 RT Toxicity at First Follow-Up, N (%)	
No	44 (94%)
Yes- add why	3 (6%)
Unknown	8 (15%)
Pain Improvement at Follow-Up, N (%)	
No Improvement	2 (4%)
Improvement	31 (56%)
No Pain on Treatment	15 (27%)
Unknown	7 (13%)
Response on Imaging at 1-6 Months	
PD	5 (13%)
SD	10 (25%)
PR	12 (31%)
CR	12 (31%)
Unknown	25 (38%)

Table 4

Laboratory Data Assessing Treatment Response Over Time (N = 55)

	Before RT[0]	1 Month Post RT[1]	3-6 Months Post RT[2]	*P*-value for Time Effect
ANC, cells/μL Median [Min, Max] # Missing	3.76 [0.16, 24.42] 1 Missing	3.17 [0, 18.68] 5 Missing	2.30 [1.15, 8.53] 20 Missing	.0196[overall] .0132[0,1] .0236[0,2] .9805[1,2]
Calcium, mg/dL Median [Min, Max] # Missing	9.00 [6.00-10.90] 1 Missing	8.7 [4.3, 10.0] 2 Missing	9.10 [6.60, 12.90] 19 Missing	.1969[overall] .1266[0,1] .8954[0,2] .1229[1,2]
Creatinine, mg/dL Median [Min, Max] # Missing	0.96 [0.36, 5.70] 1 Missing	0.93 [0.44, 6.44] 2 Missing	0.83 [0.18, 5.10] 19 Missing	.2036[overall] .8510[0,1] .0933[0,2] .1292[1,2]
Hematocrit, % Median [Min, Max] # Missing	28.25 [20.80, 37.60] 1 Missing	27.80 [19.30, 40.50] 2 Missing	31.65 [22.50, 40.00] 19 Missing	.0161[overall] .8586[0,1] .0121[0,2] .0080[1,2]
Hemoglobin, g/dL Median [Min, Max] # Missing	9.45 [7.00, 12.90] 1 Missing	9.30 [6.40, 13.40] 2 Missing	10.40 [7.50, 13.20] 18 Missing	.1221[overall] .9266[1,0] .0604[2,0] .0727[2,1]
Neutrophils, x 10^9/L Median [Min, Max] # Missing	71.90 [12.50, 97.60] 3 Missing	71.80 [29.00, 97.30] 7 Missing	61.40 [42.90, 89.80] 22 Missing	.1866[overall] .9040[1,0] .0879[2,0] .1160[2,1]
WBC, x 10^9/L Median [Min, Max] # Missing	5.60 [1.30, 34.40] 2 Missing	4.40 [0.10, 24.90] 4 Missing	4.20 [2.00, 10.00] 18 Missing	.0176[overall] .0047[1,0] .1442[2,0] .2425[2,1]

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Table 5

Laboratory Data Assessing Treatment Response Over Time (N = 55)

	Before RT[0]	1 Month Post RT[1]	3-6 Months Post RT[2]	*P*-value for Time Effect
Free Kappa, mg/dL Median [Min, Max] # Missing	23.60 [0.39, 10424.00] 2 Missing	10.96 [0.40, 1608.00] 4 Missing	14.20 [0.40, 3928.20] 19 Missing	.7112[overall] .4108[0,1] .6976[0,2] .7397[1,2]
Free Lambda, mg/dL Median [Min, Max] # Missing	6.20 [0.40, 5658.20] 2 Missing	7.21 [0.40, 5514.50] 4 Missing	6.90 [0.40, 6930.00] 19 Missing	.8378[overall] .6666[0,1] .5791[0,2] .8592[1,2]
M Spike Median [Min, Max] # Missing	1.01[0, 83.40] 8 Missing	0.44 [0, 158.40] 11 Missing	0.20 [0, 3.60] 24 Missing	Not Estimable
Protein, g/dL Median [Min, Max] # Missing	6.60 [4.30, 9.80] 2 Missing	6.10 [3.90, 9.40] 4 Missing	6.50 [4.20, 13.00] 18 Missing	.0666[overall] .0211[1,0] .4397[2,0] .1983[2,1]