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ICRC IRB proposal
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IGF-1: Is there a difference in African Americans and Caucasians with Multiple Myeloma

Study Purpose and Rational

Multiple Myeloma is an uncommon disease and approximately 20,180 people will be diagnosed this year.[1] However, it does account for 10% of all hematological malignancies.[10]. It is a monoclonal B-cell neoplasm that is associated with hypercalcemia, fatigue, anemia, kidney failure, infections, and bone fractures. All of which contribute to the morbidity of the disease. Prognostic factors on the disease include serum albumin <3 g/dL ,Serum creatinine ≥2 mg/dL platelet count <150,000/micro/L, Age ≥70 years ,Beta-2-microglobulin >4 mg/L, Plasma cell labeling index ≥1 percent, Serum calcium ≥11 mg/dL, Hemoglobin <10 g/dL, Bone marrow plasma cell percentage ≥50 percent[10]

One of the hallmarks of the disease is increased level of bone resorption and turnover with subsequent pathological fractures that can cause a lot of morbidity. Conventional skeletal surveys reveal punched-out lytic lesions, diffuse osteopenia, or fractures in nearly 80 percent of patients with MM at the time of diagnosis. [10] One of the mediators of this process is IGF-1(insulin-like growth factor-1). It is a important factor of cell survival and proliferation of MM cells. Furthermore, studies of myeloma have indicated that IGF-1 in the bone marrow contributes to the recruitment and homing of myeloma cells to the bone marrow compartment.[11]

There have been studies that have shown that overexpression IGFR maybe a major mechanism of overactivation of IGF system in cancer.[5] Elevated IGF-1 levels have been associated with breast, prostate and colon cancer.[5] Insulin also stimulates specific IGFR pathways. This study also showed that insulin resistance and obesity through the IGF system may play a role in cancer stimulation..

Interestingly, blacks have at least twice the risk of being diagnosed with MM, and also have twice the mortality rate in comparison to whites (8.3 per 100,000 black males vs. 4.3 per 100,000 white males;6.0 per 100,000 black women vs. 2.8 per 100,000 white women).[1] Obesity has been shown to be a risk factor for myeloma in both blacks and whites(2). The prevalence of obesity in blacks is higher than whites, which may explain some of the increased incidence.[2] Nevertheless, obesity has been linked to insulin resistance and IGF-1.[4,5.7] Perhaps, insulin resistance and obesity causes an effect on IGF-1 receptor and e levels of IGF-1. Obesity has been associated with lower levels of IGF-1[6,7,9], which may be secondary to insulin resistance and may cause upregulation of IFG-1 receptors, whose overexpression has been implicated in cancer. A previous study, looking at IGF-1 as a prognostic factor in MM implied that low levels of IGF-1 were associated with decreased survival and patients with low levels of IGF-1 did not reach median survival in comparison to lose with higher levels.[12] As mentioned previously, African Americans have increased prevalence of obesity, as well as multiple myeloma, and the

IGF-1 system has been implicated in obesity and other cancers, as well as proliferation of MM cells and bone turnover. My hypothesis is that IGF-1 and its receptor may be different in AA and Caucasians. If worse prognosis is associated with lower levels of IGF-1, AA will have lower levels of IGF-1 in comparison to whites. This difference may be an accurate predictor of prognosis in African Americans and Caucasians and may reflect an overall difference in mortality. If this is proven to be true, it has the potential to indicate potential genetic differences or genetic polymorphisms that may play a role in the difference in incidence and mortality associated with MM.

Study design and statistics:

The study will be a multicenter, cross-sectional , observational study of African Americans and Caucasians at several Oncology centers, newly diagnosed with Multiple myeloma, who have not received chemotherapy to have their levels of IGF-1 measured. The primary endpoint for this study is IGF -1 level. The patients will also be characterized by the prognostic factors associated with MM, including Hgb, calcium, BUN/Cr, and number of bone lesions, which is included in the work up of multiple myeloma. Additional demographic data will be taken from chart review of paper and electronic medical records.

I selected a mean difference of 15 for the effect size. Standard deviation looking at lab values at West Virginia in C8 Health project of people over 60 was 45. When using the unpaired t-test with a power of 80% and $p = .05$ gives a sample size of 143 per group for a total of 286 subjects. Student t test will be used for statistical analysis to see if there is a difference in IGF-1 levels between African Americans and Caucasians. However, the values of the IGF-1 levels will also be examined to see if the values follow a normal distribution to make sure t-test is the correct analysis for the date.

Statistical analysis will be employed to also examine CRAB prognostic factors in relation to the IGF-1 levels within the respective groups.

Study procedure:

Subjects will be asked by research coordinator whether not they would like to be included in the study at the first visit after diagnosis to Oncology office. At this time the subjects will be asked to self –identify their race/ethnicity. Subjects will have venipuncture for IGF-1 level. IGF-1 will be assessed via commercially available ELISA.

Previous workup prior to this visit will have already included skeletal survey to detect bone lesions, as well as blood work for CBC, CMP with calcium

Differences in IGF-1 levels between African Americans and Caucasians will be analyzed by unpaired t t-test.

Study drug: Not applicable

Study device: ELISA for IGF-1

Study questionnaire: Not applicable

Study subjects:

Self-identified African Americans and Caucasians who have been recently diagnosed with Multiple myeloma, but who have not undergone any treatment or chemotherapy.

Inclusion criteria: Multiple myeloma with presence of M-protein in urine and/or serum and diagnosed by bone marrow biopsy and plasma cells >10%
Age > 60
Stage I, II, or III Myeloma based on ISS

- Stage I — B2M <3.5 mg/L and serum albumin ≥3.5 g/dL
- Stage II — neither stage I nor stage III
- Stage III — B2M ≥5.5 mg/

Exclusion criteria:
Subjects that have received chemotherapy or other treatment for MM.(thalidomide, prednisone, Autologous hematopoietic cell transplantation, bortezomib, melphalan)
MGUS
Previous hematological malignancies or other cancers
Did not identify as Caucasian or African American

Recruitment of Subjects:
Multiple Oncology offices nationally, including NYPH Multiple Myeloma patients
After it is confirmed that the patient's meet the inclusion and exclusion criteria the investigators will confirm with the patient's PMD that the patient is suitable for the study and the patient is willing to discuss with the study with the research team. Study investigators will then approach patients, explain the study rationale, answer questions and provide informed consent for participation.

Confidentiality:
All study data will be coded. Study data and files will be stored in a secure location and in a password-protected database that will be accessible only to study investigators.

Conflict of interest:
There are no conflicts of interest to disclose.

Location of study:
It is a multi-center, national study that will be conducted at a variety of academic-affiliated and non-affiliated centers.

Potential Risks: Risks associated with venipuncture for blood work.

Potential Benefits: Potential to show that there is a difference in IGF-1levels in African Americans that may be able a prognostic factor and may be a genetic difference that could explain difference in incidence and mortality.

Alternative therapies:
There are no other alternative therapies in this study.

Compensation of subjects:
There will be no compensation provided to the subjects.

Cost to subjects:
No additional costs will be incurred by the subjects in this study.

Minors of Research subjects:
There will be no subjects under the age of 18. All of the subjects included will be > 60years old.

Radiation or Radioactive substances:
This study will not involve radiation or radioactive substances.

Next steps:
If there is a difference in IGF-1 levels between races, the next step would be to see if there is a difference in mortality predicted by IGF -1 between the races.
To look at IGF-1 polymorphisms to determine if there is a genetic difference in the protein that may contribute to difference in incidence and mortality.

References

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Paracrine/autocrine igf-1 vs systemic igf-1…low if-1 systemic, but local high??

insulin may stimulate specific IGF-IR signalling pathways. Over-expression of IR-A is, therefore, a major mechanism of IGF system over-activation in cancer. In this respect, IR-A isoform and hybrid receptors should be regarded as potential molecular targets, in addition to IGF-IR, for novel anti-cancer therapy. These findings may have important implications for both the prevention and treatment of common human malignancies. They underline the concept that hyperinsulinaemia, associated with insulin resistance and obesity,(arch biochem)

Obesity is likely a risk factor for myeloma, in both blacks and whites. Obesity is more prevalent in the black population, and this may help explain some of the increased incidence of myeloma. Obesity has been linked to insulin resisitance and obesitiy. Perhaps increased obesity is providing overactivation of IGF system. AA have increased occurrence of obesity and may have a difference in activation of IGF system. IGF levels may may be a predictor of prognosis in AA and Whites and may reflect difference in mortality.

Multiple myeloma (MM) is a B-cell neoplasia that is associated with an increased level of bone resorption. One important mediator of bone remodelling, insulin-like growth factor (IGF-I), has been shown to stimulate the proliferation of human myeloma cells.(Br hematology).
IGF-I is as potent a survival and proliferation factor. IGF-I is produced in the bone marrow environment by osteoblastic cells, bone marrow stromal cells and bone endothelial cells (br hematology)

IGF-1 levels were significantly lower in obese patients. The most frequent IGF-1 gen polymorphism allel is >194 bp in both obese insulin resistant patients and controls. IGF-1 levels and the other biochemical and hormonal parameters were similar in different genotype groups. The cause of lower IGF-1 levels in obese patients might be different from IGF-1 gene polymorphism and it may be insulin resistance

In vitro, IGF-1 induces proliferation of several MM cell lines.[2-4] IGF-1 can also enhance the growth-promoting effect of IL-6 on MM cells.[2,3,5] MM cell lines express the IGF-1 receptor, and stimulation of the receptor activates a distinct signal transduction cascade. This results in proliferation of MM cells as well as protection against apoptosis.[6] A mouse model of myeloma indicates that IGF-1 in the bone marrow can act as a chemoattractant for myeloma cells in vivo.[7] This suggests that IGF-1 may contribute to the recruitment and homing of myeloma cells to the bone marrow compartment(blood journal)

Nevertheless, IGF-1 was a strong indicator of prognosis. After 80 months of follow-up, myeloma patients with low levels (< 13 nM) of serum IGF-1 had not reached median survival. In the patient group with IGF-1 levels above 13 nM, median survival was 62 months (P = .006).

a highly significant survival difference between patients with "low" IGF-1 (< 13 nM) compared to the remaining patients (IGF-1 ≥ 13 nM). Median survival was not reached in the patient group with low IGF-1, compared to a median survival of 62 months in the remaining patients (P = .006). This difference was also evident in the 94 patients treated with the intended protocol (median survival not reached compared to 70 months; P = .03; Figure 3B).

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Retrospective cohort study?

5year survival white 40.1
the mortality rate for myeloma for men of African descent was nearly double the rate for white men (8.3 per 100,000 vs. 4.3 per 100,000). During the same time period, the mortality rate for women of African descent was more than twice the rate for white women (6.0 per 100,000 vs. 2.8 per 100,000).