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Students' Corner

Maximum tolerable dose of Cyclophosphamide and Azathioprine in Pakistani Patients with Primary Renal Disease

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Abstract

Objective: The immunosuppressive regimens, at present, mainly rely on western guidelines that were derived from studies conducted in western populations. No such study exists for South Asian population, which is home to almost two billion people different in both genetics and environment from west. Locally derived thresholds for side effects markedly different from western figures may warrant re-adjustment of current local immunosuppressive regimens that are at present based largely on western guidelines. In order to define optimum dose for Cyclophosphamide (CYC) and Azathioprine (AZA) based immunosuppressive therapy, we conducted this study to find out maximum tolerable doses of azathioprine (AZA) and cyclophosphamide (CYC) beyond which neutropenia and thrombocytepenia are most likely to occur in patients with primary renal pathology.

Method: Patients with systemic vasculitis and idiopathic glomerulonephritis who were on CYC and AZA were identified through review of medical records at a tertiary care hospital in Pakistan (The Aga Khan University Hospital, Karachi). Patients were categorized under three principal diagnosis i.e. systemic lupus erythematosus (SLE), primary (idiopathic) glomerulonephritis (GN) and Wegener's granulomatosis (WG). The Receiver Operating Curve (ROC) was used to calculate the maximum tolerable dose for both CYC and AZA.

Results: We identified 94 patients aged 6-82 years (median 44.5 years) with primary renal disease (Wegener's granulomatosis n=13, Systemic lupus erythematosis n=62 and idiopathic glomerulonephritis n=19) who received CYC or AZA. Of these 94 patients, 36.2% (n=34) received CYC and 63.8% (n=60) received AZA. The mean dose of CYC was 1.54 ± 0.50 mg/kg of body weight (range: 0.77-2.93). The mean dose of AZA was 1.64± 0.59 mg/kg of body weight (range: 0.47-2.97). The maximum tolerable doses calculated for CYC and AZA were 1.25 mg/kg and 1.30 mg/kg of body weight respectively. The maximum tolerable dose for CYC and AZA among males could not be calculated, because of insufficient number of patients who developed neutropenia and thrombocytopenia. The maximum tolerable doses for CYC and AZA among females were 1.34 mg/kg and 1.03 mg/kg of body weight respectively. Also we found out that AZA was relatively more likely to cause neutropenia and thrombocytopenia ($p = 0.07$).

Conclusion: We thereby recommend that CYC should be initiated at a dose no more than 1 mg/kg of body weight and AZA at an initial dose of 0.75-1.0 mg/kg of body weight. The dose may be adjusted later on the basis of clinical response and laboratory reports (JPMA 54:39;2004).

Introduction

Connective tissue disorders, vasculitides and autoimmune diseases are but a few of many chronic conditions afflicting the population. For the aforementioned set of conditions, treatment lies largely in the use of immunosuppressives, such as Cyclophosphamide (CYC) and Azathioprine (AZA). Unfortunately, these medications are not without side effects. Though decreasing inflammatory reactions associated with numerous vasculitides and connective tissue diseases, they carry the risk of bone marrow suppression that may manifest as febrile neutropenia, thrombocytopenia, anemia and increased susceptibility to infectious diseases.

The major determinant of such myelosuppression is the dosage of the cytotoxic drugs given to the patient; however, other variables may influence the probability of such an event.[1] Oral daily CYC at a dose of 2 mg/kg body weight/day in combination with corticosteroids, a regimen that was introduced by Fauci et al.[2], resulted in a steep increase in the survival rate for vasculitic and connective tissue disease and a reduction in vasculitic organ damage; however, it also caused substantial treatment-associated morbidity.[3-6] Haubitz et al.[7] in their study also used oral CYC at dose of 2 mg/kg body weight and sixty percent of their patients developed at least one episode of leukopenia; thrombocytopenia was seen in 12% of those patients. Brown et al.[8] used Azathioprine in the range of 1.3-2.7 mg/kg of body weight/day. They followed up all patients for a minimum of 2 years. Adverse effects occurred in 10 out of 13 patients. Although mild, these effects warranted a reduction in the dose of AZA. An oral dose of 2 mg/kg/day

of AZA was used by Cattan et al.[9] A significant decrease in blood leukocytes and neutrophils was noted after a month of therapy that further declined after the first year of treatment.

Current immunosuppressive regimens are based on western guidelines, which may or may not be truly applicable to the local South Asian population. It may be, therefore, more feasible to adjust therapeutic guidelines on the basis of locally derived figures than from those derived through similar studies carried out in the west.

Patients and Methods

Patients with systemic vasculitis and glomerulonephritis who were on CYC and AZA were identified through review of medical records at a tertiary care hospital in Pakistan (The Aga Khan University Hospital, Karachi Pakistan). We categorized primary renal disease under three principal diagnosis i.e. Systemic lupus erythematosus (SLE), glomerulonephritis (GN) and Wegener's granulomatosis (WG). The definitions on which these categories are based have been described in literature.[10-13] The diagnosis in each patient had been established by clinical and histological evidence of vasculitis and glomerulonephritis. A complete blood count had been done before initiation of immunosuppressive therapy and was repeated after one month. The maximum tolerable dose (the dose at which leukopenia or thrombocytopenia or both occurred) was evaluated by blood count at one month. Leukopenia was defined as total leukocyte count less than $3.8x10^9$/L of blood; neutropenia was defined as absolute neutrophilic count (ANC) less than $1.5x10^9$/L and thrombocytopenia was defined as platelets count less than $140x10^9$/L of blood. The maximum tolerable dose was defined as that dose beyond which leucopenia or thrombocytopenia or both occurred, warranting reduction of dose of the immunosuppressive drug. In all patients the status of leukopenia and thrombocytopenia had been confirmed by repeated complete blood counts. The cytotoxicity of immunosuppressive drugs was confirmed by clearly improving blood pictures following reduction of the respective doses of CYC and AZA.

Results were expressed as mean ± standard deviation and median with range. Univariate analysis was done by using Independent Sample t-test, Mann-Witney U test, Pearson Chi-square and Fisher-exact-test, wherever appropriate. A p-value less than 0.05 was considered statistically significant. All p-values were two sided. The Receiver Operating Curve (ROC) was used to calculate the maximum tolerable dose for both CYC and AZA. In ROC curve the true positive rate (sensitivity) is plotted in function of the false positive rate (1.0 - specificity) for different cut-off points. Each point on the ROC plot represents a sensitivity/specificity pair corresponding to a particular decision threshold.

Results

Ninety-four patients were identified with systemic vasculitis and glomerulonephritis with documented renal involvement who had received CYC or AZA. Out of these 94 patients, 30.9% (n=29) were male and 69.1% (n=65) were female. The mean age of patients was 35.6 ± 16.2 years (median 44.5 years; range 6-82 years). Of these 94 patients, 36.2% (n=34) received CYC and 63.8% (n=60) received AZA. The mean dose of CYC was 1.54 ± 0.50 mg/kg of body weight (range: 0.77-2.93). The mean dose of AZA was 1.64 ± 0.59 mg/kg of body weight (range: 0.47-2.97). Out of 94 patients, WG was present in 13.8% (n=13), SLE in 66.0% (n=62) and idiopathic GN in 20.2% (n=19). The number of patients who received CYC and AZA in our three-principle diagnoses is shown in the Table.

Table. Disease and drug distribution of patients.

	SLE	GN	WG	Total
CYC	14	11	9	34
AZA	48	8	4	60
Total	62	19	13	94

CYC: Cyclophosphamide
AZA: Azathioprine
GN: Primary (Idiopathic) Glomerulonephritis
WG: Wegener's Granulomatosis
SLE: Systemic Lupus Erythematosus

Of the patients who received CYC (n=34), 47.0% (n=16) were male and 53.0% (n=18) were female. Of these 16 male patients, 6.2% (n=1) developed both neutropenia and thrombocytopenia. Amongst the 18 females who received CYC, 38.8% (n=7) developed neutropenia and thrombocytopenia.

Of the patients who received AZA (n=60), 21.7% (n=13) were male and 78.3% (n=47) were female. Of these 13 males, 30.7% (n=4) developed neutropenia and thrombocytopenia. Of the 47 females, 44.7% (n=21) developed neutropenia and thrombocytopenia.

We calculated the dose at which the probability of developing neutropenia and thrombocytopenia was most likely to occur by using the ROC curve. The cut off calculated for CYC as a whole group was 1.25 mg/kg body weight (sensitivity = 88.8% and specificity = 65.2%). The cut off for AZA as a whole group was 1.30 mg/kg body weight (sensitivity = 68.0% and specificity = 60.7%). The cut off for CYC and AZA among males could not be

calculated, as there were insufficient number of patients (one and four respectively) who developed neutropenia and thrombocytopenia. The cut off for CYC among females was 1.34 mg/kg of body weight (sensitivity = 71.4% and specificity = 54.8%). The cut off for AZA among females was 1.03 mg/kg of body weight (sensitivity = 74.6% and specificity = 56.7%). AZA was more likely than CYC to cause neutropenia and thrombocytopenia (p value = 0.07).

Discussion

Immunosuppression with Cyclophosphamide (CYC) and Azathioprine (AZA) is the standard treatment for connective tissue diseases and vasculitides. It is frequently complicated by life threatening febrile neutropenia. Though less frequent, thrombocytopenia with superimposed anemia can significantly worsen a patient's quality of life. Although controlled lowering of leukocyte count into a low normal range by CYC and AZA appears to enhance the therapeutic effect, lower leukocyte counts are a definite risk factor for contracting infections. Guillevin et al observed major infections in 69.6% in a cohort of patients having vasculitides receiving daily oral CYC.[5] A major proportion of such events were associated with leukopenia.[6] However, infections did not occur in our patients as most cases that developed mild or moderate leukopenia due to CYC and AZA treatment reverted within a few days of decreasing the dose or withholding CYC and AZA. On the other hand, severe neutropenia, i.e., ANC below 1,000/ul, tends to be more protracted.[6] The experience with cytotoxic treatment is that the risk of infectious complications increases sharply when the ANC drops below this threshold, and the risk increases progressively with longer duration of severe neutropenia.[14]

As of yet there are no firm guidelines on the dose or optimum duration of treatment with CYC and AZA. Daily oral CYC at a dosage of 2mg/kg body weight/day resulted in a steep increase in the survival rate for vasculitic and connective tissue disease and a reduction in vasculitic organ damage[2]; however, it also caused substantial treatment-associated morbidity.[3-6] Haubitz et al. in their study also used oral 2mg/kg body weight CYC and sixty percent of their patients developed at least one episode of leukopenia; thrombocytopenia was seen in 12% of those patients.[7] Brown et al. used Azathioprine in the range of 1.3-2.7 mg/kg of body weight/day.[8] They followed up all patients for a minimum of 2 years. Adverse effects occurred in 10 out of 13 patients. Although mild, these effects warranted a reduction in the dose of AZA. An oral dose of 2 mg/kg/day of AZA was used by Cattan et al.[9] A significant decrease in blood leukocytes and neutrophils was noted after a month of treatment that further declined at the end of first year of treatment.[9] Contrary to these studies, neutropenia and thrombocytopenia occurred in our patients at lower doses.

Administration of CYC and AZA not only has both mutagenic and marrow suppressive potential but can induce remissions in numerous severe chronic connective tissue disorders. The severity of such side effects warrants research to derive doses at which the most beneficial trade off between treatment versus risk can be seen. Studies done in the west have attempted to derive such doses. Unfortunately such values cannot be easily applied to the larger segment of the world's population hence there is requirement for the doses to be separately derived for communities with different genetic backgrounds, environments and other such variables. Such 'variables' may not only affect the dose at which the said drugs' benefit might be seen but also the threshold at which adverse effects begin to manifest.

Conclusion

Based on our findings we recommend that CYC should be initiated at a dose no more than 1 mg/kg of body weight and AZA at an initial dose of 0.75 - 1mg/kg of body weight to minimize risk of neutropenia and thrombocytopenia while continuing to provide an effective therapeutic dose. The dose can later be adjusted on grounds of clinical response and laboratory results.

By deriving such figures, we find maximum tolerable dose of the mentioned immunosuppressive drugs to be different from figures derived in western studies thereby suggesting that current immunosuppressive regimens (based largely on western guidelines) may need adjustment to better suit the local South Asian population.

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