Acute Nonlymphocytic Leukemia and Allogeneic Transplantation

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The Association for Hospital Medical Education endorses HOSPITAL PHYSICIAN for the purpose of presenting the latest developments in medical education as they affect residency programs and clinical hospital practice.
Acute nonlymphocytic leukemia (ANLL) represents approximately 85% of adult acute leukemias. The annual incidence is 2.25 per 100,000, which represents an incidence of slightly more than 5000 cases per year in the United States.\(^1\) The past 3 decades have seen substantial progress in the management of ANLL. In 1970, remission rates for ANLL were 50% to 60%; among patients achieving a complete remission, long-term disease-free survival was expected in only 5% to 10% of patients.\(^2\) Cytosine arabinoside and daunorubicin had been established as effective induction therapy of ANLL. The major problem that limited the achievement of a complete remission was the inability of patients to survive the period of chemotherapy-induced bone marrow aplasia long enough for the chemotherapy to be effective. Advances of the 1970s and early 1980s, including the availability of platelet support, the introduction of more effective antibiotics, and the development of clinical algorithms that include therapy for presumed fungal infections, have decreased the death rate during the early treatment of ANLL. As a result, by 1990, complete remission rates of 80% were frequently reported in patients younger than 50 years.

The development of allogeneic transplantation during the 1970s meant that cure of leukemia was a meaningful prospect for the 40% to 50% of patients who achieved a complete remission and who also had a human leukocyte antigen (HLA)-matched sibling. In the 1980s, the introduction of consolidation therapy, including the use of high-dose cytosine arabinoside (HIDAC), was associated with cure rates as high as 50% in patients younger than 40 years who had achieved a complete remission. The introduction of autologous transplantation into the therapeutic mix meant that for some patients, 3 potentially curative strategies were available from which to choose.

Other notable advances during the past decades have included the development of specific therapy for acute promyelocytic leukemia, the recognition of the prognostic implications of specific chromosomal abnormalities, and the broadening of the potential donor pool for allogeneic transplantation through the use of matched unrelated donors. Numerous clinical controversies still exist in the management of ANLL. However, over the space of a few decades the diagnosis of ANLL has gone from being an almost certain sentence of death to a disease associated with cure for a large portion of patients.

CLINICAL PRESENTATION AND PROGNOSTIC FEATURES

INITIAL CASE PRESENTATION

A 26-year-old woman seeks medical care because of fatigue and increased bruising. She has been in good
health and is taking no medications. Except for ecchymoses on her thighs and a petechial rash, the results of the physical examination are normal. Specifically, there is no adenopathy or hepatosplenomegaly. Because of the petechial rash, routine blood counts are obtained and reveal a hematocrit of 24%, a leukocyte count of 1.2 × 10^9/mm³ with 42% granulocytes, 5% monocytes, and 53% lymphocytes, and a platelet count of 11 × 10^9/mm³. A bone marrow examination is performed, which reveals a hypercellular marrow with decreased megakaryocytes. The marrow cells have been essentially replaced with blasts. Flow cytometry reveals that the blasts are positive for CD13 and CD33. By histochemical studies, the cells stain with Sudan black, chloroacetate esterase, and nonspecific esterase. Both the flow cytometry results and the histochemical studies establish the diagnosis of acute nonlymphocytic leukemia as opposed to acute lymphoblastic leukemia. A specimen is sent for cytogenetic analysis and the results are pending.

- Is presentation with petechiae and pancytopenia typical for leukemia?
- What information may be provided by the cytogenetic study?

EVALUATION AND CLASSIFICATION OF ACUTE NON-LYMPHOCYTIC LEUKEMIA

Laboratory Features

Although many clinicians mistakenly assume that all patients with acute leukemia will have an elevated leukocyte count, leukemia is a disease of the bone marrow. Patients with ANLL may present with pancytopenia, and the leukocyte count is elevated in only one half of patients with ANLL; only 20% present with a leukocyte count greater than 100 × 10^9/mm³. The elevated leukocyte count that occurs in acute leukemia results from the presence of blasts, and an elevated blast count is strongly suggestive of acute leukemia. However, blasts in the peripheral blood are not specific for acute leukemia; occasional blasts can be seen in the peripheral blood in patients with myelodysplasia and in some cases of aplastic anemia.

An elevated leukocyte count (greater than 100 × 10^9/mm³) is a poor prognostic feature in ANLL because of the acute risk of leukostasis (ie, sludging of blasts, primarily in the lung and brain), and because of the increased risk of developing central nervous system leukemia.

Clinical Features

Patients with ANLL may present with symptoms related to anemia, thrombocytopenia, or neutropenia. Because the signs and symptoms are not specific for leukemia, bone marrow aspiration and biopsy are needed to establish the diagnosis. Patients with leukemia may also present with fever. Although fever may be caused by the leukemia, if a patient is neutropenic, fever must be presumed to result from infection. Minimal hepatomegaly, splenomegaly, and adenopathy may be found at presentation. Gum infiltration and skin involvement (leukemia cutis) are uncommonly seen, and are most commonly associated with acute myelomonocytic leukemia or acute monocytic leukemia (M4 and M5 subtypes of ANLL). Very rarely, ANLL may present as an extramedullary tumor, granulocytic sarcoma. Even if the bone marrow is normal at presentation, leukemia eventually occurs in nearly all patients with granulocytic sarcoma. Therefore, the diagnosis of granulocytic sarcoma is an indication for a patient to be treated as if leukemia were present.

Diagnostic Studies

The diagnosis of the type of acute leukemia (lymphocytic vs. nonlymphocytic) can be established by flow cytometry and histochemical studies performed on bone marrow or peripheral blood blasts. Antigens for CD33 and CD15 antibodies are identified in 90% of cases of ANLL. Eighty percent of cases express HLA-DR antigen; however, HLA-DR is generally absent in the acute promyelocytic subtype of ANLL (subtype M3).³

Classification and Prognosis

The French-American-British (FAB) subclassification of ANLL is presented in Table 1, which also presents the relative incidence of each of the subtypes. This subclassification is based on histochemical staining and has prognostic value. Remissions are achieved less frequently in patients with M5 and M6 disease, and are achieved rarely, if at all, in adult patients with M7 disease.

Certain chromosomal abnormalities have clinical associations and prognostic significance (Table 2). For this reason, when a bone marrow aspiration and biopsy are performed in a patient suspected of having ANLL, the bone marrow should be sent for cytogenetic analysis.

Age is a critical prognostic factor in ANLL with younger patients having a more favorable prognosis. In patients younger than 50 years, remission rates in the range of 70% to 80% may be achieved. In patients older than 60 years, remission rates are generally between 40% and 60%. Above the age of 70 years, remission may be expected in only 25% of patients, and because long-term disease-free survival is rarely achieved in these patients, it is legitimate to consider supportive care rather than chemotherapy in these patients. The presence of a myelodysplastic syndrome prior to the development of
ANLL is also a negative prognostic feature. Even when adjusted for age, the possibility of achieving a complete remission is reduced by approximately one half when ANLL evolves from MDS.

INITIAL THERAPY FOR ACUTE LEUKEMIA

INITIAL TREATMENT AND CLINICAL COURSE OF CASE PATIENT

The case patient is diagnosed as having ANLL, M4 type. A bone marrow specimen sent for cytogenetics reveals no chromosomal abnormalities. Following platelet transfusions, a Hickman catheter is placed and the patient is started on cytosine arabinoside 100 mg/m² of body surface area per day by continuous infusion for 7 days and idarubicin 12 mg/m² per day by intravenous bolus injection for 3 days. Allopurinol 300 mg/day is also administered. Peripheral blood cell counts fall, with the leukocyte count dropping to less than 0.1 × 10³/mm³ and the platelet count dropping to less than 10 × 10³/mm³. The patient receives erythrocyte transfusions to keep the hematocrit above 25% and platelet transfusions to keep the platelet count above 10 × 10³/mm³. Administration of levofloxacin and fluconazole are started empirically at the time chemotherapy is initiated.

On day 6, the patient develops a fever of 102°F. Physical examination reveals no source of infection. A chest radiograph is unremarkable. Blood cultures are obtained and cefepime is added to the antibiotic regimen. Over the next 2 days, the patient becomes afebrile. Blood cultures are reported as negative.

On day 14, the bone marrow histologic examination is repeated and reveals a hypoplastic marrow with no evidence of leukemia. The patient remains hospitalized, receiving levofloxacin, cefepime, and fluconazole. On day 21, the patient spikes another fever to 102°F. Again, results of the physical examination are normal. Blood cultures are obtained. The chest radiograph is normal. Fluconazole is discontinued, and amphotericin B is initiated. After a test dose of amphotericin B, a daily schedule of 0.5 mg/kg body weight per day is initiated. Blood cultures are reported as negative. On day 23, the leukocyte count starts to rise, and on day 29, the leukocyte count is 1.2 × 10³/mm³ with 42% neutrophils (absolute neutrophil count [ANC] = 504/mm³). Cefepime and amphotericin B are discontinued. The platelet count has also risen slowly and is now 45 × 10³/mm³ without transfusion support. The patient remains afebrile after discontinuation of antibiotics and amphotericin B. The patient is discharged on day 31.

On day 42, the patient returns to the clinic and the following blood counts are observed: hematocrit, 34%; leukocyte count, 3.7 × 10³/mm³ with 68% neutrophils, 4% monocytes, 28% lymphocytes; and a platelet count of 154 × 10³/mm³. A bone marrow examination is performed and reveals a normocellular marrow with

<table>
<thead>
<tr>
<th>FAB Type</th>
<th>Descriptive Term</th>
<th>Percent of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Acute myeloblastic leukemia, minimally differentiated</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>M1</td>
<td>Acute myeloblastic leukemia, without differentiation</td>
<td>10–20</td>
</tr>
<tr>
<td>M2</td>
<td>Acute myeloblastic leukemia, with differentiation</td>
<td>30–45</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia</td>
<td>5–10</td>
</tr>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukemia</td>
<td>35–45</td>
</tr>
<tr>
<td>M5</td>
<td>Acute monocytic leukemia</td>
<td>2–10</td>
</tr>
<tr>
<td>M6</td>
<td>Erythroleukemia</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryoblastic leukemia</td>
<td>5–10</td>
</tr>
</tbody>
</table>

ANLL = acute nonlymphocytic leukemia; FAB = French-American-British subclassification of ANLL.
adequate megakaryocytes and normal myeloid and erythroid maturation (i.e., a normal marrow).

- Why was the bone marrow examination performed on day 42 in the out-patient clinic, rather than at the time of discharge?
- What are the principles underlying supportive care of the leukemic patient receiving chemotherapy?
- Would therapy have been different if the case patient had been found to have acute promyelocytic leukemia?

**CHEMOTHERAPY**

Therapy of acute leukemia is generally divided into induction therapy and post-induction therapy. Induction therapy refers to the initial treatment, which is designed to produce a remission. A complete remission is defined as a return of blood counts to near-normal values (ANC > 1500/μL and platelet count > 100 × 10^3/μL) with a normal bone marrow (< 5% blasts in a normocellular marrow). Obtaining bone marrow to document a complete remission should be delayed a week or two after granulocyte counts have risen to levels greater than 500/μL. If the bone marrow examination is performed earlier, the percentage of blasts may be increased and early normal recovery may be confused with persistent leukemia.

If therapy is stopped after a remission has been achieved, the relapse rate is 100%. Therefore, the standard approach is to deliver some post-induction therapy to eliminate the residual leukemia that cannot be detected. The general policy is to deliver intensification at higher doses than were used for induction. Intensification may also be referred to as consolidation though this latter term may imply to some clinicians that doses have not been intensified. Maintenance therapy is generally used to refer to the low dose administration of drugs for months to years after induction and consolidation/intensification therapy.

The most commonly used regimens for induction therapy of ANLL is the 7 & 3 regimen, a combination of 7 days of cytosine arabinoside administered by continuous infusion, and 3 days of an anthracycline or anthracenedione (Table 3). Cytosine arabinoside and idarubicin is probably the most commonly used regimen; randomized trials have demonstrated its superiority to cytosine arabinoside and daunorubicin.4 Other regimens used for induction therapy include the TAD regimen, which adds 6-thioguanine to cytosine arabinoside and daunorubicin, and the 7 & 3 & 7 regimen, which adds etoposide to cytosine arabinoside and daunorubicin. Some of the regimens used as consolidation therapy, including HIDAC regimens (see Table 4), have been used as induction therapy. However, they have not been consistently shown to produce results superior to those achieved with standard 7 & 3 regimens.

Regardless of what regimen is used, general policy is to perform a bone marrow examination on day 14 to assess the response. If the marrow is hypocellular at that time, with no evidence of leukemia, one can simply continue to follow and support the patient and await marrow recovery. A repeat marrow examination should be performed after blood cell counts have recovered to document that a complete remission has been achieved.

If the day 14 marrow shows persistent leukemia, the options are to either repeat the regimen used as induction therapy or to switch to another regimen (e.g., a HIDAC regimen that might be used for consolidation). One important exception to this scenario should be noted. In patients with acute promyelocytic leukemia (APL), remissions may be achieved even if bone marrow hypocellularity is not achieved at day 14. Therefore, in patients with APL, if persistent leukemia is noted on

**Table 3. Regimens Commonly Used for Induction Therapy of Acute Nonlymphocytic Leukemia**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Components</th>
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| **7 & 3 regimen**| Cytosine arabinoside 100–200 mg/m² of body surface area per day by continuous IV infusion for 7 days  
                    Plus 1 of the following for days 1–3:  
                    - Idarubicin 12 mg/m² of body surface area per day IV bolus injection  
                    - Daunorubicin 45 mg/m² of body surface area per day IV bolus injection  
                    - Mitoxantrone 12 mg/m² of body surface area per day IV bolus injection |
| **TAD regimen**  | Cytosine arabinoside 100 mg/m² of body surface area every 12 hours for 7 days and  
                    Daunorubicin 60 mg/m² of body surface area per day IV bolus injection for days 5–7 and  
                    Thioguanine 100 mg/m² of body surface area every 12 hours for 7 days |
| **7 & 3 & 7 regimen** | Cytosine arabinoside 100–200 mg/m² of body surface area per day by continuous IV infusion for 7 days and  
                    Daunorubicin 45 mg/m² of body surface area per day IV bolus injection for days 1–3 and  
                    Etoposide 75 mg/m² of body surface area per day IV for 7 days |

IV = intravenous.
day 14, one has the option of continuing all-trans-retinoic acid (ATRA) therapy without chemotherapy (see Treatment of Acute Promyelocytic Leukemia, page 7). In APL, the marrow may not appear to be free of leukemia until day 45.

**Supportive Therapy**

**General Considerations**

Supportive care is critical in the management of ANLL. In a review published in 1974, Beard and Fairley noted that remission rates in ANLL generally ranged from 50% to 65%. However, in the studies that they reviewed, remission rates were routinely 20% higher in the patients who survived 4 to 6 weeks after initiation of therapy. Unfortunately, 30% to 40% of patients died before therapy could be effective. Between 1975 and 1990, in conjunction with the development of effective broad-spectrum antibiotic regimens and the development of clinical algorithms that included early empirical use of antifungal therapy, early deaths during leukemia therapy have become less and less frequent, occurring in only 5% to 10% of patients. As a result, as would be predicted from the observation of Beard and Fairley, remission rates have risen 20% even though chemotherapy has changed minimally.

Intravenous hydration and allopurinol 300 mg/day should be started upon initiation of chemotherapy and continued as long as induction chemotherapy is given. In patients presenting with a leukocyte count greater than $100 \times 10^3/mm^3$, the dose of allopurinol may be increased to 600 mg/day for 3 days, and patients should be monitored for tumor lysis. While it is reasonable to consider leukapheresis to lower the blast count in patients presenting with a markedly elevated leukocyte count, randomized trials have never been conducted to determine whether or not that approach is superior to simply lowering the blast count by initiation of chemotherapy. Nevertheless, leukapheresis is generally recommended when signs or symptoms of leukostasis are present (eg, pulmonary infiltrates, hypoxia, confusion). It is also advisable to establish intravenous access with a Hickman or Groshong catheter prior to initiation of therapy because patients are likely to need simultaneous chemotherapy, transfusions, antibiotics, and, possibly, total parenteral nutrition.

**Principles of Antibiotic Therapy**

All drugs effective in ANLL are myelotoxic, and therapy of ANLL produces severe thrombocytopenia and neutropenia, generally lasting 4 weeks. Several principles have been established for antibiotic therapy in neutropenic leukemic patients. The choice of antibiotics depends on which organisms are cultured in a given institution and on information regarding sensitivities of the likely pathogens. Although gram-negative infections, predominantly *Pseudomonas aeruginosa*, were the most common organisms 15 to 20 years ago, with the widespread use of semi-permanent catheters, the incidence of gram-positive infections and gram-negative infections has become approximately equal, and coagulase-negative staphylococci have become the most common cause of bacteremia.

The following principles govern the supportive care of the cytopenic leukemic patient undergoing therapy. Platelets should be transfused to maintain the platelet count above $10 \times 10^9/mm^3$. Higher levels are necessary in the face of gastrointestinal or other mucosal bleeding. Persistent fever (temperature > 100.5°F for more than 4 hours) in the face of a granulocyte count below 500/mm³ necessitates a careful evaluation for a source of infection followed by the administration of empiric antibiotics. The most common sources of documented infection in neutropenic patients are line infections, pneumonias, and perirectal infections. However, for most febrile leukemic patients, no source of infection is found. Even if no source of infection is found, empiric antibiotics should be initiated. There is no single optimal antibiotic regimen and patients are generally treated with a combination of a quinolone and a cephalosporin (eg, cefepime or ceftaroline) or a quinolone and imipenem.

When antibiotics are initiated, they should generally be continued for as long as the patient is neutropenic, even if the fever resolves. If patients remain febrile after the initiation of antibiotics, one can consider adding vancomycin or switching one of the other antibiotics; for example, changing a cephalosporin to imipenem or changing the quinolone to aztreonam. Although aminoglycosides are a therapeutic option, they must be used with caution. In this clinical setting, nephrotoxicity that may occur with administration of aminoglycosides may compromise the future ability of the patient to receive HIDAC consolidation therapy or an allogeneic bone marrow transplant—the 2 curative approaches to this disease.

To limit the emergence of vancomycin-resistant enterococci, vancomycin should not be part of the initial empiric combination regimen. If vancomycin is administered empirically, it should be discontinued after 72 hours unless blood cultures are positive for an organism requiring vancomycin, or unless a catheter tunnel infection is thought to be highly probable.

In patients who remain febrile on broad-spectrum antibiotics for 4 to 7 days, antifungal therapy in the form of amphotericin B (or a liposomal form of that...
drug) should be initiated even if patients have been receiving empirical fluconazole.

Use of Growth Factors

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been shown to decrease the duration of neutropenia in patients receiving chemotherapy for ANLL. However, with the exception of 1 trial in patients older than 55 years, studies have not shown an increased remission rate or an improvement in survival secondary to the use of these myeloid growth factors. Additionally, leukemic blasts have receptors for G-CSF and GM-CSF, raising the possibility that growth factors might contribute to relapse of leukemia. Therefore, it is reassuring to note that follow-up studies have not shown shortened remission durations or increased relapse rates in patients with ANLL who have received growth factors during induction or consolidation therapy. Nevertheless, there is no firm basis for the routine use of growth factors in patients receiving induction therapy for ANLL.

TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA

Although the various FAB subtypes of ANLL generally receive similar therapy, APL (FAB subtype M3) is an exception to this principle. APL is associated with a specific chromosomal abnormality, t(15;17), a translocation involving the receptor site for retinoic acid. The disease is characterized by maturation arrest at the promyelocytic stage. Because promyelocytic granules contain a procoagulant, treatment of APL with standard chemotherapy is associated with disseminated intravascular coagulation and an approximately 10% risk of fatal intracranial hemorrhage during induction therapy.

This risk of fatal intracranial hemorrhage was all but eliminated with the introduction of ATRA into clinical practice. ATRA appears to kill cells by “maturing” them to death, avoiding the creation of a coagulopathy. Unfortunately, early trials of ATRA were associated with the retinoic acid syndrome, a syndrome of intrapulmonary capillary leakage that often accompanied elevated leukocyte counts during initiation of therapy. Although ATRA was associated with a decreased risk of intracranial hemorrhage, the improvement in remission rates was minimal because of the occurrence of fatalities associated with the retinoic acid syndrome. Appreciation of this syndrome led to its management with corticosteroids, (dexamethasone 10 mg every 12 hours IV for 3 days) and, more importantly, its prevention by combining ATRA with chemotherapy as induction therapy for APL. Combining ATRA with chemotherapy limits the occurrence of elevated leukocyte counts during induction therapy and minimizes the risk of retinoic acid syndrome. One regimen frequently used in treatment of APL is the A-IDA regimen, which consists of ATRA 45 mg/m² of body surface area per day, given orally in divided doses, until complete remission (maximum 90 days), plus idarubicin 12 mg/m² of body surface area on days 2, 4, 6, and 8.

When treating patients with APL, the general policy is to use an induction/consolidation regimen that includes both ATRA and chemotherapy to avoid producing ATRA resistance. In a large-scale clinical trial, patients who received ATRA for induction, ATRA followed by HIDAC for consolidation, and ATRA maintenance therapy achieved a 3-year relapse-free survival rate of 75%.

CURATIVE CONSOLIDATION THERAPY

CONSOLIDATION CHEMOTHERAPY OF CASE PATIENT

The patient and her siblings were HLA typed at the time of induction therapy. Her older brother was found to be a 6-of-6 match. However, after reviewing the therapeutic options, the patient elected to receive consolidation therapy with HIDAC (3 g/m² of body surface area over 3 hours, every 12 hours, for 12 doses) followed by daunorubicin 45 mg/m² of body surface area day for 3 days.

- Is the choice of consolidation chemotherapy an acceptable choice when an HLA-matched family donor is available?
- What are the chances of cure for this patient with consolidation chemotherapy as compared to allogeneic transplantation?

OPTIONS FOR CONSOLIDATION THERAPY

In the absence of consolidation therapy, remissions in ANLL usually last from 4 to 12 months. However, 3 potentially curative options for consolidation therapy exist: consolidation chemotherapy with a regimen containing HIDAC, allogeneic transplantation, and autologous transplantation. Controversy still exists as to which of these approaches are optimal. For patients without an allogeneic donor, combination chemotherapy including HIDAC is generally chosen (Table 4). It is not clear which HIDAC regimen is superior, and the regimens listed in Table 4 have not been subjected to head-to-head comparisons. Nevertheless, HIDAC regimens, including those presented in Table 4, have produced long-term disease-free survival in 26% to 49% of patients.
In patients who have a matched related donor, the general clinical trend has been to proceed with an allogeneic transplant. This course of action was supported by trials conducted in the 1980s that showed allogeneic transplantation to be superior to the consolidation chemotherapy regimens used at that time. However, a survival value for allogeneic transplantation has not been consistently demonstrated when allogeneic transplantation has been compared to HIDAC consolidation. Furthermore, because patients in whom high-dose chemotherapy consolidation is unsuccessful are able to undergo transplantation at the time of relapse, the overall strategy of using a HIDAC consolidation regimen, followed by allogeneic transplantation for chemotherapy failures, may be a superior clinical strategy compared to allogeneic transplantation in first remission.

This hypothesis has not been subjected to randomized trials, however, because patients with a matched related donor have generally been excluded from randomization and assigned to transplantation. A recent large-scale trial showing a slight, but significant, superiority of HIDAC consolidation as compared to allogeneic transplantation is further support for the use of HIDAC consolidation. In that trial, patients with ANLL in remission were assigned to allogeneic transplantation if they had a matched related donor. Other patients in remission were randomized to either HIDAC consolidation or autologous transplantation. Although relapses were less frequent among patients assigned to allogeneic transplantation, excess treatment related mortality negated this potential benefit of allogeneic transplantation. As a result, in that trial, 4-year survival was 52% after consolidation chemotherapy, 46% after allogeneic transplantation, and 43% after autologous transplantation.

The use of autologous transplantation as consolidation therapy is counter-intuitive because leukemic cells may be harvested and reinfused. Furthermore, the best results using autologous transplantation have been achieved when used after high-dose consolidation therapy has been administered (ie, at a time when many patients may have already been cured by chemotherapy alone). Nevertheless, empirical results suggest that autologous transplantation may play a role in the consolidation therapy of ANLL, although the optimal indications for its use have not been defined.

## ALLOGENEIC TRANSPLANT

### STEM CELL TRANSPLANT OF CASE PATIENT

Following completion of high-dose consolidation chemotherapy, the case patient returns for routine follow up every 2 months. Fourteen months after completion of consolidation chemotherapy, routine blood counts reveal pancytopenia. A bone marrow examination shows 15% blasts, compatible with early relapse.

The patient is hospitalized and given high-dose cyclophosphamide and total body irradiation followed by administration of allogeneic peripheral blood stem cells from her HLA-matched sibling. Daily cyclosporin and short-course methotrexate are administered to prevent graft-versus-host disease (GVHD). Following a period of supportive care for severe pancytopenia, the patient begins to engraft on day 14.

On day 17, a skin rash is noted over the patient’s palms and back. A biopsy is obtained. The patient is started on methylprednisolone 0.5 mg/kg body weight twice daily. The biopsy confirms GVHD. Liver function tests are normal. The patient has no diarrhea. The rash slowly resolves and the methylprednisolone is tapered gradually over several weeks. Cyclosporin is continued.

On day 42, a screening test for cytomegalovirus (CMV) antigen is found to be positive and the patient is treated with ganciclovir 5 mg/kg body weight twice daily for 7 days, followed by ganciclovir 5 mg/kg body weight twice daily.
weight once daily for 2 weeks. The leukocyte count falls to below $1.0 \times 10^3/\text{mm}^3$ during this therapy, and G-CSF is administered for a short period of time.

Beginning on day 100, the cyclosporin is gradually tapered. The patient continues to do well.

- **What principles underlie the supportive care for a patient undergoing allogeneic transplantation?**
- **What are the major potential complications of allogeneic transplantation?**
- **What are the major manifestations of GVHD?**

### GENERAL PRINCIPLES OF ALLOGENEIC TRANSPLANT

Allogeneic transplantation employs extremely high doses of chemotherapy or chemotherapy plus total body irradiation to eliminate the malignancy. For patients with acute leukemia undergoing allogeneic transplantation, the most commonly used regimen is cyclophosphamide in combination with total body irradiation. This high-dose therapy, given as preparative therapy for the transplant, also permanently ablates the recipient’s bone marrow. Thus, the availability of a suitable transplant donor allows treatment to be delivered at doses that would ordinarily be fatal if a donor were not available. Infusion of bone marrow or peripheral blood stem cells from the donor not only provides for recovery of the patient’s blood counts, it also potentially produces a graft-versus-leukemia (GVL) effect, in which the donor’s lymphocytes can kill residual leukemic cells.

### IDENTIFYING A STEM CELL DONOR

Allogeneic transplantation may be considered as a curative consolidation approach in patients who are in a first complete remission. Additionally, allogeneic transplantation is the only curative modality for patients with ANLL who are refractory to chemotherapy or who relapse after a response to chemotherapy. Therefore, in order to more completely assess therapeutic options, HLA-A, -B, and -DR typing should be performed at the time of diagnosis in all patients with ANLL who are younger than 55 years. All siblings should also be typed, and if there is a no sibling match, parents and children should be evaluated, as well.

If no sibling or family match is found, allogeneic transplant using a matched unrelated donor (MUD) may be of value at the time of relapse in younger patients. However, since MUD transplants are associated with a greater risk of fatal GVHD than are matched related transplants, MUD transplants are not routinely performed as consolidation therapy. The increased risk associated with transplants involving unrelated donors probably relates to the fact that minor transplantation antigens that are not routinely evaluated are less likely to be matched in an unrelated transplant setting as compared to a matched related donor. Additionally, until recently, when HLA-A, -B, and -DR typing has been done, the HLA-A and -B typing was generally done by serologic methods. In the family setting, a serologic match is almost certain to be a genotypic match as well. However, in the unrelated setting, a match that is documented by serologic techniques is unlikely to be a true genotypic match. In the future, the use of DNA methods for all HLA typing may lead to better matching for unrelated donors and may decrease the morbidity and mortality of transplants from unrelated donors.

### COMPLICATIONS

#### Regimen-Related Complications

Unfortunately, allogeneic transplant is associated with a number of potentially fatal complications. A logical approach to considering these clinical problems is to consider when in the course of transplantation the problems are likely to occur. The first problems to occur are those considered regimen-related toxicity. The preparative therapy used in allogeneic transplantation is likely to produce 2 to 3 weeks of bone marrow hypoplasia before engraftment occurs. Thus, patients receiving allogeneic transplant are at the same risk of infection and bleeding as patients undergoing chemotherapy for leukemia, and the supportive care principles are the same.

Other regimen-related complications associated with allogeneic transplantation include veno-occlusive disease (VOD) of the liver and the less common syndromes of radiation injury to the heart or lungs, the latter being manifested as alveolar hemorrhage. VOD involves fibrous obliteration of small hepatic venules and sublobular veins and is diagnosed when any 2 of the following 3 events occur within 20 days of transplantation: hyperbilirubinemia (serum bilirubin levels $>2\text{ mg/dL}$), hepatomegaly or right upper quadrant pain of liver origin, and sudden weight gain of more than 2% of body weight resulting from fluid accumulation.

Because patients suspected of having VOD are not good candidates for liver biopsy because of their low platelet counts, the diagnosis is a clinical one. In distinguishing VOD from acute GVHD, time of onset may be a helpful factor. VOD generally occurs within 14 days of completing preparative therapy, whereas acute GVHD most commonly occurs after engraftment (ie, after day 14) and in conjunction with other signs of acute GVHD, such as a skin rash. The risk of VOD is increased among patients with elevated transaminase levels before

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transplantation and among patients receiving mismatched or unrelated transplants. Other causes of elevated bilirubin values which must be considered in the post-transplant setting include reactions to cyclosporin or methotrexate, and infections with hepatitis B or hepatitis C virus, CMV, or herpes simplex virus. Despite extensive investigation, no therapy has been established as effective in the treatment of VOD by randomized clinical trials. VOD is generally managed by supportive care such as maintaining fluid balance, but may lead to a fatal outcome.

Graft-Versus-Host Disease

Despite the use of HLA-matched donors, acute GVHD is the major complication of allogeneic transplantation. Although hyperacute GVHD may occur prior to engraftment, GVHD essentially becomes a clinical consideration at the time that bone marrow recovery starts to occur. The skin, the liver, and the gastrointestinal tract are the target organs for acute GVHD. The staging and grading of acute GVHD is presented in Table 5. Skin involvement, in the form of a rash on the palms and the back, is generally the first manifestation of GVHD. Involvement of the liver in the absence of skin manifestations is quite uncommon in acute GVHD; however, gut involvement may be seen in the absence of skin GVHD.

Theoretically, GVHD requires the 3 factors: (1) the transplantation of immunocompetent cells, (2) the inability of an immunoincompetent recipient to reject the cells, and (3) the presence of HLA disparity between donor and recipient. All of these necessary factors for GVHD are present when allogeneic transplants are performed in patients with ANLL.

Acute GVHD can be prevented, to some degree, by the prophylactic administration of methotrexate in combination with cyclosporin or tacrolimus. A commonly used schedule is cyclosporin 3 mg/kg body weight per day by continuous IV infusion starting the day before the transplant, and methotrexate 15 mg/m² of body surface area on day 1 and 10 mg/m² of body surface area on days 3, 6, and 11. Serum cyclosporin levels are obtained, and the dose of the drug is adjusted to maintain the level between 150 and 450 ng/mL.

Cyclosporin prevents the expansion of T-cell clones that mediate GVHD. Although the drug is effective in preventing GVHD, it is minimally effective in treating GVHD. Acute GVHD is treated by administration of high doses of corticosteroids such as methylprednisolone. Such therapy may be successful; however, acute GVHD, and the infectious complications that are associated with the immunosuppressive therapy needed to treat acute GVHD, are the major causes of morbidity and mortality of allogeneic transplantation. Complications of acute GVHD are worse in older patients, and a general rule of thumb is that the incidence of fatal complications of acute GVHD is approximately equal to 70% to 80% times the age of the patient.

By convention, GVHD occurring before day 100 following transplantation is classified as acute GVHD, whereas GVHD occurring after day 100 is classified as chronic GVHD. This delineation is somewhat arbitrary,

Table 5. Staging and Grading of Acute Graft-Versus-Host Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Maculopapular rash &lt; 25% of body surface</td>
<td>Serum bilirubin 2–3 mg/dL</td>
<td>Diarrhea 500–1000 mL/day</td>
</tr>
<tr>
<td>++</td>
<td>Maculopapular rash 25%–50% of body surface</td>
<td>Serum bilirubin 3–6 mg/dL</td>
<td>Diarrhea 1000–1500 mL/day</td>
</tr>
<tr>
<td>+++</td>
<td>Generalized erythroderma</td>
<td>Serum bilirubin 6–15 mg/dL</td>
<td>Diarrhea &gt; 1500 mL/day</td>
</tr>
<tr>
<td>++++</td>
<td>Desquamation and bullae</td>
<td>Serum bilirubin &gt; 15 mg/dL</td>
<td>Severe pain or ileus</td>
</tr>
</tbody>
</table>

Clinical Grade of Acute Graft vs. Host Disease

<table>
<thead>
<tr>
<th>Grade</th>
<th>Degree of Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+ to ++ skin rash; no gut involvement; no liver involvement; no decrease in clinical performance</td>
</tr>
<tr>
<td>II</td>
<td>+ to +++ skin rash; + gut involvement and/or + liver involvement; mild decrease in clinical performance</td>
</tr>
<tr>
<td>III</td>
<td>++ to ++++ skin rash; ++ to +++ gut involvement and/or ++ to +++ liver involvement; marked decrease in clinical performance</td>
</tr>
<tr>
<td>IV</td>
<td>Similar to grade III but with ++ to ++++ organ involvement and extreme decrease in clinical performance</td>
</tr>
</tbody>
</table>
as acute GVHD usually occurs by day 50, and GVHD having the pattern of acute disease may occur after day 100.

Whereas acute GVHD is an inflammatory condition involving the skin, with or without involvement of the liver and gut, chronic GVHD is most often a scleroderma-like condition characterized by thickening and scarring of the skin. The lacrimal glands, salivary glands, and liver may also be involved in chronic GVHD. The major risk factor for chronic GVHD is acute GVHD, but chronic GVHD may also occur as a de novo condition.

The use of allogeneic peripheral blood stem cells, in contrast to allogeneic bone marrow, has been associated with an increased risk of chronic, but not acute, GVHD. Chronic GVHD is associated with a delayed recovery of immunologic function, and the major cause of death among patients with chronic GVHD is bacterial infection.

At present, GVHD and GVL occur in parallel. Optimally, if the specific cells responsible for GVHD and GVL could be identified, and if the cells proved to be separate populations of immune-competent cells, the occurrence of GVHD and GVL could be separated. At present, however, this remains only a theoretical consideration. Studies have shown that the relapse rate of ANLL after allogeneic transplantation is approximately twice as high in patients who do not experience GVHD or who experience only grade I acute GVHD, as compared to patients with grade II to IV acute GVHD or with chronic GVHD. Similarly, the relapse rate among patients receiving syngeneic transplants (identical twin donors) is similar to the relapse rate in patients who receive an allogeneic matched transplant but do not experience GVHD.

Cytomegalovirus Infection

Whereas acute GVHD becomes a clinical consideration at the time of engraftment, CMV infection becomes an important consideration in patients undergoing allogeneic transplantation approximately 4 weeks after allogeneic transplantation. If both recipient and donor are CMV-negative, the risk of CMV infection after transplantation can be kept below 5% either by using CMV-negative blood products, or, more simply, by using a leukocyte filter on all blood products administered after transplantation. Unfortunately, in most transplants, either the patient, the donor, or both are positive for CMV. This puts the recipient at risk for fatal CMV disease, usually in the form of CMV pneumonia or CMV gastroenteritis. Although ganciclovir is effective in the treatment of CMV disease, the drug is myelotoxic. As a result, in clinical trials, prophylactic use of ganciclovir has not been shown to reduce overall mortality. When ganciclovir is given routinely to all CMV-positive patients, deaths due to neutropenia balance the deaths prevented by prophylactic ganciclovir. Instead, in order to create a favorable risk-to-benefit ratio with respect to the use of ganciclovir, patients are generally monitored for CMV antigen, and only patients having positive tests for CMV antigenemia are treated expectantly with ganciclovir.

Basing the decision to use ganciclovir on antigenemia has been shown to decrease the 100-day mortality due to CMV. However, while CMV infection has traditionally been rare after day 100, recent studies suggest that modern strategies for treating CMV antigenemia may be delaying the development of CMV infections until after day 100. In patients with CMV viremia that is resistant to ganciclovir, or in patients who cannot tolerate ganciclovir due to significant neutropenia, foscarnet may be used. However, foscarnet may be associated with nephrotoxicity, hypocalcemia, and hypomagnesemia.

Fungal Infections

With effective treatment of bacterial infections and of CMV, the fungal infection aspergillosis has become the primary cause of infectious deaths in patients undergoing allogeneic transplantation. Prolonged post-transplant therapy with fluconazole for 75 days has been shown to decrease the risk of fatal Candida infections following allogeneic transplantation. However, effective procedures to decrease the risk of aspergillosis have not been established for transplant recipients who are chronically immunosuppressed by treatment of GVHD.

SUMMARY

ANLL is the most common leukemia seen in adults. With standard induction chemotherapy and standard supportive care using platelets, antibiotics, and antifungal therapy, complete remission rates of 80% can be achieved in patients younger than 50 years. However, complete remission merely means that blood counts have returned to normal (or near normal) and that the bone marrow contains fewer that 5% blasts. Unless maintenance/consolidation therapy is given, remissions rarely last more than a few months.

Three types of consolidation therapy are effective: high-dose chemotherapy (including HIDAC), autologous transplantation, and allogeneic transplantation. These approaches may produce cures in 40% to 50% of patients younger than 40 years, with slightly lower cure rates in patients between the ages of 40 and 55 years. Because allogeneic transplantation may also cure patients who have relapsed after initial therapy, it extends the possibility of
cure to populations of leukemia patients who would otherwise be incurable.

Achieving a cure with allogeneic transplantation requires the preparative regimen to eliminate the tumor, with or without an additional GVL effect. Additionally, patients undergoing allogeneic transplantation must be monitored closely for a number of potentially life threatening complications including VOD, GVHD, CMV infection, and aspergillosis. Management of these complications is generally the factor that determines whether or not a specific patient has a successful outcome or a fatal outcome.

REFERENCES


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