CNS RELAPSE RATES AFTER CRANIAL IRRADIATION IN ADOLESCENT AND ADULT ACUTE LYMPHOBLASTIC LEUKEMIA POPULATION: AN INSTITUTIONAL EXPERIENCE.

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ABSTRACT

The biology and outcome in adult Acute Lymphoblastic Leukemia (ALL) is dissimilar to childhood leukemia. 5 year Event-free survival is 63-78% in childhood and 30-39% in adults. Central Nervous System (CNS) recurrences invariably leads to systemic recurrences. CNS relapse rates, have been reported upto 50-75% and Prophylactic Cranial Irradiation (PCI) reduces it to 4%. This gave us the impetus to evaluate the results of our institutional protocol of using slanting field technique with dose of 18 Gray in 10 fractions for PCI in adolescent and adult population. MATERIALS AND METHODS: This is a retrospective analysis of adolescent and adult ALL, from year 2008-2012, of our institute being treated for leukemia and with PCI. Documentation of bone marrow under remission and a negative CSF cytology was obtained. Radiotherapy was delivered using the slanting field technique, 18 Gray/10 fractions. Radiotherapy volume included intracranial contents, the subarachnoid space and meninges. RESULTS: One, two and three year CNS relapse were 3.95%, 6.28%, 7.67% of the 430 patients evaluated. Three Year DFS was 32.09%. CONCLUSION: It was observed that our CNS relapse rates and DFS in adult population using the conventional technique and with doses of 18Gray were well in accordance with other studies.

KEYWORDS: Adult, Acute Lymphoblastic Leukemia, CNS Relapse Rate, Prophylactic cranial Irradiation.
INTRODUCTION:

Acute lymphoblastic leukemia is primarily a malignancy of childhood but can be seen in adult population as well. It accounts to approximately 1% of all adult cancers. (1) The two peaks of incidence of ages are 2-5 years and >40 years. (2) The biology, treatment compliance, treatment related morbidity, drug metabolism and outcome in adult ALL is also dissimilar to childhood leukemia. (3, 4, 5, 6) 5 year Event free survival (EFS) have been reported to be upto 63-78% in childhood while in adults it is as dismal as 30-39% in B-cell lineage. (2, 7-12) Adults have less favorable prognosis compared with children, with long term Disease Free Survival (DFS) ranging between 25-50% in adult population. (13) Over the last decade, 5 Year Overall Survival (OS) remains to be around 80% in childhood and 30-40 % in adult ALL as there are higher rates of induction death in adults. (14)

Central nervous system (CNS) relapse is an overriding event to prevent remission once chemotherapy can prolong hematological remission. CNS has been recognized as a sanctuary site, in which very high doses of chemotherapy can penetrate but with associated toxicity and morbidity, due to which it is not the preferred choice for CNS prophylaxis. (15, 16, 17) CNS recurrences invariably leads to systemic recurrences suggesting that CNS disease is capable of reseeding the blood and marrow. CNS relapse rates, if untreated have been reported to upto 50-75% in adults and children. (18) Prophylactic Cranial Irradiation (PCI) of the CNS early in remission can eradicate the residual leukemic blast cells and prevent isolated relapses. (19) Studies have documented a reduction in the isolated relapse rates from 67 to 4%. (20) Moreover, adult population presenting as CNS disease ranges from 5-10%, and 5 year overall survival (OS) being further bleak upto 29%. (21)

The primary determinants of outcome in adults are higher age, associated co-morbidity limiting the treatment, high White blood cell count and genetic characteristics (presence of Philadelphia chromosome) of their ALL. The CNS prophylaxis regimes historically varied through chemotherapy alone or cranio-spinal irradiation with chemotherapy or cranial irradiation with intrathecal chemotherapy. Eventually cranial irradiation and intrathecal chemotherapy has emerged to give lowest relapse rates and at the same time confer least toxicity. Prophylactic cranial irradiation is usually delivered using either the slanting technique or the German helmet technique. (18) Eventually over the span of time, doses for irradiation has also been reduced from 24 Gray to 18 Gray, as relapse rates in the lower dose group were not statistically significant with lower toxicity. (22) Further lower doses upto 12 Gray are also being used. There is no risk stratification consensus in adult leukemia. Although many classifications are used based on age, disease characteristics and treatment response. (14) Adult ALL are generally taken as high risk group, adolescent ALL are high risk in pediatric protocol. This gave us the impetus to evaluate the results of our institutional protocol of using slanting field technique with dose of 18 Gray in 10 fractions in the adolescent and adult population group.

MATERIALS AND METHODS:

This is a retrospective analysis of adolescent and adult population of Acute Lymphocytic Leukemia (ALL), from year 2008-2012, of our institute being treated for leukemia and with cranial irradiation. Prophylactic cranial irradiation was given in the patients having been completed the induction phase of remission. Documentation of bone marrow under remission and a negative CSF cytology was obtained. Radiotherapy was delivered once blood counts were normal. Radiotherapy was delivered using the slanting field technique, using 6 MV photons with bilateral parallel opposed beams upto 18 Gray in 10 fractions at the rate of 1.8 Gray per fraction for 5 days a week for 2 weeks. Radiotherapy volume included all the intracranial contents, the subarachnoid space and the meninges. Care was taken to avoid the lens by placing the lateral border at the canthus. Inferior most extent was kept at the caudal border of the second cervical vertebrae. The prescribed dose was calculated at midplane. (18)
RESULTS:
We evaluated 430 ALL patients from the year 2008-2012. 314 of the patients were males and 116 were females. Male to female ratio being 2.71:1. 153 were adolescents, 90 patients were from age group 20-29yrs, 51 patients belonged to age group from 30-39 yrs, 83 patients were of 40-49 yrs, 37 patients were of age 50-59yrs, 16 patients were more than 60 yrs. 86 patients were of T-cell type and rest 344 were B-cell type. Philadelphia chromosome was positive in 96/430 patients (22.33%). All the patients were treated as per our institutional protocol on the lines of induction, remission and maintenance phases {329 patients were started on MCP 841 protocol and 101 patients were put on Berlin Frankfurt Munich (BFM90 protocol)}. One Year CNS relapse was seen in 17 out of 430 patients (3.95%). Two Year CNS relapse rates were seen in 27 patients out of 430 patients (6.28%). Three Year CNS relapse rates were seen in 33 out of 430 patients (7.67%). Three Year Disease Free Survival was 32.09% (138/430 patients). 4 patients developed testicular relapse at 3, 5, 6 and 14 months after prophylactic cranial irradiation and received 24Gray/ 12 fractions for the same. There were no acute and late toxicity reported.

DISCUSSION:
Male to female ratio declines from 1.75 to 0.97 from the younger adults to older adults. (23) At our institute this ratio was found to be slightly higher, as the young adults and adolescents dominate the population group. T-cell ALL is found to be in 15% childhood and 25% in adults ALL (24) more common in adolescents and males. Our population also consists of 86 T-cell ALL patients. This accounts to 20% of the total patients. Unfavorable genetics in the form of Philadelphia chromosome positivity has been reported to be as high as 25% in adults as compared to as low as 3 % in children. (25, 26) In our study group also it was found to be upto 22.33%.

Our One Year CNS relapse was seen in 17 out of 430 patients (3.95%). Two Year CNS relapse rates were seen in 27 patients out of 430 patients (6.28%). Three Year CNS relapse rates were seen in 33 out of 430 patients (7.67%). Ching et al. from the St. Jude Child Research Hospital (SJCRH) also reported that depending on the efficacy of the systemic therapy CNS relapse can range between 2-10%. (27) Similarly a Swedish study from Uppasla University, CNS relapse rates were reported to be upto 5% in adult protocol group.(2) We have used 18Gray/10 fractions as the dose for prophylaxis in the CNS. Hata et al. also used 18 Gray as the dose for prophylactic cranial radiotherapy instead of 24 Gray and reported one CNS relapse out of 35 patients and concluded 18 Gray to be as effective as 24 Gray in preventing the CNS relapses. (16) Moreover, doses ≥ 2500rad or 25Gray have been related with high rates of encephalic post irradiation syndrome. (28) Our patients tolerated the treatment fairly well, as also the dose were reduced from 24 Gray to 18 Gray, which is our institutional policy. Halberg et.al also reported lesser neurotoxicity with 18 Gray than 24Gray. (29) The Disease free survival, has been reported in the Cancer And Leukemia Group B (CALGB) studies is in the range of 40-50% in age group < 30 yrs, 30- 40% in the age group 30-59 yrs, and follows further decline to 20 % for the age group > 60 yrs. Our Three year Disease Free Survival is found to be 32.09% which is also comparable with the reported results. (9, 30-34) Testicular involvement is seen in <1% of adults. (18) It was found to be in 4/430 of our patients (0.93%).

CONCLUSION:
The outcome following therapy in adults remains unsatisfactory. It was observed that our CNS relapse rates in adult population using the conventional slanting technique and with doses of 18Gray were well in accordance with other reported studies. Also the Disease free survival rates of our population was also found to be similar to other reported results. Therefore 18Gray with slanting technique is safe and effective in adult ALL patients.

REFERENCES:
14. A.S. Advani and H.M. Lazarus (eds.), Adult Acute Lymphocytic Leukemia, Contemporary Hematology. Chapter 14 Treatment of Acute Lymphoblastic Leukemia in Young Adults p 211.


23. A.S. Advani and H.M. Lazarus (eds.), Adult Acute Lymphocytic Leukemia, Contemporary Hematology, chapter 9 Treatment of Acute Lymphoblastic Leukemia in Middle-Age and Older Adults p 117-126.


