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A RETROSPECTIVE VIEW ON RECENT APPROACHES IN MANAGEMENT OF LEUKEMIA

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ABSTRACT

Leukemia is the most prevalent kind of cancer that is not caused by ageing, despite its low total incidence. 30% of all malignancies seen in children under the age of 15 are caused by it. Acute lymphocytic leukemia is diagnosed in this demographic about five times more commonly than acute myelogenous leukemia, accounting for around 78% of diagnoses of juvenile leukemia. In an attempt to pinpoint the etiology of acute leukemia, epidemiologic studies have examined possible contributing variables such hereditary, infectious, and environmental causes. Ionizing radiation is the sole environmental risk factor specifically connected to ALL or AML. Both types of acute nonage leukemia are intended to only occasionally and weakly correlate with the strongest environmental causal factors. The demography of non-age leukemia and the risk factors that have been connected to the development of non-age ALL or AML are the main topics of our study. Ionizing radiation, non-ionizing radiation, hydrocarbons, fungicides, alcohol consumption, cigarette smoking, and illicit drug use are a few of the environmental risk factors mentioned. Understanding these specific threat traits may motivate actions to cut down on possibly hazardous exposures and get rid of the complaint threat. It is also taken into account other aspects such the mother's reproductive history, birth features, and inheritable and infectious risk factors. The comprehensive characterization and experimental confirmation of all genetic alterations causing leukemogenesis and treatment failure in childhood and adult ALL, as well as the integration of genomic profiling into the clinical environment to improve risk assessment and targeted therapy, are among the future challenges.

KEYWORDS: Leukemia, malignancy, acute lymphocytic leukemia, acute myelogenous leukemia, risk factors, leukemogenesis, genomic profiling, risk assessment, targeted therapy.

INTRODUCTION

Hematologic malignancy known as acute lymphoblastic leukemia (ALL) develops in the bone marrow or in extramedullary sites as a consequence of unchecked lymphoid ancestor cell isolation, growth, and accumulation. Even though ALL most frequently affects children, treating ALL in adults can be much more challenging. An important source of inspiration for the curement of ALL is multiagent chemotherapy regimen utilised to treat pediatric ALL fifty years ago. This authority covers prevention, induction, connection, and conservation therapy for the central nervous system (CNS).Adult ALL has high full absolution rates (80–90), but the cure rate is only 50% because of relapses. In situations involving kids, the 5-year OS is around 90, while in cases involving adults and elderly, it is between 30 and 40. This problem may be influenced by adults with advanced risk traits, increasing comorbidities, and the emergence of chemotherapy resistance after recurrence. As a consequence of the goal to ameliorate adult ALL concerns, significant advancements have been achieved in pharmacological development, threat assessment, and disease etiology knowledge (Paul S *et al* 2016).Substantial development has been made in interpreting the biology of acute lymphoblastic leukemia (ALL), which is now recognised as a growing number of distinct entities. The discovery of varied gene expression patterns may lead to the identification of patient subgroups with different prognoses and therapy outcomes. The precise classification of prognostic groups based on cytogenetic-molecular tagging has enabled the development of threat-aware therapies. Complete response (CR) rates for adult ALL therapy algorithms that effectively included pediatric ALL treatment approaches were similar to those for pediatric ALL. Particularly notable improvements may be seen in subgroups like mature-B-cell or T-lineage ALL. (Faderl S 2003)

Epidemiology

In the bimodal distribution of ALL, individuals achieve the first peak at around five times their biological age, whereas the opposite peak occurs at about fifty times the

individual's age. As 80% in children and 20% cases in adults, it is primarily regarded as a pediatric leukemia. A patient is generally 14 years old when they get a diagnosis. When the patient is under 20 years old, around 60% of instances are found, followed by about 25% when she is about 45, and 11% when she is 65. In late childhood, nonage, and the young majority, ALL is rather infrequent. (Paul S *et al* 2016).

When it comes to children, white children are more often impacted than African-American children. Although there is little difference between males and females in childhood prevalence rates, males are more likely than females to have ALL as they get older. Over time, there has been no change in the prevalence of ALL. Recently, there has been an unexplainable little rise in the number of instances. (Faderl S 2003)

Etiology

The majority of the time, ALL has no identified cause. The Down pattern, Klinefelter pattern, Fanconi anaemia, Bloom pattern, ataxia-telangiectasia, and Nijmegen breakdown pattern are examples of inheritable runs that account for less than 5% of ALL cases. (Paul S Mayo Clin Proc. 2016 Nov) Despite the fact that the exact origin of ALL is unclear, genetic, maternal, socioeconomic, and environmental variables have all been taken into account. (Kantarjian, et al (2003). In 21(down pattern) syndrome instances, the risk of getting ALL is 20 times greater than in the general population. In addition, Fanconi anemia, the Bloom pattern, and ataxia-telangiectasia are chromosomally very fragile hereditary diseases associated with ALL. As a consequence of the tiny lemon explosions, other radioactive exposures comparable to the Chernobyl tragedy, exposure to corrective radiation, and in utero exposure, more instances of ALL have been documented. ALL incidences have been linked to an increase in the use of amphetamines before and during pregnancy, diet pills, and drugs that alter consciousness, as well as exposure to electromagnetic fields. The use of hair dyes, smoking, having a fireplace near artificial lighting, and being close fuel, diesel, and automobile pollution are additional risk factors. (Kantarjian, et al (2003).Other factors that have been linked to an increased incidence of nonage leukemia include ionising radiation, fungicides, and detergent usage during pregnancy. (Onciu M. 2009)

Symptoms

- Patients with acute leukemia often express tremendous tiredness and a general feeling of helplessness in their complaints. This is because it has been shown that acute leukaemia reduces the number of healthy blood cells, which leaves the patient anaemic and exhausted.
- One of the most typical signs of acute leukaemia is a high temperature, which is typically accompanied by shaking and heavy sweating. One of the most frequent signs of acute leukaemia is a high fever.
- Infections occur more often It is well knowledge that acute leukaemia inhibits the immune system, causing it compromised and becoming major challenge to fight off infections. This increases the risk of contracting recurrent infections like bronchitis or pneumonia.
- An acute leukaemia side effect is a decrease in platelets, which are essential for blood coagulation. Bruises and bleeding might happen from this. Because of this, bleeding and bruises could happen more often, including nosebleeds, gum bleeding, and even blood in the urine or stool. Acute leukaemia, especially in its latter stages, may result in joint and bone stiffness, especially in the hips and legs.
- One of the side effects of acute leukaemia is enlargement of the lymph nodes, which may be felt as fullness under the skin.
- Anxiety and swelling in the abdomen might be exacerbated by spleen and liver enlargement brought on by acute leukaemia. This discomfort and edoema could be the result of acute leukaemia.
- Given that there are several various medical disorders that might produce these symptoms, it is essential to see a medical expert in order to get an accurate diagnosis.

Risk factors

The known and hypothesized risk factors for leukaemia may be divided into three categories: environmental, lifestyle, and family and genetic factors.

Family factors

Only a very small percentage of cases involve inheritance, according to Kasim et al. (2005). A few chromosomal abnormalities are connected to leukaemia. For instance, the Philadelphia chromosome is linked to CML (usually through translocation 9/22). Greaves (2007) states that chromosomal disorders increase the likelihood of getting leukemia

Environment-related factors

These include exposure to benzene, chemotherapy, high doses of ionising radiation, and electromagnetic fields. According to Wallace (1989), benzene is a detergent that has been used in the leather, publishing, and petrochemical sectors, among other things. Exposure may come from both within the building and from outside sources like cigarette smoking. Long-established links between elevated leukaemia frequency and mortality exist, particularly for AML.

For AML, ALL, and CML, ionising radiation has been identified as a risk, but not for CLL. Pierce et al. calculated proportion of nuclear attack victims from 1950 to 1990 for the Life Span Study (LSS). 249 leukaemia deaths of the 1,572 individuals examined demonstrated a connection to radiation exposure. Preston et al. found that radiation exposure in Hiroshima and Nagasaki was to blame for 50 of all leukaemia incidences between 1950 and 1987. (Preston and others)

1994. Low dose radiation has no effect on the etiology of the illness, despite the fact that high dose radiation exposure raises the incidence of leukaemia (Zeeb and Blettner, 1998).

Risk factors connected to a lifestyle

Diet, obesity, and smoking all increase the risk of leukaemia. By exposing smokers to particular chemicals, including benzene, which are known to promote the illness, smoking increases the prevalence of leukaemia, especially myeloid leukaemia (Siegel & Friedman, 1993). In a substantial case-control study, smoking was linked to acute leukaemia, especially in elderly patients (Sandler et al., 1993). Smoking was shown to be causally related to myeloid leukaemia in a research conducted in Norway (England et al., 1997). In addition, neither the 2004 studies from the Surgeon General nor the International Agency for Research and Cancer (IARC) discovered any connection between active smoking and AML. (Andıç N *et al*).

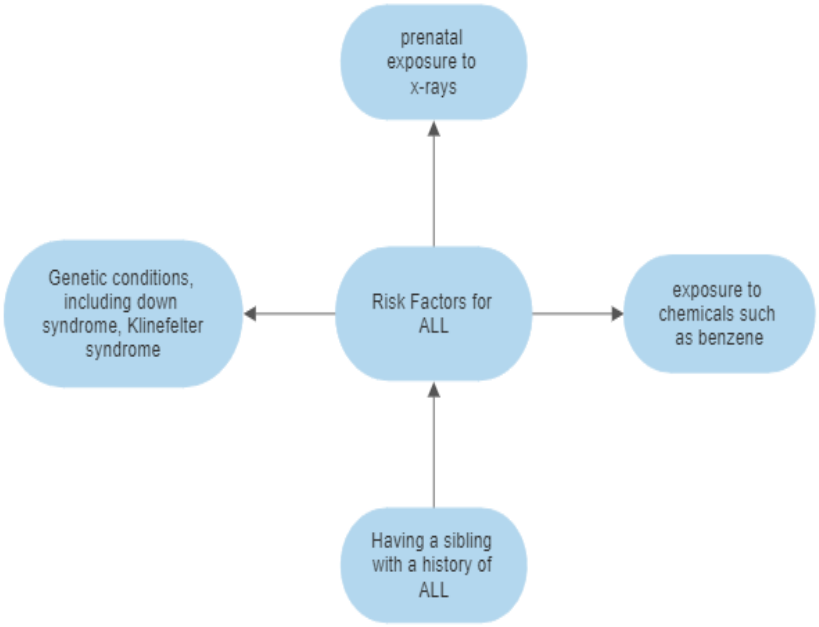

Fig. 1: Risk factors for ALL.

Diagnosis

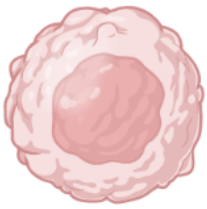

Fig.2: Tumor cell.

Fig.3: Oncolytic virus.

A prime illustration of the significant prenatal and clinic diagnostic diversity in adult ALL is the discovery of several ALL subtypes. It is crucial to differentiate between mature Burkitt (B)- ALL, B- or T-cell precursor ALL, and Philadelphia(Ph) chromosome-positive from Ph-negative ALL due to the very specialised therapies available for distinct ALL subtypes. (3) The bone marrow must have 20% or more lymphoblasts in order to diagnose ALL. The French-American-British structural characterization, which distinguished three subtypes of ALL based on cell size, cytoplasm, nucleoli vacuolation, and basophilia, were first used to identify ALL. Cytogenetic investigations are crucial for understanding the root causes of leukaemia and finding distinct prognostic subgroups. Different outcomes for children and adults with ALL are influenced by the occurrence of favourable and unfavourable karyotypes. Recently, various novel mutations in ALL have been discovered with the use of molecular research, including DNA copy number analysis, microarray profiling, and next-generation sequencing, which may result in abnormal pathway activation and cell survival. In both children and adults, B-cell ALL accounts for the bulk cases—roughly 90% in each case—while T-cell ALL reports for other instances. (Paul S *et al* 2016).

Novel Therapy: Molecular Targeted (Inaba *et al* 2021)

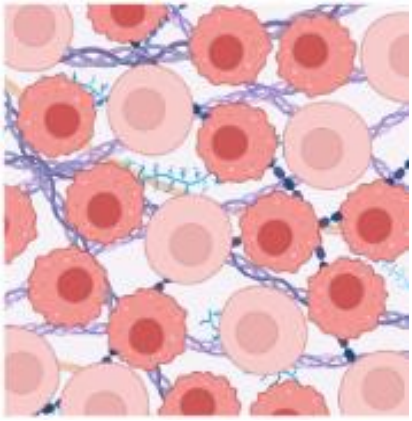

Fig.4: Tumor microenvironment.

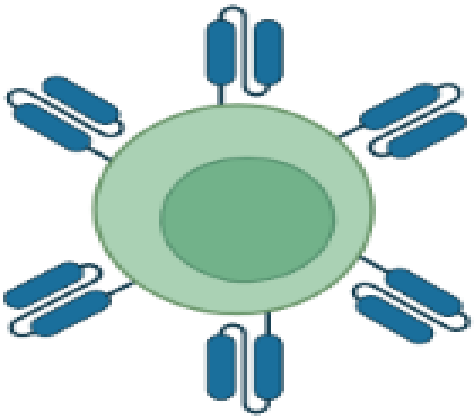

Fig.5: CAR-T cell.

Agents that Block Tyrosine Kinase

Tyrosine kinase inhibitors have been added to conventional chemotherapy to improve its effectiveness. While less than 10% of paediatric ALL cases benefit from this focused approach. As more ALL driving mutations and their targets are identified, the utilization of TKIs will increase.

BCL-2 and BCL-XL inhibitors

Through involvement between pro- and anti-apoptotic proteins, members of the B-cell lymphoma 2 (BCL-2) protein families play important function in intrinsic mitochondrial apoptosis pathway. Venetoclax with chemotherapy showed modest promise in phase I trials when used in paediatric and adolescent patients with ALL.

Agents that block proteasomes

Proteasome inhibitors are useful in the management of ALL and combine well with the doxorubicin and corticosteroids used in chemotherapy. Research is being done on recent proteasome inhibitors such carfilzomib and ixazomib.

Immunotherapy

Proteasome inhibitors are helpful in the treatment of ALL and work well with the chemotherapeutic drugs doxorubicin and corticosteroids. Recent proteasome inhibitors like carfilzomib and ixazomib are the subject of research. (Inaba *et al* 2021).

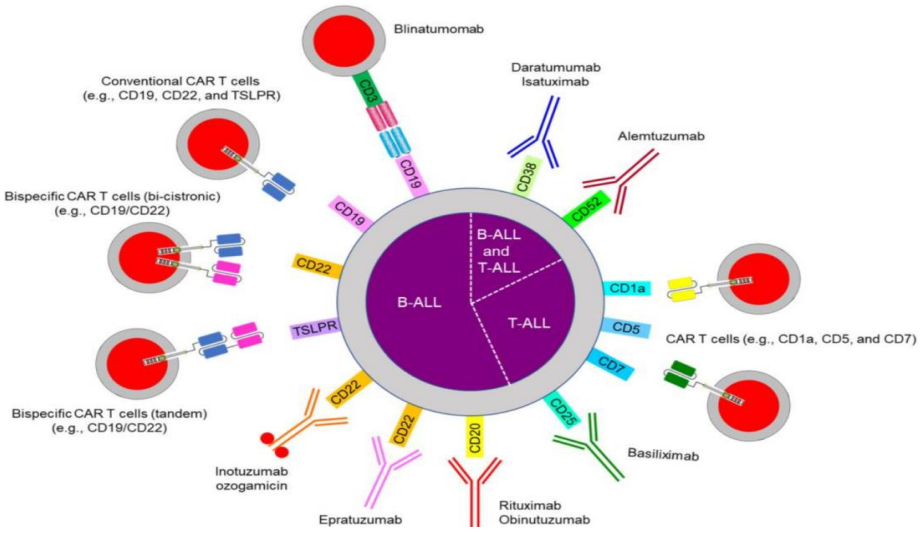

Fig. 6: Leukemia, acute lymphoblastic and immunotherapy. Acute lymphoblastic leukemia (ALL), thymic stromal lymphopoietin receptor (TSLPR), and chimeric antigen receptor (CAR) are among the terms.

Causes

Changes (mutations) in a bone marrow cell's DNA or other inheritable components result in acute lymphocytic leukaemia. A cell's DNA often contains instructions on how to grow and when to die. The mutations in acute lymphocytic leukaemia allow bone marrow cell to

continue dividing and proliferating. Then, the RBC formation goes out of control. White blood cells that are leukemic are produced in the bone marrow by developing cells known as lymphoblasts. These aberrant cells could congregate and push away healthy cells while failing to perform their essential functions. The origin of the DNA alterations that might lead to acute lymphocytic leukaemia is unknown. (Döhner H *et al* 2015)

Geriatric ALL

The average age of ALL instances referred to as "older" or "senior" persons and has been 60 or above. Historically, their 5-year OS has been terrible, at roughly 95. Bad biology and the difficulty of the elderly to take IC have been blamed for this prognosis. However, issues are improving as a result of the development of new TKIs and immunotherapies, the objectification of MRD for direct treatment, and the rising safety of ASCT for elderly cases. These new techniques, however, make it more difficult to manage these circumstances. The biology of the complaint, approved medical procedures, and cutting-edge treatment options for older ALL patients are the main topics of this section. (American Society of clinical Oncology Educational Book 40 (2020)

Ageing Patients with ALL and Biologic Issues

High-threat inheritable anomalies are frequent in older ALL patients. The Philadelphia chromosome was observed in around 50% of these instances. Previously, it was believed that the Philadelphia chromosome had low prognosis, but TKIs have greatly enhanced issues. The Philadelphia-like hand, which has been seen in around 24 elderly persons, has lately been linked to a bad outgrowth. Age influences with combinations predominate, with elderly people showing high amounts of CRLF2. Low hypodiploidy, complex cytogenetics, IKZF1 mutations, chromosome 17 abnormalities, and KMT2A rearrangements are more frequent in older persons with ALL than high hyperdiploidy. Finally, the B-cell phenotype is more common in older cases compared to the prevalence of the T-cell phenotype.

Patients with Philadelphia Chromosome-Negative ALL: Results of Conventional Therapy

Standard ALL therapy includes comprehensive induction therapy as well as post-remission therapy. Older people may find this challenging due to their comorbid diseases, including diabetes, heart problems, lung abnormalities, neuropathy, polypharmacy, and a decline in performance level. The widest research with IC for geriatric patients with Philadelphia-negative ALL, German Multicenter Study Group for ALL trial, 268 cases advanced than age 55 were attended with enhanced aggressive Berlin-Frankfurt- Munster Authority followed by post remission therapy. Clinical trials have identified some poor problems, but because many cases refuse treatment, problems are almost certainly worse when analysing "all moneybags." Rituximab was provided to those with CD20-positive complaints. The 5-time OS was 23 and 62 of the cases having an ECOG shows rating of 0 to 1. Corrections to the study included the addition of triadic intrathecal chemotherapy, asparaginase during post remission care, and tablets of methotrexate and cytarabine.

Philadelphia chromosome and ALL

The issues with Philadelphia chromosome-positive ALL have essentially been resolved by TKI treatment. Imatinib is an example of a first-generation TKI that has shown to have lower toxin levels and greater rates of absorption than chemotherapy alone. But with imatinib, absolution times have typically been short (8 months on average). Dasatinib, a more recent TKI, has shown better results. Nevertheless, only 20 cases had significant molecular absolutes and the corresponding survival rates at 20 months, both OS and complaint-free, were 69.2 and 51.1 respectively. Despite the fact that all cases had absolute hematologic results, this is the case. The resistant T315I Bcr-Abl mutation, which was present in 12 of the 17 patients that had relapsed, was the primary relapse mechanism among cases treated with earlier-generation TKIs. The only TKI being used in this instance is ponatinib. The combined effects of ponatinib and steroids were computed by the GIMEMA group. One-time OS, total molecular absolution, and CR each had independent frequencies of 95, 46, and 87.5. Major side effects of ponatinib were decreased to 13 (in 44 cases). Due to the cardiovascular risks associated with ponatinib, care is suggested, and the medication's dose should be reduced until full molecular absorption has been reached. (Noah A. Brown *et al* 2020)

Recent Clinical Trials for Philadelphia-Negative ALL Patients

As a result of adverse effects associated with conventional IC, several recent studies are lowering chemotherapy and introducing novel medicines. Isotuzumab, anti-CD22 antibody combined with cytotoxic medication calicheamicin, shown enhanced rates of CR, MRD, and zilches in cases with R- R B-ALL requiring salvage therapy. Inotuzumab and low-intensity chemotherapy have recently been used in cases with B- ALL with Philadelphia-negative that were at least 60 years old. Inotuzumab and low-intensity chemotherapy are usually well-tolerated drugs with a distinctive hepatic VOD toxin for curement of R- R B-ALL in response. 52 patients were treated, and the average age was 68. In 8% of instances, VOD occurred more often than treatment-related mortality, which occurred in 12% of cases. A typical 29-month follow-up period demonstrated a fantastic 2 times progression-free survival rate of 59%. The Bcl-2 asset of chemotherapy and navitoclax + venetoclax was computed in R- R ALL, where Bcl-2 is overexpressed in ALL, and venetoclax is likely to be a Bcl- 2 asset in both B- ALL and T- ALL. (Noah A. Brown *et al* 2020).

Future Strategies for Geriatric with ALL

Philadelphia anticipates a lot of new agents, which is both positive and detrimental for ALL. These techniques are being examined in clinical studies. Problems in ageing seniors are probably going to become better if these medicines are objectified and replaced with less-intensive treatment. Due to Philadelphia-like differences and MLL rearrangements, TKI-based therapy and MLL barriers combined with low-cure treatment may be different choices for the patients. Although auto T-cells are currently being used in clinical trials, the FDA has not yet approved their use in adults under the age of 26. Given their emotional clinical effort, they are likely to develop into a viable option for older adults as their venom is optimised. Future clinical studies will certainly include the use of MRD to direct therapy as blinatumomab has recently acquired FDA permission for use in MRD-positive patients. Transplantation is gradually becoming a possibility for instances that originally would not have been considered when issues with reduced-intensity ASCT are addressed and there are more benefits. Recent studies demonstrate that effective "senior" campaigners have favourable results. (DeAngelo *et al* 2020)

New Technologies in Every Treatment

Because of advancements in ALL therapy, the danger level given to certain categories, like T-lineage ALL and mature adult B-cell ALL, has altered. Because of the substantial progress in therapy over the last 20 years, prognostic, clinical, laboratory, and biologic signs that were formerly considered to be useful are now of limited use. Other prognostic factors can be explained by overriding inheritable molecular abnormalities, which are increasingly recognised as significant predictors of outgrowth. (Faderl S *et al* 2003)

Current genetic techniques

Recent advances in high throughput analysis of DNA clone number and mRNA expression, as well as the sequencing of the human genome, have made it feasible to create a "molecular portrayal" of leukaemia. Gene-expression profiling may be used to classify ALL patients, provide fresh understanding of the pathways underlying the several inheritable subtypes of ALL, and establish connections between novel pathways underlying treatment resistance and potential therapeutic targets (Rob Pieters Volume 55)

Possession and Novel therapeutic methods

With increased chemotherapy and additional SCT, there still appears to be a small window of chance for adult ALL to improve. This is particularly true for the sizeable groups of older individuals with ALL who have not been looked at in several studies. The regular emergence of novel, creative therapeutic approaches in recent years is so beneficial. One of these cutting-edge approaches to treating adult ALL involves molecular targeting employing kinase impediments, which substantially disrupt molecular pathways engaged in pathogenesis. Antibody therapy provides a novel specific therapy without the traditional poison of chemotherapy. The expansion of SCT must involve novel techniques that calculate on graft-versus-leukemia products similarly to non-myeloablat. (Hoelzer D *et al* 2002).

Stem cell transplantation and chemo

Table 1 shows the outcomes of chemotherapy, which partially included SCT, in treating adult ALL. The table includes recent smaller trials with more than 100 patients that show promising outcomes with intensive treatment regimens, as well as big multicenter studies with >500 patients that likely gave the highly accurate view of the prognosis of adult ALL.

Adoption of treatment

Prednisone, vincristine, anthracyclines, and L-asparaginase are often utilized in induction chemotherapy. In several treatments that are frequently referred to as early intensification, additional medications such cyclophosphamide, cytarabine, mercaptopurine, and others are administered. To increase CR rates and subsequently remission quality in adult ALL, many novel strategies are presently being investigated.

Dexamethasone

Prednisone is substituted with dexamethasone because it may have more antileukemic effects on systemic illness but also results in larger drug concentrations in cerebrospinal fluid. However, prolonged utilized of dexamethasone can be linked to a higher threat of septicemias and fungal infections, which may be avoided by reducing administration frequency and dosage.
(Inaba H *et al* 2021)

Cyclophosphamide

In various investigations, the function of cyclophosphamide (C), which is often given at the start of induction treatment, has been examined. The 3-drug induction with and without C did not vary in terms of the CR rate, according to a randomized research by the Italian GIMEMA group (81% vs. 82%).6 High CR rates were nonetheless attained with regimens using C procurement in a number of non–randomized studies, especially in adult T-ALL.

Anthracycline

The strength and scheduling of anthracycline doses may be crucial in ALL induction treatment.16 Daunorubicin was formerly often given on a weekly basis, but newer studies have increasingly used dosage enhanced with doses of 30-60 mg/m^2 given every 2-3 days.

A monocenter researches showed a relatively high CR rate for intense anthracycline treatment, while a larger multicenter experiment did not find this.18 greater induction mortality may be linked to intensive anthracycline treatment. As a result, these kinds of treatments are advised together with extensive supportive

care and maybe utilization of growth hormones. (Inaba H *et al* 2021)

L-asparaginase

Three alternative preparations with noticeably varying half-lives are available for L-asparaginase (A), which is also often used in induction therapy: Native E. coli A, Erwinia A, and PEG-L-A. The application schedule must be changed to achieve equivalent effectiveness, which is typically daily for Erwinia, every other day for E. coli, and once to twice per week for PEG-A. A children ALL randomized study that found that Erwinia had considerably worse survival rates than E. coli A, both of which were administered on the same schedule, serves as an example of the significance of A pharmacokinetics.20 A randomized experiment distinguish PEG-A with E. coli A in paediatric ALL found that the latter had a greater early response rate but no difference in the long-term prognosis.

Cytarabine at high doses

In order to obtain stronger antileukemic activity and in addition to prophylaxis CNS recurrence without cranial irradiation, high-dose cytarabine in induction treatment has been employed in various studies.

Greater induction mortality was partly responsible for the increased CR rates produced by upfront application before to conventional chemotherapy as opposed to application subsequently. Furthermore, any HDAC-based induction treatment may raise the risk of severe neutropenias during future chemotherapy rounds.

Growth Elements

The preventive utilization of growth factors has highly significant function in treatment of adult ALL with increased dosage intensity of induction therapy. Numerous researches shown that G-CSF may administered along with induction treatment and greatly shorten neutropenic episodes.23,8 Due to decreased early mortality G-CSF also had higher CR rate (90% vs. 81%) in a placebo-controlled trial.8 Therefore, it is likely possible to attain a greater dosage intensity and improved tolerance of chemotherapy with G-CSF support. Whether this results in an increased LFS or overall survival is yet uncertain.

After-induction care

SCT, high-dose chemotherapy regimens, and intense rotational consolidation treatment make up majority of post induction therapy. Trials using rigorous multidrug consolidation treatment often had better results (median: 27–36%) than trials without consolidation (median: 25%).13 Additionally, this was supported by lone randomised studies or historical comparisons1,10, but not by other trials.6,7 Scheduling the intensification could be important. To conquer drug resistance and reach therapeutic medication levels in the cerebrospinal fluid, high-dose chemotherapy, HDAC or HDM, has been utilized. The conclusion is that the addition of HDAC, HDM, or both may be advantageous, especially when incorporated in chemotherapy regimens that involve rigorous rotating conventional dose chemotherapy with LFS rates that are more than 40%. (Inaba H *et al* 2021)

Transplanting stem cells

Consolidation therapy for adult ALL must include bone marrow-derived stem cell transplantation and, to a greater or lesser degree, peripheral blood stem cell transplantation (PBSCT). Allogeneic SCT should be given to first CR patients with a compatible sibling donor, or should it only be given to those with high risk characteristics? Additionally, it is important to assess the benefit of matched unrelated SCT, which can be linked to a decreased recurrence rate, autologous SCT, and novel techniques including non myeloablative transplantation and innovative conditioning regimens, such as those using radiolabeled antibodies and donor leukocyte infusions. Early SCT (mostly from matched related donors) has been used in a number of recent or continuing researches, however it has not yet been shown that this method affects final results.

(**Table 1:- Study findings on adult acute lymphoblastic leukemia) Studies with >500 patients (ALL).**

Group	GMALL 02/84 1	FGTALL 2	MRC-UKALL XA3	MRC/ECOG 4	GMALL 05/935	GIMEMA 02886	Total (%-weighted mean)
Year	1993	1993	1997	1999	2001	2002	
n(pts)	562	581	618	920	1163	794	4638
Age	28	33	>51		35	28	
Induction	V,P,A,D,C, AC,M,MP	V,P,D/R,C[AD,AC]	V.P,A,D	V,P,D,A,C,AC, MP	V,P,A,D,C,AC,M, MP	V,P,A,D,C,[HDAC,Mi]	
Consolidation	V,DX,AD,A C,C,TG.VM	ADAC,A	[AC,VP,D,TG]	HDM,A [AC,VP,V,DX, D,C,TG]+ SCT	V,DX,AD,AC,C, TG,VM,AC,HDM ,A,C[HDAC,Mi]	V,HDM,HD AC, DX,VM	
Maintenance	MP,M	MPM,V,C, P,AD,AC	MP,M,V,P	MP,M,V,P	MP,M	MP,M,V,[A C,MI,VM, HDAC,HD M,DX]	
CR (%)	75	76	82	89	83	82	82
LFS	39% at 7y	30% at 10y	28% at 5y			29% at 9y	31%

Recent studies with >100 patients

Group	Pethema ALL-937	CALGB 8	CALGB 8	MDACC 10	Lombardia 11	Netherlands 12	Total (%-weighted mean)
Year	1998	1998	1999	2000	2001	2001	
n(pts)	108	198	120	204	121	193	944
Age	28	35	44	39	35	33	
Induction	V,P,D,A,C	V,P,D,A,C	HDAC,C,D,V, BX	VAD,DX, C	I,V,A,P.[C]	Standard	
Consolidation	HDM,V,D,P,A,C, VM,AC	CMP,AC,V ,A,M,AD,D X,TG,P	AD,HDAC,V,B X,C,D,VP + SCT	HDM,HDA C,C,P	I,V,C,VM,HD AC,HDM,DX +SCT	HDAC, VP16 + allo /auto SCT	
Maintenance	MPM [V, P, Mi, A, C, VM, AC]	MP,M,V,P	n.r.	MP,M,V,P	MP,M	---	
CR (%)	86	85	85	91	84	82	86
LFS	41% at 4y	36% at 3y	36% at 3y	38% at 5y	49% at 3y	35% at 5y	38%

Abbreviations: n.r not reported; CR complete absolution; LFS, leukemia free survival; V, vincristine; P, prednisone; A, asparaginase; D, daunorubicine; C, cyclophosphamide; AC, cytarabine; M, methotrexate; MP, mercaptopurine; DX, dexamethasone; announcement, adriamycin; TG, thioguanine; VM, teniposide; R, rubidazone; VP, etoposide; HDAC, high cure AC; HDM, high cure M SCT. Stem cell transplantation Mi. mitoxantrone BX. betamethasoneI. Idarubicin.

Table 2: Adult acute lymphocytic leukemia (ALL) therapy and management options.

Molecular therapy
• Direct suppression of pathogenic molecular abnormalities.
➢ Farnesyl transferase inhibitors, tyrosine kinase inhibitor STI571.
Antibody therapy
• Leukemic blasts are selectively suppressed based on the expression of their surface antigens.
Non-myeloablative stem cell transplantation
• Extension of stem cell transplantation indications to elderly/comorbid patients using graft-versus-leukemia effects.
Minimal residual disease evaluation
• Examination of each patient's reaction to therapy.
➢ A therapy's components, such as induction, innovative medicines, and risk stratification, are evaluated.
Microarray analysis
• Gene expression patterns are analysed, and differentially expressed genes are chosen.
➢ Identification of target genes and prognostic variables for new.

Future directions

As per the inspiring results obtained using monoclonal antibodies, bispecific antibody structures, and CAR T-cells, corrective tools vital to solve issues in cases of adult ALL may now be available. These therapeutic options can be combined to produce the deepest remittals possible because they are additive rather than competitive. In the frontline environment, they are now logically combined, which can diminish the requirement of prolong IC and avoid ASCT in several patients.

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