Management and treatment in acute lymphoblastic leukemia: A review article

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ABSTRACT

Acute lymphoblastic leukemia (ALL) or acute lymphoid leukemia is a type of acute leukemia, or cancer of the white blood cells that characterized by the overproduction of immature and cancerous white blood cells known as lymphoblasts. Patients with ALL, overproduction of lymphoblasts are characteristic in the bone marrow and continuously multiply, causing damage and death by inhibiting the production of normal cells (platelets, red and white blood cells) in the bone marrow and by spreading to other organs. ALL is most common in childhood with a peak incidence at 2–5 years of age, and another peak in old age. Development of ALL can be initiated from any lymphoid cell blocked at a particular stage of development, including primitive and stem cells with multilineage potential. Transplantation of hematopoietic stem cell from an allogeneic source is being increasingly used for pediatric patients with ALL in subsequent complete remission or second remission after marrow relapse, as well as in patients in first complete remission but with high-risk characteristics. But, for approximately 75% of the patients, HLA-identical sibling donors are not available.

Genetic abnormalities in ALL:
Specific genetic abnormalities (e.g., chromosomal gains or losses, resulting in hypodiploidy or hyperdiploidy, respectively; chromosomal translocations, leading to dysregulation of gene expression or the formation of transforming fusion genes; and deletion or functional inactivation of tumor-suppressor genes) are found in the blast cells of 60% to 75% of patients with ALL[1-4]. The recognition of these abnormalities is so helpful to understand the prognosis and pathogenesis of the disease. In a recent study, criteria for defining a low risk of recurrent and newly diagnosed B-cell–precursor ALL disease in children are: an age of 1-9 years and a leukocyte count < 50,000 per cubic millimeter[1]. Patients with higher leukocyte counts and age groups were considered to be at high risk. Among children less than one year old, 70 to 80 percent have rearrangements of the MLLgene. In adolescent and adult patients, the frequencies of BCR–ABL fusion and MLL rearrangements are high. A risk-assignment system according primary genetic abnormalities has great intuitive appeal; however, the predictive value of genetic abnormalities criteria is not high. For example, a relapse would be occurs as many as 20 percent of children with ALL who have hyperdiploidy or the ETV6–CBFA2fusion. Although the presence of BCR–ABL fusion cells usually indicates high-risk leukemia warranting hematopoietic stem-cell transplantation, patients with leukocyte counts at diagnosis and this pattern of genetic abnormality have low and maybe good early responses to prednisone therapy may be cured by only intensive chemotherapy[5]. Poor prognosis would take place in Patients with markedly hypodiploid leukemic cells and near-haploid or, regardless of their initial white cell count or age, should undergo therapy as aggressive as that given to patients with standard-risk leukemia. Infants with the (t;4;11) translocation and MLL–AF4 fusion, patients with B-cell–precursor ALL with MLL gene rearrangements, usually have a low response to chemotherapy. But, some patients with MLL rearrangements who have a good response: patients with T-cell leukemia, t(1;19) translocation and MLL–ENL fusion. Although T-cell ALL is treated commonly as standard-risk leukemia at many centers, patients with delayed early responses or high leukocyte counts (more than...
100,000 per cubic millimeter) require even more intensive central nervous system specific therapy than other patients with this type of immunopheno type[6].

Analyses of cancer cell chromosomes revealed that specific and recurrent genomic abnormalities, such as 9 and 22 chromosomes translocation in CML (‘Philadelphia’ translocation) are related to particular cancer types. Finally, it was showed that the total genomic DNA from human cancers into phenotypically normal NIH3T3 cells may cause converting them into cancer cells[7].

One of the most important characters of ALL is lack of expression of the T-lineage cell surface markers such as CD1a and CD8; aberrant expression of myeloid and weak or absent expression of CD5, and a gene expression profile reminiscent of the murine early T-cell precursor. ALL cases commonly present with a high burden of DNA number alterations. To define the landscape of genetic alterations in ALL, a study perfumed to match leukemic and normal DNA from 12 children with ALL to determine the frequency of mutations. They identified an average of 1.140 sequence mutations and 12 structural variations per case. 54% of the missense mutations were predicted to be deleterious indicating that many of these variants are involved in leukemiaogenesis[8].

Primary care in ALL patients:

An important step in providing suitable medical care to survive child from cancer is to obtain accurate information about the prior therapy and diagnosis. A medical history obtained from the patient probably will not be complete, the age of treatment, the time since treatment, and the exposure to some therapies that may bealter cognitive function. The current recommendation for help providers in pediatric oncology is to provide every patient with a treatment summary, while adult survivors may not have access to such information[9]. Treatment summary contains information regarding the previous diagnosis, therapy, and potential side effects of therapy after a while. If taking a treatment summary is not possible, the patient, medical records, and the patient’s parents are reliable resources to construct a summary. Treatment summary taking, provides a chance to follow-up patients based on the known risks of therapy, and the presence of symptoms and signs to suggest conditions associated with previous disease or treatment[10]. Adult patients who have been survived from childhood cancer are at higher level of risk for subsequent cancers, because of former exposures to radiotherapy or chemotherapy and, in some other survivors, because of increased familial risk of cancer. The cumulative incidence of a secondary cancer possibility thirty years after ALL treatment is 5.2% but patients in continuous remission for more than twenty years after diagnosis have almost no risk of ALL recurrence, but the risk of myelodysplasia and therapy-associated with acute myelogenous leukemia, (usually during the first fifteen years after treatment) would be increased; this risk and latency after depending on the primary chemotherapy received[11]. About 80% of solid tumors in ALL survivors occur in patients who received radiation therapy as a part of their therapy plan. It seems the incidence of secondary solid tumors in ALL patients does not appear to plateau over time. In a study that carried out on 2169 ALL survivors, the cumulative incidence of a secondary solid tumor after radiation treatment within 20 years after remission was 5.4% and 30 years after remission was 10.8%. Tumors that appear after radiotherapy include soft-tissue sarcomas, thyroid cancers, parotid-gland tumors, brain tumors, squamous-cell and basal-cell carcinomas, and bone sarcomas. Irradiation to the cranium is associated with an increased risk of meningioma, with cumulative incidence of 4% to 6% within 30 years after leukemia diagnosis[12]. Studies involving MRI surveillance for meningioma show a higher cumulative incidence of occult disease (within 20 years, 15-22%) and have shown synchronous detection of multiple meningiomas in some cases. In the CCSS, the cumulative incidence of nonmelanoma skin cancer in ALL survivors was 10% at 30 years, and these skin cancers accounted for nearly 30% of the secondary cancers among ALL survivors in a British cohort. Given the increased risks of a secondary cancer, guidelines for the care of ALL survivors emphasize a detailed assessment of the family history with attention to a possible cancer-predisposition syndrome; physical examination, particularly of skin and of irradiated sites; and education regarding healthy lifestyle behaviors, sun protection, and prompt reporting of signs and symptoms[12,13]. Guide-lines do not recommend active surveillance for meningiomas in asymp to matic survivors, but there should be a low threshold for radiographic evaluation of neurologic symptoms in patients who received cranial irradiation[14].

The development of treatments that target cancer stem cells is an important objective, but the challenges are formidable. First, to design treatments that selectively eradicate stem cells of cancerous tissue, it is necessary to have the cognate normal stem cell or progenitor cell. This step needs the development of assays to characterize the function of normal stem cells and the means to define physical features that will allow their isolation. Second, we need the way to describe stem cells of cancerous tissue and appropriate functional assays must be validated. Third, it is critical to know how cancer stem cells alter from normal stem cells to malignant cells, particularly with regard to mechanisms that control cell survival and responses to injury[15]. Ideally, a treatment plan should target pathways uniquely used by cancerous stem cells to resist extrinsic insults or to maintain steady-state viability. Fourth, it’s better to know how therapies that effectively target the tumor cells fail to eradicate cancer stem cells. The reasons for this phenomenon may provide important and useful clues for developing more effective regimens with fewer side effects to attack to tumor stem cells and the bulk of the
Another challenge in targeting cancerous stem cells is to understand how the properties of stem cells make them difficult to kill. Cancer stem cells of Leukemia reside in a largely quiescent state with regard to cell-cycle activity, like their normal counterparts. Consequently, typical cytotoxic drug regimens that target rapidly dividing cells are unlikely to eradicate these types of cells. Therefore a requirement of selective targeting will be using regimens that kill cells independently of the cell cycle, or that selectively induce cycling of cancer stem cells. Another common feature of stem cells is expression of proteins related to the efflux of xenobiotic toxins.[17] A variety of cancer cells, especially during relapse, express such proteins, thus providing resistance to many chemotherapeutic agents. A newer concern is that normal progenitor cells and stem cells may be more sensitive than cancer stem cells to the effects of chemotherapy drugs. For example, Normal colon stem cells, inhibit DNA repair mechanisms and so undergo apoptosis in response to DNA damage: this mechanism prevent the accumulation of harmful mutations.[18]. If, cancerous cells in colon evade this protective mechanism, chemotherapy regimen could preferentially spare them. Recent studies have demonstrated that normal hematopoietic stem cells undergo premature senescence when exposed to ionizing radiation or busulfan. This process interrupts the potential development and growth of hematopoietic stem cells.[3]. If leukemia stem cells fail to undergo senescence, then it would expect that malignant stem cells have a growth advantage after treatment with certain agents. Moreover, successive cycles of chemotherapy only exacerbate the situation by increasing harm to the normal stem cells and increasing the growth advantage of cancer stem cells, which are resistant to senescence. If a clinical remission is achieved, a relapse can be initiated by the presence of residual drug resistant cancer stem cells. Hence, developing better methods for quantization and detection of cancer stem cells in patients receiving cancer therapy is necessary. Important findings in leukemia revealed that the level of residual disease that correlates with the longterm outcome; if the primitive leukemia cells counts can be reduced below critical threshold levels, it may not be necessary to completely eradicate the malignant bulk. Whether these residual primitive cells are truly cancer stem cells remains to be determined, but the findings suggest that sensitive real-time methods of cancer stem cells detection are a critical priority[19]. In designing specific drug regimens for stem cells cancer tissue, many strategies should be considered. Given the likelihood that impairs regulation of self-renewal is central to pathology of cancerous stem cell; targeting pathways that mediate self-renewal is an effective option. Another important factor is the degree toleration which inhibition of self-renewal mechanisms can be done, because the pathways controlling self-renewal mechanisms are central to a variety of biologic functions. But, even if the targeting of self-renewal pathways is possible, we do not know if it would kill cancer stem cells completely or just suppress them[20]. For these reasons, an alternative is to interrupt the cancer stemcellspecific survival pathways. For example, strategies that inhibit survival mechanisms of the cell may be selectively cytotoxic to leukemia stem cells. Ligand based or antibodybased therapy also appears to be a promising way to destroy cancer stem cells. A few number of target antigens on cancer stem cells have been discovered, and with further characterization of purified populations, other targets are likely to become available. It remains to be clarifying, but, whether these and other targets will distinguish stem cells cancerous tissue from normal tissues[21].

The knowledge about heterogeneity of ALL disease has led to treatment directed according to genotype, phenotype, and risk. So, mature B-cell ALL is the only subtype of ALL that is treated with short term intensive chemotherapy. For other patients, specific treatment approaches differ but consistently emphasize on remissions that use induction therapy followed by intensification therapy and continuation treatment to eradicate residual leukemia.[22]. Therapy targets the central nervous system, which starts as soon as possible in the clinical course, is given for varying periods, depending on the intensity of systemic treatment, the relapse risk in patients, and whether or not cranial irradiation is used. It should be noted that the effect of individual drugs within the context of a combination regimen depends on the types of drugs, dosage and schedule of administration on the given simultaneously[23]. Eradication of more than 99 percent of the initial burden of leukemia cells, to restore normal hematopoiesis and performance status is the goal of remission-induction therapy. This treatment phase almost includes the administration of a vincristine, glucocorticoid, and at least one other agent (commonly anthracycline, an asparaginase, or both). Children with high risk or very high risk ALL status and almost all young adults receive 4 or more drugs during therapies that induce remission[24]. Improvements in chemotherapy and supportive care have resulted in complete remission rates of about 98% for children and about 85% for adults. However, for children, intensive induction therapy may not be necessary with a standardrisk ALL, provided that they receive adequate postinduction intensification therapy.Overly aggressive induction therapy may, in fact, causes increased morbidity and mortality rate. The use of high-dose cytarabine, cyclophosphamide, or high-dose ofanthracycline has yielded no specific benefit in adults, maybe because such therapy is poorly tolerated by older patients. Maybe because of its longer half-life and its increased penetration into the central nervous system, the use of dexamethasone in post remission and induction therapy appears to provide better control in the central nervous system and systemically than do either prednisolone or prednisone[25]. But, a study recommended that an increased dose of prednisolone in the therapy regimen of other intensive treatment can yield results similar to those achieved with dexamethasone. The development of a tyro-sine kinase inhibitor such as imatinibmesylate, has enhanced the management of leukemia with fusion of
BCR-ABL, especially in elderly adults. Imatinib can use as a single agent or as a part of combination regimens has successfully induced and consolidated remissions. Although its ability to improve the chance of cure rate remains uncertain, imatinib has definitely contributed to extended disease-free survival and improved quality of life among these patients with ALL[4].

**Stem cell therapy:**

Allogeneic stem cells transplantation is usually indicated for patients who do not have a suitable response to the initial treatment and those who have a second remission after a hematologic relapse. But, in children who have late relapses after anti-metabolite treatment (>36 months after induction), may be defer transplantation until a subsequent relapse, because patients with ALL disease have a significant chance of cure with retrieval chemotherapy alone. There is controversy about Transplantation during the first remission[26]. But, because of their poor prognosis, patients with the BCR–ABL, or MLL–AF4fusion gene are commonly treated with transplantation of allogeneic stem-cell during the first remission. For patients who require transplantation of allogeneic stem-cell but have no suitable family donors, allograft from matched unrelated donors is a good option and have yielded encouraging results[27]. Results of another study show the, grafts transplantation from unrelated donors was as effective as transplantation of matched sibling donor grafts. Transplantation of autologous bone marrow and blood stem cell of umbilical cord has also been attempted. Preliminary results proved that transplantation of cord-blood stem cells is possible, especially in children; an important advantage of this approach is that it does not require the same degree of histocompatibility as transplantation of hematopoietic stem cells from adults. Whether the lower risk of GVHD (graft-versus-host disease) might be occurred by a diminished graft-versus-leukemia effect and hence a higher risk of relapse remains to be determined[5].

Transplantation from allogeneic sources the ultimate form of treatment intensification procedure. In adults with ALL, long term disease free survival rates of 30% to 40% have been achieved with the use of chemotherapy regimen, as compared with 45% to 75% with the use of transplantation from allogeneic source. Interpretation of these findings is complicated by the criteria used to choose patients for transplantation and by the limit numbers of patients studied[28]. Even so, transplantation from allogeneic sourcesobviously benefits many veryhighrisk adult and pediatric patients, such as those has been detected as BCR-ABL+ALL or those with a poor initial response to treatment regimen. Findings show that the procedure also appears to improve the clinical outcome in adults who have some certain subtype of ALL such as t(4;11), but whether it has advantages for infants with the same genotype remains unclear. Some studies suggest that among adults patients, transplantation with cells from cord blood could or from a matched unrelated donor results similar to those achieved with matched relateddonor transplantation. So, the indications for transplantation should be strongly evaluated inlight of improvements in this procedure and in chemotherapy procedure (nejmra052603).

**Conclusion:**

Transplantation of hematopoietic stem cell from an allogeneic source is being increasingly used for pediatric patients with ALL in subsequent complete remission or second remission after marrow relapse, as well as in patients in first complete remission but with high-risk characteristics. But, for approximately 75% of the patients, HLA-identical sibling donors are not available, and unrelated donors, matched at the allelic level, cannot be found in time for all patients[29]. Thus, alternative donor sources transplantations such as unrelated haploidentical stem cells or cord blood are increasingly used. The Perugia Group has first shown that in adult patients with hematologic malignancies (including ALL) who received a transplant from an HLA-disparate relative, that the infusion of a huge number of T cell depleted CD34 cells ensures sustained engraftment of donor hematopoiesis and lowering the risk of acute and chronic GVHD. The feasibility of haplohematopoietic stem cell Transplantation was reproduced also in children, especially in patients with ALL, transplanting high numbers of positively selected stem cells. But, data on the role of haplohematopoietic stem cell Transplantation in childhood ALL are still limited and analyzing report outcomes and risk factors that are available in the literature include a limited number of children is necessary[30].

**REFERENCES**