Acute Lymphoblastic Leukemia in Adults

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Opinion statement

The therapy of acute lymphoblastic leukemia (ALL) in adults has built on the remarkable success achieved in the treatment of this disease in children. However, older age and other adverse risk factors seen more commonly in adults than in children have lessened the success of the treatment of ALL in comparison with what has been achieved in children. The treatment of ALL depends on the use of intensive multi-agent chemotherapy given over 6 to 9 months in combination with central nervous system prophylactic therapy with cranial radiation and intrathecal chemotherapy followed by maintenance chemotherapy for 2 to 3 years. This therapy has allowed younger patients with newly diagnosed ALL to achieve complete remission in 80% to 90% of cases, but has still resulted in subsequent relapse in most patients. For high-risk patients with ALL, allogeneic blood and marrow transplant (BMT) from a related or unrelated donor can improve the outcome compared with chemotherapy. The role of autologous transplantation in ALL remains uncertain, as does the role of allogeneic transplant in standard-risk patients. This issue continues to be the subject of large, randomized trials. New agents and improvements in supportive care bring the hope that more patients with ALL will be cured in the future.

Introduction

The treatment of acute lymphoblastic leukemia (ALL) in adults has evolved from the profound success achieved with the treatment of this disease in children [1]. Long-term event-free survival can now be achieved in more than 70% of children with ALL. In adults, complete remission rates with multi-agent chemotherapy approach those achieved in children and now exceed 85%. However, the durability of these remissions is poor, and many patients will relapse, resulting in event-free survivals that are under 40% [2]. The inferior outcome of adult patients with ALL has been attributed to several prognostic factors which are outlined below.

Modern classification schemes of ALL divide the disorder into three subtypes of clinical significance based on whether the antigenic profile of the leukemic cells is that of a mature B cell (Burkitt's), an immature B cell (precursor-B or pre-B), or a T cell (Fig. 1, Table 1). The latter disorder is to be distinguished from T-cell leukemia/lymphoma, which is associated with human T-cell leukemia virus (HTLV-1) and occurs endemically in Japan, the Caribbean, and the southeastern region of the United States and is not discussed further in this review. Therapy for immature B and T-cell ALL is similar and is to be distinguished from that applied in mature B cell ALL (outlined below). Precursor-B cell ALL represents 70% to 75% of all cases of ALL, whereas T-cell ALL represents 20% to 25% and mature B cell ALL only 5% of cases.

The inferior outcome of adult ALL compared with pediatric ALL is largely related to several significant prognostic factors. The most obvious factor is age: multiple trials have demonstrated an inferior outcome in older adults, particularly in patients over the age of 60, but also seen in patients over the age of 30 who have an intermediate prognosis between that of patients younger than 30 and more than 60 years of age [2•,3••]. The other major prognostic factor relates to the findings of cytogenetic and molecular analyses of leukemia cells at diagnosis. The presence of the Philadelphia chromosome (Ph+), representing a translocation between chromosomes 9 and 22 [t(9;22)] juxtaposing the abelson (*abl*) tyrosine kinase gene on chromosome 9 with genes in the

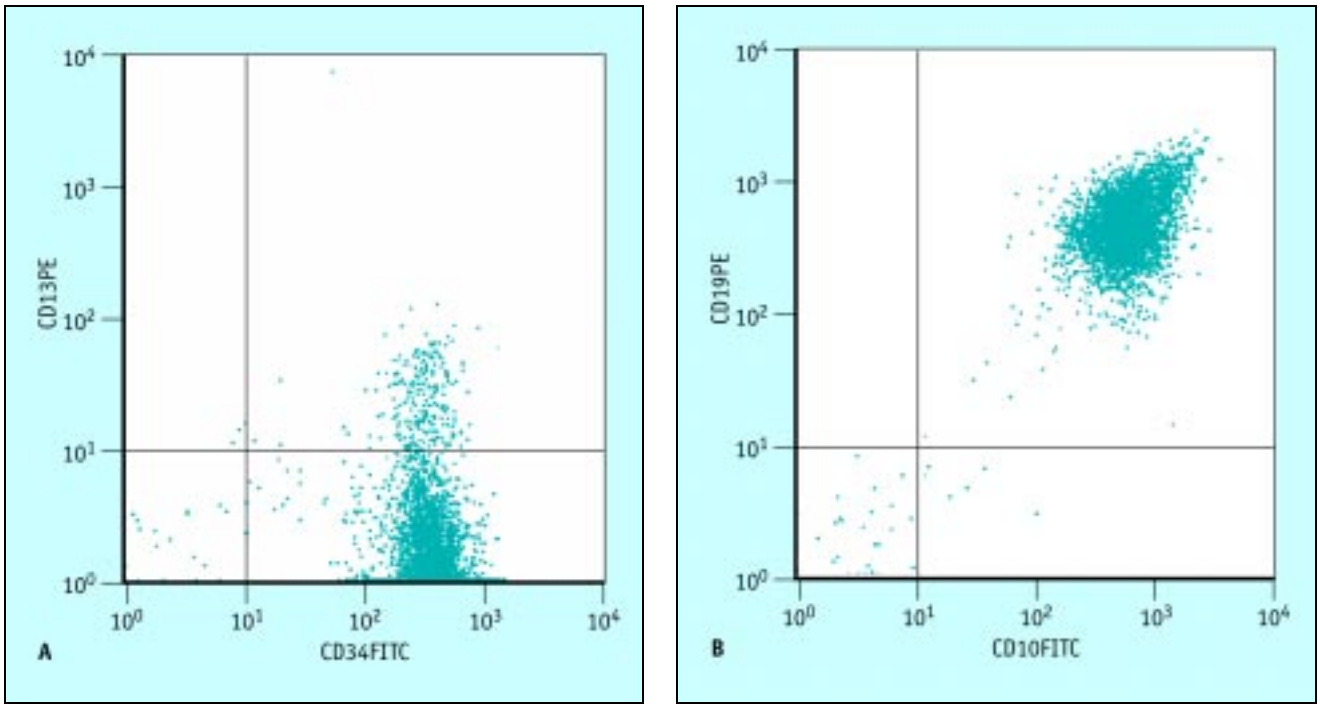

Figure 1. Flow cytometric profile of a bone marrow aspirate from a patient with Philadelphia chromosome positive pre-B ALL stained with antibodies against CD34, CD13, CD10, and CD19 demonstrating strong positivity for CD19, 10, and 34, and essentially negative staining for the myeloid antigen CD13.

Table 1. Antigenic profile of the common subtypes of acute lymphoblastic leukemia

Precursor-B ALL: CD19+, CD10+ or -, CD34+. TdT+
B ALL: CD19+, CD20+, CD22+, CD45+, surface immunoglobulin +
T ALL: CD7+, CD5+, CD2+, CD4 and 8 + or -, CD34+, TdT+

breakpoint cluster region (*bcr*) of chromosome 22 to produce an aberrant tyrosine kinase (*bcr-abl*), is an essential step in the pathogenesis of both chronic myelogenous leukemia and some cases of ALL. The presence of a *bcr-abl* gene rearrangement in ALL is associated with a very poor prognosis in patients treated with chemotherapy alone. The *bcr-abl* gene is found in up to 30% of adults with ALL as compared with less than 4% of children, thus contributing to the poorer outcome of adults. The t(4;11) juxtaposes the *AF4* gene on chromosome 4q21 with the *MLL* gene on chromosome 11q23 and is associated with a poor prognosis with chemotherapy treatment alone. Both the t(9;22) and t(4;11) are seen predominantly in cases of pre-B ALL. Recently studies from the Cancer and Leukemia Group B (CALGB) cooperative group have noted poor prognoses with cytogenetic abnormalities of –7 and +8 as well [4]. An additional translocation of importance juxtaposes the c-myc oncogene on chromosome 8q24 to the heavy or light chain immunoglobulin genes [t(8;14), t(2;8), and t(8:22)] and is seen exclusively in mature B cell ALL. Other prognostic factors of importance that contribute to the poorer outcome of adult ALL are white blood cell (WBC) count of more than 30,000/mL at presentation and failure to achieve a complete remission within 4 to 6 weeks of initiating chemotherapy.

The clinical manifestations and physical findings in patients with ALL can be directly correlated with decreased production of normal hematopoietic cells and invasion and enlargement of lymphoid organs (lymph nodes and spleen) with leukemic cells. The cell type (red blood cells [RBC], WBC, or platelets) most severely affected by replacement of the bone marrow generally predict the patient's dominant clinical presentation. It is important to distinguish ALL from other disorders that can mimic its presentation, particularly nonmalignant disorders such as infectious mononucleosis, and other lymphoid malignancies such as chronic lymphoproliferative disorders, including lymphomas. In a patient with suspected ALL who presents with significant lymphadenopathy, the presence of a high-grade lymphoma should be considered. The cells of both lymphoblastic lymphoma and Burkitt's lymphoma can give either a lymphomatous or a leukemic presentation. A diagnosis of leukemia is usually established, however, when the bone marrow shows more than 25% involvement by the malignant process.

The mainstay of the therapy of ALL is multi-agent chemotherapy. In the past decade, intensification of the initial (termed induction) chemotherapy has resulted in higher complete remission (CR) rates and improved event-free survival [3••]. Currently, effective regimens include an initial 6 to 9 months of induction and intensi-

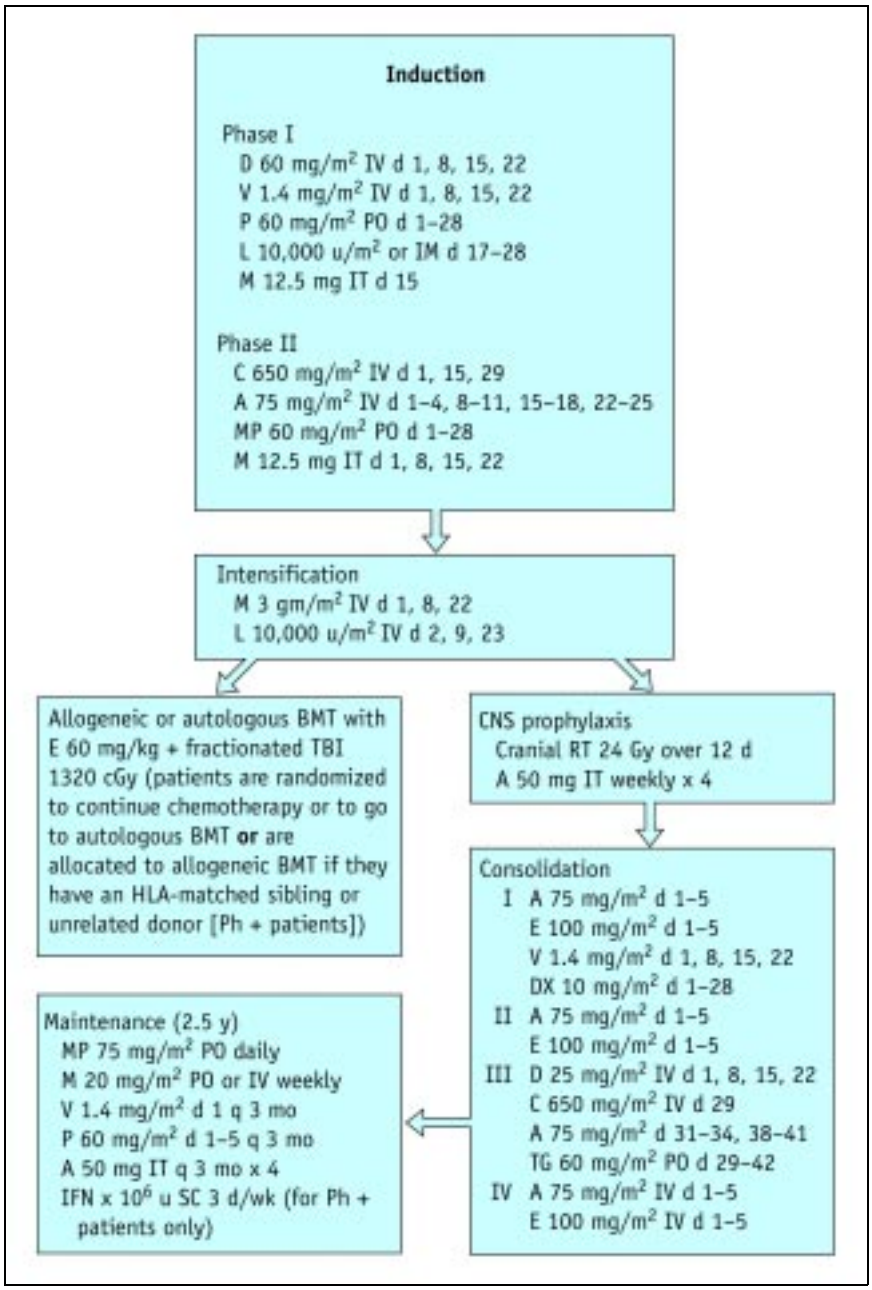

Figure 2. Algorithm of chemotherapy treatment on MRC/ECOG 2993 trial for ALL in adults, ages 18–60. A—cytarabine; BMT—blood and marrow transplantation; C—cyclophosphamide; D—daunorubicin; DX—dexamethasone; E—etoposide; IFN—alpha interferon; L—L-asparaginase; M—methotrexate; MP—6-mercaptopurine; P—prednisone; RT—radiation therapy; TBI—total body irradiation; TG—6-thioguanine; V—vincristine.

fication and consolidation therapy with daunorubicin, vincristine, prednisone, L-asparaginase, cyclophosphamide, cytosine arabinoside, methotrexate (MTX), and 6-mercaptopurine (6-MP). Incorporated into this phase of therapy is prophylaxis or treatment of the central nervous system (CNS) with cranial irradiation and intrathecal chemotherapy because of the high risk of development of CNS leukemia in patients with ALL. This initial intensive phase of therapy is followed by prolonged maintenance therapy for 2 to 3 years incorporating daily 6-MP and weekly MTX, both given orally, combined with intermittent boluses of therapy with vincristine and prednisone and often including late consolidation or intensification therapy with combinations of the agents listed above [3••]. See Figure 2 for an outline of the drugs and schedule of a modern multi-agent chemotherapy regimen. Complete remission rates of 75% to 90% (40% of >60 years of age) and disease-free survival rates of 40% (<20% if >60 years old) can be achieved with these programs (Table 2). For B cell ALL, studies adapted from the pediatric population have demonstrated that high-dose alkylator therapy with cyclophosphamide or ifosfamide and high-dose methotrexate-based regimens given intensively for 4 to 6 months can result in remission rates of 70% to 80% with disease-free survival of 50% to 60% [5].

The role of blood and marrow transplantation (BMT) in the therapy of ALL is not yet clearly defined. Although many pilot phase II trials have suggested favorable outcomes with allogeneic BMT in patients with ALL in first remission with high-risk features [6], a retrospective

Table 2. Outcome of treatment for acute lymphoblastic leukemia

Complete remission rates: 75%–90% (40% if >60 years old)
Disease-free survival (DFS): 40% (higher if younger and/or good risk; lower for elderly or poor risk)
Blood and marrow transplant DFS: 60%–70% if in first complete remission; 10%–40% if beyond first remission

review of registry data did not show a clear benefit for BMT when compared with two German cooperative group chemotherapy studies [7]. A prospective French trial (LALA 87) compared matched sibling allogeneic BMT to autologous BMT or chemotherapy in younger adult patients with ALL in first remission and found no difference in outcome between the three groups overall, but patients with high-risk features as defined above had a better outcome with allogeneic BMT [8]. Thus, allogeneic BMT for patients with high-risk features of ALL [especially poor risk cytogenetics such as Philadelphia chromosome (t9;22) positivity or t(4;11)] should be strongly considered for matched related or unrelated BMT in first remission, whereas in other patients BMT in first remission or early first relapse or second remission is an acceptable consideration. Entry of ALL patients on randomized trials remains crucial to improve and refine the therapy of this difficult disease. The Eastern Cooperative Oncology Group in the United States and the Medical Research Council in Great Britain are currently conducting a very large randomized trial of chemotherapy versus autologous BMT in younger patients with ALL (E2993). Patients with HLA-matched siblings can be allocated to allogeneic BMT. This large study should help further define the role of BMT in the therapy of ALL.

Treatment

Diet and lifestyle

- Maintenance of a well-balanced diet, regular activity, and a positive attitude enhance ones ability to tolerate the intensive chemotherapy and BMT that are components of the therapy of ALL. There are, however, no unique or unusual dietary or lifestyle features that have been identified as essential in the treatment of ALL.
- Children with certain chromosomal abnormalities, such as Down syndrome, Fanconi anemia, ataxia telangiectasia, and Bloom syndrome, are at higher risk of developing ALL. Siblings, especially twins, are at a slightly higher risk of developing ALL than is the general population.

Pharmacologic treatment

Daunorubicin

	Multiple drugs in the daunorubicin class called anthracycline antibiotics exist (*eg*, adriamycin, idarubicin, and mitoxantrone). Daunorubicin has been the most commonly used agent in acute lymphoblastic leukemia.
Standard dosage	Most commonly, either 60 mg/m^2 weekly for the initial 4 weeks of therapy or 45 mg/m^2 daily for the first 3 days of therapy by intravenous push.
Contraindications	Patients with congestive heart failure, ejection fractions below 50%, or other evidence of significant heart disease should either avoid use of daunorubicin or other anthracycline antibiotics or have these problems corrected (if possible) before initiating therapy.
Main drug interactions	Concomitant use with cyclophosphamide could increase cardiotoxic potential.
Main side effects	Cardiotoxicity, nausea, vomiting, stomatitis, myelosuppression, alopecia, pigmentation of nail beds, urticaria, elevation in serum bilirubin, AST, and alkaline phosphatase, and severe tissue necrosis with extravasation. A procedure for treatment of tissue extravasation should be in place and caution used if injected via peripheral vein. Injection via a freely flowing central venous catheter is preferred. Cumulative lifetime doses of more than 550 mg/m^2 should be avoided because of the increased risk of irreversible cardiotoxicity above this dose level. In patients who have received radiation therapy that includes the heart in the radiation field should avoid doses above 400 mg/m^2. Dosage modification is required in patients with impaired hepatic or renal function. Give allopurinol to prevent uric acid nephropathy.

Special points Daunorubicin is one of the most important drugs in the initial induction therapy of ALL in adults.

Cost effectiveness The average wholesale price (AWP) is $84.25 for a 10-mg injectable dose; the average dose for a patient with body surface area (BSA) of 2.0 m^2 at 60 mg/m^2 per dose is 120 mg.

Vincristine

The vinca alkaloids, vincristine and vinblastine, are highly effective agents in the treatment of lymphoid malignancies. Vincristine is a commonly used agent in ALL.

Standard dosage 1.4 mg/m^2 (maximum dose 2 mg) by intravenous push in a schedule of administration similar to daunorubicin above.

Contraindications Patients with peripheral neuropathy may have significant worsening of their condition. Because of the known neural toxicity of vincristine, patients with the demyelinating form of Charcot-Marie-Tooth syndrome should avoid its use.

Main drug interactions L-asparaginase may decrease vincristine clearance, and acute pulmonary reactions may occur with concomitant use of mitomycin C.

Main side effects Neurotoxicity, including numbness and weakness from peripheral neuropathy, cranial nerve paralysis, CNS depression, seizures, orthostatic hypotension, alopecia, rash, hyperuricemia, syndrome of inappropriate antidiuretic hormone (SIADH), constipation, paralytic ileus, nausea, vomiting, diarrhea, stomatitis, jaw, muscle, and leg pain, cramping, motor difficulties, and dyspnea. Tissue necrosis with extravasation can also occur with vincristine, and similar precautions to those outlined with daunorubicin above should be taken with injection.

Dosage modification is required in patients who have impaired hepatic function or preexisting neuromuscular disease. Intrathecal administration results in death and must be avoided at all costs. Give allopurinol to prevent uric acid nephropathy.

Cost effectiveness AWP is $58.42 for a 2-mg injectable dose.

Corticosteroids

The two most commonly used corticosteroids in the treatment of ALL are prednisone and dexamethasone. Corticosteroids, in general, have strong lympholytic properties that make them important therapeutic agents in the treatment of ALL.

Standard dosage Prednisone 60 mg/m^2/d orally daily the first 3 to 4 weeks of induction therapy or dexamethasone 10 mg/m^2/d. A similar dose can used for 5 days during maintenance therapy every 1 to 3 months.

Contraindications Corticosteroids are immunosuppressive and, like other chemotherapy drugs, can predispose to serious infections, including bacteremias and fungemias. Its use in high dosages may unmask the presence of latent diabetes mellitus or exacerbate preexisting diabetes mellitus. Corticosteroids should be used with caution in patients who have hypothyroidism, cirrhosis, hypertension, congestive heart failure, ulcerative colitis, and thromboembolic disorders. A short taper is preferred over sudden discontinuation of high-dose therapy.

Main drug interactions Barbiturates, phenytoin, and rifampin decrease corticosteroid effectiveness. In turn, corticosteroids can decrease the effectiveness of salicylates and vaccinations.

Main side effects Development of iatrogenic cushing syndrome, suppression of the pituitary-adrenal access, growth suppression, glucose intolerance and diabetes mellitus, hypokalemia, alkalosis, peptic ulcer, nausea, vomiting, muscle weakness, osteoporosis, fractures, cataracts, glaucoma, acne, peripheral edema, hypertension, headache, vertigo, seizures, psychoses, and pseudotumor cerebri.

Cost effectiveness AWP for a 50-mg prednisone tablet is $0.23 and average daily dose in a patient with BSA of 2.0 m^2 is 120 mg/d.

L-asparaginase

	Leukemia cells in patients with ALL, in contrast to normal cells, are frequently unable to synthesize the amino acid asparagine and depend on an exogenous source of asparagine to survive. Therefore, these leukemia cells are exquisitely sensitive to the rapid depletion of asparagine produced by L-asparaginase, which contains the enzyme L-asparagine amidohydrolase.
Standard dosage	Two commonly used regimens during induction therapy are 6000 IU/m^2 every 3 days for 12 doses and 10,000 IU/m^2 daily for 12 doses.
Contraindications	Patients with pancreatitis should not take asparaginase because this is a known side effect. Hypersensitivity to the *Escherichia coli* L-asparaginase should result in switching to either the Erwinia or polyethylene glycol forms of L-asparaginase.
Main drug interactions	Can counteract the effect of methotrexate but is often used 24 hours following methotrexate therapeutically to counteract some of the potential adverse effects of methotrexate. Decreases the metabolism of cyclophosphamide. Increases hepatotoxicity when given with mercaptopurine and can increase the risk of neuropathy with vincristine. It can also exacerbate the hyperglycemia seen with prednisone.
Main side effects	Pancreatitis, nausea, and vomiting, myelosuppression, hepatotoxicity, renal dysfunction, coughing, laryngeal spasm, hyperglycemia, transient diabetes mellitus, rash, pruritus, urticaria, hypotension, drowsiness, seizures, fever, chills, malaise, and coma. L-asparaginase can cause depletion of clotting factors and result in bleeding or thrombosis.
Special points	Levels of fibrinogen should definitely be monitored during L-asparaginase therapy and, if the fibrinogen level falls below 100 mg/dL, replacement therapy with cryoprecipitate should be administered. Consideration should also be given to monitoring protein C and S and antithrombin III levels with replacement as indicated.
Cost effectiveness	AWP is $56.80 for 10,000 IU.

Methotrexate

	Methotrexate functions by inhibiting the action of dihydrofolate reductase and blocking the conversion of dihydrofolates to tetrahydrofolates, thus blocking the transfer of one-carbon groups that are essential to the synthesis of purine nucleotides. Analogs of methotrexate were among the first agents found to have activity in ALL.
Standard dosage	High-dose therapy during induction or consolidation therapy can be 1 to 3 g/m^2 in multiple doses. Intrathecal therapy doses are 12.5 to 15 mg. Maintenance therapy dose is 20 mg/m^2 orally on a weekly schedule.
Contraindications	Severe renal or hepatic impairment.
Main drug interactions	Salicylates may delay methotrexate's clearance from the blood. Sulfonamides displace methotrexate from protein binding sites. Increased toxicity can be seen with concomitant use of nonsteroidal anti-inflammatory drugs. Probenecid decreases the renal elimination of methotrexate. Urinary alkalinizers increase methotrexate renal excretion but are recommended for use after high-dose therapy to accelerate clearance of the drug. Other drug interactions include live virus vaccines, pyrimethamine, phenytoin, and 5-Fluorouricil.
Main side effects	Nausea, vomiting, diarrhea, anorexia, stomatitis, enteritis, myelosuppression, hepatotoxicity, nephropathy (azotemia, hematuria, renal failure), cystitis, interstitial pneumonitis, anaphylaxis, diabetes, alopecia, rash, hypo- or hyperpigmentation of skin, photosensitivity, vasculitis, malaise, fatigue, dizziness, encephalopathy, seizures, confusion, fever, headaches, chills, arthralgias, blurred vision.
Cost effectiveness	AWP for 50-mg injection is $4.75 and for a 2.5-mg tablet is $3.30.

Cyclophosphamide

	Cyclophosphamide is the main alkylating agent used to treat ALL. Its introduction into the therapy in conjunction with cytarabine has improved the outcome, in particular, of T-cell ALL [9].

Standard dosage	650 to 1200 mg/m^2 at various intervals during induction and consolidation therapy.
Contraindications	High-dose therapy can cause cardiotoxicity, and cyclophosphamide should be used with caution in patients with severe underlying heart disease. Dosage adjustments are required in the presence of significant renal or hepatic impairment.
Main drug interactions	Its use in combination with cardiotoxic drugs such as daunorubicin could increase the cardiotoxic potential of daunorubicin. Drugs that affect hepatic microsomal enzymes (*eg*, phenobarbital, phenytoin, chloramphenicol) increase cyclophosphamide toxicity. Its use with succinylcholine could lead to prolonged neuromuscular blockade. Dosage modification is required in patients who have impaired hepatic function or preexisting neuromuscular disease.
Main side effects	Cardiotoxicity with high-dose therapy, hemorrhagic cystitis, alopecia, hypokalemia, amenorrhea, SIADH, hyperuricemia, nausea, vomiting, taste distortion, myelosuppression, oligospermia, interstitial pulmonary fibrosis.
Cost effectiveness	AWP for a 500-mg vial is $11.02 and for a 2000-mg vial is $44.06.

Cytarabine

	Cytarabine is a pyrimidine antimetabolite also known as cytosine arabinoside or Ara-C. It undergoes intracellular activation to form AraCTP and causes potent inhibition of DNA synthesis.
Standard dosage	A commonly used regimen is 75 mg/m^2/d by intravenous or subcutaneous injection for 4 consecutive days at weekly intervals during induction and maintenance therapy.
Contraindications	Hypersensitivity to cytarabine.
Main drug interactions	Decreases the effectiveness of gentamicin and flucytosine. Decreases oral absorption of digoxin.
Main side effects	Nausea, vomiting, stomatitis, anorexia, diarrhea, myelosuppression, hepatic dysfunction, headache, peripheral neuropathy, malaise, confusion, seizures, fever, alopecia, rash, myalgia, bone pain. An Ara-C syndrome of fever, myalgia, bone pain, rash, conjunctivitis, and malaise can occur 6 to 12 hours after administration. A syndrome of sudden respiratory distress progressing to pulmonary edema and diffuse interstitial pneumonitis has been seen with high-dose therapy. A keratitis can occur, especially with higher doses, and prophylactic corticosteroid eye drops should be given with high-dose therapy. Hemorrhagic conjunctivitis can also occur.
Special points	A serious and not uncommon toxicity is cerebellar dysfunction with ataxia. It should be monitored for, especially in patients on high-dose therapy and cytarabine promptly discontinued if cerebellar dysfunction develops. Cerebral toxicity with somnolence, personality changes, and coma has also been rarely reported.
Cost effectiveness	AWP for cytarabine is $7.38 for a 100-mg vial and $29.33 for a 500-mg vial.

Etoposide

	Etoposide is an epipodophyllotoxin and a topoisomerase II inhibitor which has known efficacy in ALL and plays a role in the consolidative therapy of the disease in some regimens. It is also a common component of the high-dose conditioning regimen used in blood and marrow transplantation. An alternative name for etoposide is VP-16.
Standard dosage	A dose used in consolidation therapy is 100 mg/m^2/d for 5 days. In combination with total body irradiation for BMT, the usual dose is 60 mg/kg over 4 hours on 1 day.
Contraindications	No absolute contraindication. Dosage should be adjusted in patients with severe hepatic and renal impairment.
Main side effects	Nausea, vomiting, diarrhea, mucositis, alopecia, myelosuppression, hypotension, tachycardia, peripheral neuropathy, somnolence, fatigue, fever, headache, chills, hepatotoxicity, thrombophlebitis, and bronchospasm.
Special considerations	Administer over a period of at least 30 to 60 minutes intravenously in lower doses and over 4 hours with the high-dose regimen for BMT.
Cost effectiveness	The AWP for a 100-mg vial is $124.45.

Mercaptopurine

	An oral purine antimetabolite. Generally given for 1.5 to 2 years as maintenance therapy.
Standard dosage	Daily dosages of 60 to 75 mg/m^2/d orally are given during induction and maintenance chemotherapy.
Contraindications	Use with caution in the presence of severe liver disease. Dosage adjustment is required in the presence of renal impairment or hepatic failure.
Main drug interactions	Allopurinol may potentiate bone marrow suppression in patients on mercaptopurine and require mercaptopurine dose reductions of 66% to 75%. Also interacts with warfarin.
Main side effects	Main side effects are nausea, vomiting, diarrhea, stomatitis, myelosuppression, hepatic toxicity, renal toxicity (including oliguria and hematuria), hyperuricemia, drug fever, rash, or hypopigmentation.
Special points	In children, blood levels of mercaptopurine metabolites correlate with relapse risk and appear related to phenotypic expression of the enzyme thiopurine methyltransferase.
Cost effectiveness	The AWP for a 50-mg tablet is $2.33.

Interventional procedures

Right central venous catheter placement

	The placement of a semipermanent indwelling central venous catheter (also known as a right atrial catheter) is essential for patients undergoing induction and consolidation therapy of ALL. These catheters are placed by surgeons or interventional radiologists via a subclavian approach with construction of a subcutaneous tunnel in the upper chest and an exit site for the catheter in the lower chest wall. A double or triple lumen catheter usually is placed to facilitate the intravenous administration of drugs and blood products and for the frequent blood withdrawals that are required for laboratory tests and blood cultures.
Standard procedure	Placement of central venous catheter with subcutaneous tunnel.
Contraindications	Severe thrombocytopenia (<30–50 x 109/L) or coagulation abnormalities. Placement can proceed once the thrombocytopenia or coagulation abnormalities are improved or corrected.
Complications	Pneumothorax, arterial puncture, hematoma formation, cellulitis along subcutaneous tunnel, catheter-associated bacteremia or sepsis.
Cost effectiveness	Considered essential for administration of intensive ALL therapy. Precludes need for frequent peripheral intravenous accesses and frequent needle sticks. Cost varies considerably depending on type of catheter and type of setting where placement occurs.

Other therapies

Cranial radiotherapy

Standard procedure	Radiation therapy to the whole brain in a dosage of 2400 cGy in 10 fractions of 240 cGy each is typically given after initial induction and intensification therapy. Patients with documented CNS leukemia may also receive 1200 cGy of spinal radiation. The cranial irradiation is sometimes given in conjunction with doses of intrathecal methotrexate or cytarabine to treat or prevent the development of meningeal leukemia. Without prophylactic therapy, a high proportion of patients will go on and develop meningeal involvement.
Contraindications	None, unless patient has received prior cranial irradiation in high doses for another malignancy.
Complications	Nausea, vomiting, alopecia, fatigue, delayed somnolence syndrome (drowsiness, apathy, anorexia, irritability or dizziness, usually self-limited).
Cost effectiveness	An essential component of the therapy of ALL to prevent CNS relapse.

Blood and marrow transplantation

As outlined previously, blood and marrow transplantation has a definite role in the treatment of patients with high-risk ALL. Its role in standard risk patients in first remission is less well-defined. Patients who are in early relapse or second or greater remission of their disease can benefit from BMT because further chemotherapy is not usually able to maintain long-term disease-free survival.

The relative role of allogeneic (from a related or unrelated donor) versus autologous transplant has been compared in prospective and retrospective studies [8,10,11,12••]. Autologous transplant is associated with low transplant-related morbidity and mortality but high relapse rate because of the lack of a graft-versus-leukemia effect associated with allogeneic transplant and the risk of reinfusing occult leukemia cells in the blood or marrow stem cell product. Conversely, allogeneic transplant is associated with a lower relapse rate but higher treatment-related mortality. Treatment-related mortality tends to increase in older patients, patients with significant comorbidities, and patients with advanced disease who are heavily pretreated. If transplant is indicated, the first choice of donor is an HLA-matched sibling. If a closely matched sibling is not available, then an autologous or unrelated donor allogeneic transplant can be considered [12••]. The optimal choice depends on individual patient characteristics.

Standard procedure High-dose chemotherapy usually with cyclophosphamide (60 mg/kg/d for 2 days) or etoposide (60 mg/kg for 1 day) preceded or followed by fractionated whole body radiation therapy in doses of 1200 to 1440 cGy is followed by infusion of allogeneic or autologous bone marrow or peripheral blood stem cells. In the allogeneic setting, prevention of graft-versus-host disease (GVHD) with cyclosporine or tacrolimus combined with low-dose methotrexate is given. Patients require intensive supportive care with antibiotics and blood products to support them through this therapy.

Contraindications Elderly age and significant comorbidities or organ dysfunction.

Complications Numerous, but can be broadly categorized as infectious (usually bacterial, fungal, or viral), organ toxicity (mucositis, veno-occlusive disease of the liver, renal dysfunction, cardiomyopathy, pulmonary toxicity including acute respiratory distress syndrome), acute and chronic GVHD, and relapse of the patient's primary disease. In the allogeneic setting, relapse can be treated with infusion of donor lymphocytes to induce a graft-versus-leukemia effect, although this approach has not been found to be as effective in ALL as in myeloid malignancies. Death within the first 100 days of transplant from toxicity can occur in anywhere from 5% to 40% of patients (allogeneic higher than autologous).

Cost effectiveness Hospitalization for transplant can cost anywhere from $50,000 to $200,000 or more depending on the type of transplant (allogeneic is higher than autologous) and the complications that develop. However, the procedure can be cost effective compared with recurring cycles of chemotherapy that would be necessary in the relapsed setting.

Emerging therapies

- Several new chemotherapeutic agents have shown promise in the therapy of ALL. One of particular interest is 506U78, which is a prodrug of guanine arabinoside, a purine analog, that has shown remarkable efficacy in the therapy of relapsed and refractory T-cell ALL [13]. Several agents have shown activity in vitro, including FR901228 [14], UCN-01, a protein kinase C inhibitor [15], flavopiridol, a cyclin kinase inhibitor [16], and arsenic trioxide [17]. These agents have either not entered or are just entering clinical trials.
- Monoclonal antibody therapy has found application in many human malignancies and may have a role to play in ALL. Campath-1H, an anti-CD52 chimeric monoclonal antibody, appears to have activity in ALL [18]. A CD19 specific antibody conjugated to a tyrosine kinase inhibitor, genistein, has also shown promise in nonhuman primates and in preliminary studies in humans [19].

- A novel agent known as STI 571, which is a specific tyrosine kinase inhibitor, appears to specifically inhibit the *bcr-abl* tyrosine kinase found in chronic myelogenous leukemia and *bcr-abl* positive acute leukemias, including primarily ALL. In a clinical trial, it had significant cytoreductive activity and reduced the presence of Philadelphia chromosome positive cells in some patients [20].
- The results of randomized trials such as the MRC/ECOG 2993 trial should provide further knowledge of the role of blood and marrow transplant in the treatment of adult patients with standard- and high-risk ALL. New developments in blood and marrow transplant, including use of cord blood transplants and less intensive conditioning regimens (nonmyeloablative), have the potential to make BMT applicable to a wider number of patients and also safer by lessening many of the toxic side effects associated with the procedure.

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