LETTER TO THE EDITOR

Outcomes of Children with Relapsed Acute Lymphoblastic Leukemia in India

Asian Pacific J Cancer Prev, **12**, 1101-1102

Dear Sir

There is paucity of data addressing outcome of relapsed childhood acute lymphoblastic leukemia (ALL) from India (Arya et al, 2010; Kulkarni et al 2010). Hence, this study was conducted to assess the published outcome of relapsed ALL in India over the last 2 decades, identify shortcomings and suggest remedial measures.

The search strategy was constructed using a combination of MESH headings and text words relating to outcome of relapsed ALL in Indian children (age ≤18 years) and electronic databases MEDLINE (PubMed), EMBASE, SCOPUS and Cochrane Central Register of Controlled Trials – CENTRAL were searched. Search dates of January 1990 to November 2010 were specified without language restrictions. International Society of Paediatric Oncology annual meeting abstracts were handsearched to identify unpublished data. Full copies of all relevant and potentially relevant studies were obtained. Pertinent data was extracted. Due to significant clinical heterogeneity and paucity of data in the few included studies, we provide a descriptive summary of results extracted from individual studies.

Eight studies, 8 case reports and 1 abstract from single center studies in 6 centers were identified (Table 1). Predominantly very early or early and isolated or combined bone marrow relapse is most common albeit with higher incidence of extramedullary relapse in some series. Several studies on ALL outcome, using primarily uniform initial treatment regimen, describe relapse pattern

Table 1. Literature Addressing Outcome of Relapsed ALL from India

Authors	n	Age	Relapse (%)	Isolated BM	CNS	Testis	EM	Combined +BM	-BM	Timing@@ VE	E	L	Treated	Outcome (%)
Studies##														
Arya et al, 2010	254	<15	40 (17.9)	23	7	2	1 (bone)	6	1	16+ (40)	7+ (17.5)	13+(32.5)	NA	NA
Kulkarni et al 2010**	532	<15	11** (2.06)	9	1	-	-	1	-	5 (45.5)	5 (45.5)	1 (9)	Nil	Nil
Kulkarni et al, 2010	407	<15	30 (7.37)	-	-	17	-	11	2	8 (26.7)	16 (53.3)	6 (20)	13	7 (23.3)
Kulkarni et al, 2009	762	<15	127	51	24	17	3	29	3	56 (44.1)	49 (38.6)	22 (17.3)	NA	NA
Goyal et al), 2005	-	2-9	12 -	-	12	-	-	-	-	3$(25)	6$(50.0)	3$(25)	12	8 (66.7)
Chandy et al++, 2001	-	-	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	7	?*
Vaidya et al, 1996	422	0-25	84 (19.9)	54	3	11	2	13	1	NA	NA	NA	NA	9
Choudhary et al, 1992	152	1-13	22 (14.5)	-22@		-	-	-NA		NA	NA	NA	NA	NA
Abstracts														
Kulkarni et al, 2010	-	-	45 (8.46)	-	24	-	-	21	-	22 (48.8)	18 (40.0)	5 (11.2)	NA	NA
Case reports														
Bhatti et al, 2010	1	10	- -	-	-		1 (gut)	-	-	1	-	-	yes	died
Kulkarni et al, 2009	1	5	- -	-	-		1 (O)	-	-	-	1	-	yes	lost
Radhakrishnan et al, 2009	1	10	- 1	-	-	-	-	-	-	-	1	-	yes	died
Wadhwa et al, 2007	1	4	- -	-	-	-	-	1(+O)	-	-	1	-	yes	NA
Naithani et al, 2006	1		- -	-	-		1 (O)	-	-	-	-	1	yes	alive!
Padmanjali et al, 2004	1	6	- -	-	-		1 (bone)	-	-	-	1	-	no	lost
Geetha et al, 1999	1	4	- 1&	-	-	-	-	-	-	-	-	1	yes	died
Lodha et al, 1998	1	5	- -	-	-	-	1 (+T)	-	-	-	-	1	yes	NA

##In all the studies and abstract initial treatment in all patients was primarily a uniform, non-risk stratified therapy regimen (like MCP841 protocol or modified UKALLX protocol). @@relapse classified as very early (within 18 months of starting therapy), early (from 18 months of start of therapy till within 6 months of completion of therapy) and late (beyond 6 months of completing therapy), #Isolated extramedullary relapse except CNS and testis^age at initial diagnosis in years, +relapse classified as early on-therapy (within 12 months of starting therapy) late on-therapy (from 12 months of starting therapy to completion of therapy) and off therapy relapse (beyond completion of therapy), **All with second relapse,)patients with isolated testicular relapse were treated with modified CCG-112 protocol, $3 patients relapsed on therapy, 6 within 6 months off therapy and 3 beyond 6 months off therapy, @unclear if any of the relapsers had combined relapse and relapse at sites other than CNS not described, ++all patients underwent hematopoietic stem cell transplant, other treatment details not described, *3 patients out of 10 (7 of which were relapsed) patients surviving; outcome of relapsed ALL unclear, (only off therapy relapses included, !!underwent HSCT, &unclear if only isolated relapse; BM: bone marrow, CNS: central nervous system, O: ocular, T: testicular, NA: not available, SIOP: International Society of Pediatric Oncology, VE: very early, E: early, L: late relapse. Numbers in parenthesis indicate percentages.

but do not address treatment and outcome of relapsed ALL (Table 1) (Kulkarni et al., in press). Except as described by Goyal et al, limited therapy has been administered to most relapsed patients in sharp contrast to intensive therapy and bone marrow transplant employed in resource plenty nations. 2 studies on testicular relapse, 1 study on post-treatment relapse and 6 case reports have clearly depicted outcome of relapse (Shama et al, 2005). Only 1 study and a case-report have discussed use of hematopoietic stem cell transplant (HSCT) in 8 relapsed patients. The survival outcome except in a sole study is poor (Shama et al., 2005).

Based on the currently available data, the percentage of patients with relapsed ALL is likely high in India. Outcome of only a small fraction of the expected number of relapsed patients (out of the estimated 10000 new childhood ALL cases diagnosed annually) is published. It is currently difficult to estimate the overall post relapse survival for the entire country. However it is likely to be poor given the significant resource limitation along with socioeconomic and infrastructural constraints in several centers (Kulkarni et al, 2011). Additionally, high percentages of early, on therapy and extramedullary relapse in several series necessitate reappraisal of treatment protocols.

There is clear need of generation of accurate epidemiological data and reporting of all cases with a consolidated nationwide effort. Prospective trials with facilities for HSCT are pivotal in our endeavour to deliver adequate/appropriate therapy and care. Determination of cytogenetics, molecular and biological characteristics of relapsed disease would be helpful in identifying high-risk features relevant to local population and in advocating risk adapted therapy. With a potentially enlarging cohort of patients with relapse, focus needs to be on therapy and salvage of relapsed disease along with improvements in upfront therapy.

References

Arya LS, Kotikanyadanam SP, Bhargava M, et al (2010). Pattern of relapse in childhood ALL: Challenges and lessons from a uniform treatment protocol. *J Pediatr Hematol Oncol*, **32**, 370-5.

Kulkarni KP, Marwaha RK (2011). Second relapse in childhood acute lymphoblastic leukemia: a call for action. *Indian J Pediatr*,**78**, 362-3.

Kulkarni KP, Arora R, Marwaha RK (2011). Survival outcome of childhood acute lymphoblastic leukemia in India: a resource limited perspective over 40 years. *J Pediat Hematol Oncol*, (In press)

Kulkarni KP, Marwaha RK, Trehan A, Bansal D (2010). Testicular relapse in childhood acute lymphoblastic leukemia: the challenges and lessons. *Indian J Cancer*, **47**, 134-8.

Shama G, Bhagwat R, Pai SK, et al (2005). Isolated testicular relapse in acute lymphoblastic leukemia - effective treatment with the modified CCG-112 protocol. *Indian J Cancer*, **42**, 65-9.

Ketan P Kulkarni, Ram Kumar Marwaha*

*[1]Pediatric Hematology Oncology, Stollery Children Hospital, University of Alberta, Canada, [2]Division of Pediatric Hematology-Oncology, Advanced Pediatric Center, PGIMER, Chandigarh, India *For correspondence : ketanpkulkarni@gmail.com*