Treatment of Adult ALL

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Initial Evaluation

The initial evaluation of cases of suspected adult ALL should include histochemistry, flow cytometry, cytogenetics, and molecular testing for bcr-abl. Histochemical stains with peroxidase and esterase can help identify cases of myeloid leukemias or biphenotypic leukemias. Flow cytometry will help establish a diagnosis of ALL and will indicate whether the lineage is B or T-lymphocyte in nature. The small percentage of cases of mature B-cell ALL (Burkitt's leukemia) will be identified by the lack of TdT and by the presence of surface immunoglobulin expression. There is also strong expression of CD20, not seen in most ALL. For the dominan group of precursor B-lineage ALL, the lack of CD10 expression can point in the direction of a pro-B ALL that may have the 11q23 cytogenetic abnormality. Of note is that almost all cases with Philadelphia chromosome-positive (Ph+) ALL co-express CD19 and CD10. Among the T-cell ALLs, it is important to identify the presence of CD2 expression. The primitive pre-thymic T-cell ALL cases have a poor prognosis, as do the mature post-hymic cases that co-express CD2 and CD3 but lack CD1a expression.

Standard cytogenetics are very important in the evaluation of ALL. Only a small fraction of adult cases will have true hyperdiploidy, as is seen in pediatric ALL, but these cases have an unusually favorable prognosis and should be identified. In the adult situation one is primarily concerned with identifying t(4,11) or other 11q23 abnormalities and identifying t(9,22) or the Philadelphia chromosome. A small percentage of cases have monosomy 7, and this is also a very high-risk patient group..

It is imperative that cases with B-precursor ALL be evaluated with molecular probes for bcr-abl, and this abnormality can be missed with standard cytogenetics. These patients require a different approach including tyrosine kinase inhibitors and should also have allogeneic stem cell transplant as part their initial therapy when possible.Among the bcr-abl-positive ALLs, the p190 abnormality is somewhat more frequent than p210 and also indicates a more aggressive disease.

Induction therapy

With modern induction chemotherapy at least 90% of younger adults (up to age 60) should enter complete remission. The backbone of induction therapy includes Daunorubicin, Vincristine, Prednisone, and Asparaginase. It is not clear that the addition of Cyclophosphamide adds to the effectiveness. Patients with Ph+ ALL should have imatinib or dasatinib added concurrent with initial chemotherapy, and this has made a major difference in both short-term and long-term prognosis. The remission rate has improved from 60% to 90% with the use of concurrent chemotherapy and the tyrosine kinase inhibitors. Patients over age 60 with ALL tolerate asparaginase poorly, and this should probably be omitted for these older adults.

Many adult oncologists feel uncomfortable with the use of L-asparaginase, and it is important to recognize how useful this drug has been in the

management of ALL. Early studies in pediatrics showed a significant single-agent response rate, and when it was added to vincristine and prednisone the complete remission rate increased substantially from 80% to 90%. Early studies in adults also showed an improvement in complete remission rate from 30% to 50% with the similar addition of asparaginase to vincristine and prednisone. Common toxicities of asparaginase include hyperglycemia which requires monitoring and management, as well coagulopathy which tends not to cause bleeding but rather can lead to an incidence of thrombosis. The more serious toxicities of Asparaginase include hepatotoxicity which can be severe and even fatal. There are also occasional severe anaphylactic reactions that can be quite dangerous. Recent studies in pediatrics have highlighted the efficacy of asparaginase and its important role in post-remission therapy and in increasing the long-term cure rates. A large EORTC study randomized patients between E. coli and Erwinia L-asparaginase. The Erwinia form was significantly less toxic with less neurotoxicity and less coagulopathy; however, there was a significant decrease in effectiveness with event-free survival decreasing from 73% to 60%. Pharmacokinetic investigation demonstrated that the Erwinia Asparaginase produced a more short-term asparagine depletion, four rather than eleven days, and this is probably the explanation for both the decreased toxicity and decreased effectiveness. The Pediatric Oncology Group in the United States performed a randomized study between pegylated Asparaginase either weekly or every other week. There was a significant improvement in the complete remission rate of patients treated in first relapse, 97% versus 82% (p= 0.003), with the weekly asparaginase. Pharmacokinetic studies in pediatrics have suggested an age dependence to the way Asparaginase is handled, with children over age 10 requiring 25% lower dose than younger children. The pharmacology of asparaginase in adults has not been well worked out, but it may be that pediatric doses cannot be strictly translated into adult therapy.

Post-remission therapy

Once remission is achieved, postremission therapy should be chosen based on a risk-adapted strategy. Approximately one-third of adult patients have a very favorable prognosis. These can be defined by the achievement of complete remission after one course of chemotherapy and the lack of adverse cytogenetics or molecular abnormalities. In addition these favorable patients are defined either as B-precursor patients who are both young (age less than 30 years) and with a low white blood count (WBC < 30,000). Thymic T-cell patients defined by expression of CD2 and usually having a mediastinal mass also have a very favorable prognosis. Alternatively a one-third of patients have a high-risk disease. These can be defined either by the requirement for more than one course of induction therapy to achieve remission, by the presence of adverse cytogenetics such as the Philadelphia chromosome, t(4,11), or monosomy 7, or by the presence of a white blood count greater than 100,000/uL in B-precursor patients. The remaining third of patients have a standard prognosis.

Favorable patients as defined above have an excellent outcome with at least a 70% cure rate with modern chemotherapy regimens. In my opinion these patients should not be treated with allogeneic transplantation in first remission. Poor risk patients by definition fare extremely poorly with chemotherapy, and there is no reasonable expectation of cure. These patients should be treated with allogeneic stem cell transplantation in first remission when possible.

The optimal therapy for standard risk adults with ALL (under age 60) remains to be defined. Most large trials of chemotherapy have suggested an event-free survival of approximately 35% in these patients. The results with allogeneic transplant in first remission appear superior to this and are in the range of 50%. However, it is possible that improved chemotherapy regimens could produce comparable outcomes to those seen with allogeneic transplantation. The UCSF 8707 program has produced 10-year event-free survival close to 60% in this patient group, and these results are similar to those seen with allogeneic transplantation.

In searching for ways to improve the postremission therapy of adults with ALL, several lines of investigation are possible. There has been suggestion that increasing the dose intensity of daunorubicin may improve outcomes, but this has not yet been rigorously tested in prospective trials. The importance of using asparaginase and not deleting this from the regimen in response to manageable toxicities has already been mentioned. Pediatric studies have demonstrated that pulse dexamethasone has major advantage compared to prednisone. There has been an improvement in the control of CNS disease possibly based on the

better CNS penetration of dexamethasone. Overall event-free survival has also improved in the pediatric population, but this has not been directly tested in adults. Another possibly major advantage of pulse dexamethasone over prolonged exposure to prednisone is the reduction in the incidence of late-complication avascular necrosis.

Nelarabine has recently been approved in the U.S. for the treatment of relapse patients with T-lineage disease. The safety of incorporating nelarabine into up-front therapy has been demonstrated in pediatric studies, but has not yet been tested in adults. It is possible that the addition of this agent to up-front therapy could improve the outcome for patients with T-cell disease.

One of the simplest and possibly most effective ways to improve outcomes of therapy for adults with ALL is to adhere to the principles of dose density and to avoid treatment delays. The comparison of the treatment of adolescent ALL between those treated with adult and pediatric regimens has shown a startling difference in outcomes with cure rates in the range of 35% to 40% for adults and 65% to 70% in pediatrics. Although there are many possible explanations for this difference, it is likely that the more rigorous adherence to schedule in the pediatric population plays a large role in this difference.

Autologous transplant in ALL

The role of autologous stem cell transplantation in the management of ALL remains to be defined. Randomized studies have not shown an advantage of autologous transplant over conventional therapy. However, it is possible and even likely that strategies for autologous transplantation can be improved so that outcomes may be improved. At UCSF we have collaborated with investigators at both Stanford and the City of Hope to develop a new strategy for autologous transplantation in ALL. This relies on intensive pre-transplant consolidation therapy with high-dose cytarabine (2000 mg/m2 bid x 4 days) and etoposide (40 mg/kg CIVI over 4 days) and a collection of peripheral blood stem cells early during the hematologic recovery from this chemotherapy. Although it was hypothesized that this would also serve as a form of in vivo purging, during early years of this protocol we added an antibody-based in-vitro purging to the regimen. One of the important components of our approach was the use of a very intensive preparative regimen combining high doses of total-body irradiation (1320cGy) with high-dose etoposide (60 mg/kg) and Cyclophosphamide (100 mg/kg). This is a regimen which is too toxic to be used in allogeneic transplantation, but it is manageable in the autologous setting. At this time we have treated a total of 30 patients, either very-high-risk patients in first remission as defined above or patients in second remission. With median follow-up of four years, five-year event-free survival is 44%. We are particularly gratified by the excellent outcome of patients with Philadelphia chromosome-positive ALL in whom a small number of patients have a 70% event-free survival.

Conclusions

In summary improvements in the treatment of adult ALL are needed on many fronts. It is possible that non-transplant chemotherapy regimens may be improved, and it is also possible that new strategies for autologous transplantation may define a role for this treatment plan.