Burkitt's and Burkitt-like Lymphoma

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Opinion statement

Burkitt's and Burkitt-like lymphoma (BL/BLL) are aggressive B-cell malignancies with a high proliferative rate that may be fatal within months if not treated promptly. Furthermore, treatment of BL/BLL requires comprehensive supportive care to avoid disease-related complications such as acute renal failure secondary to tumor lysis syndrome. Improvements in our understanding of the biology of BL and BLL have led to more effective therapeutic protocols. Clinical trials have demonstrated that short duration, multi-agent, dose-intensive chemotherapy regimens combined with aggressive central nervous system therapy results in long-term survival rates in children and young adults near 70% to 80%, whereas long-term disease-free survival rates in older adults remains suboptimal at 15% to 25%. Outcomes in HIV-associated BL/BLL are improved because of more effective chemotherapy regimens and enhanced HIV care. Autologous bone marrow transplantation has proven feasible in many patient populations with BL/BLL and may lead to cure in selected patients. Improved therapeutic strategies are warranted, such as integrating agents such as monoclonal antibodies to combination dose-intensive chemotherapy. Moreover, further study into the molecular biology of BL/BLL with attention to the role of c-myc dysregulation is needed to help predict prognostic factors and for the development of molecular targeted therapies. Clinical trials remain critical to determine the most effective treatment regimens that will continue to improve cure rates in this aggressive but treatable disease.

Introduction

Burkitt's non-Hodgkin's lymphoma (BL) and Burkitt-like lymphoma (BLL) are high-grade lymphomas that require prompt systemic chemotherapy. The prognosis of BL/BLL had been poor because of its rapid doubling time of 24 hours, frequent extranodal involvement (especially abdominal and central nervous system [CNS] involvement), and high rates of relapse. Despite the aggressive growth pattern of BL/BLL, it is a curable disease. During the last 20 years, survival rates have improved in children through the use of shorter duration, dose-intensive systemic chemotherapy protocols and early prophylaxis and treatment of the CNS disease. Similar regimens have been adapted in adults using shorter, intensive, multi-agent chemotherapy plans, which have resulted in similar improved long-term survival rates, with more than 50% of all adults cured of their disease [1••,2•,3••,4,5••,6]. Furthermore, attentive medical care is imperative to prevent and treat disease-related complications such as tumor lysis syndrome (TLS). Surgery and radiation play minor roles in the management of BL/BLL. Bone marrow transplantation (BMT) is a feasible and therapeutic option for patients with relapsed disease, including selected patients with HIV, but the issue of early transplant in high-risk patients has not been resolved. Incorporation of newer therapeutic agents, such as monoclonal antibodies, in combination with dose-intensive chemotherapy programs is being studied in adult patients with BL/BLL. Research into the cellular and molecular biology of BL/BLL with attention to the role of c-myc dysregulation is being pursued.

Treatment

Lifestyle factors

- Burkitt's lymphoma accounts for fewer than 1% of lymphomas in adults. Acute lymphocytic leukemia (ALL) French-American-British (FAB) L-3 accounts for 2% to 4% of all cases of ALL in adults [7••]. BL and ALL FAB stage L-3 represent different clinical phenotypes of the same disease. Adult patients commonly have a combination of lymphomatous and leukemic manifestations. BL, originally termed undifferentiated lymphoma in the Rappaport classification, was classified as small non–cleaved-cell lymphoma Burkitt's type in the working formulation and then classified as BL in the revised European-American Lymphoma classification [8]. The World Health Organization classifies BL as a distinct category, but recognizes its several morphologic variants, specifically BLL and Burkitt's with plasmacytoid differentiation (AIDS-associated) [9,10•]. In a recent analysis of BLL, the t(8;14) translocation was identified in approximately 80% of the patients. The tumor cells contained a high fraction of actively growing cells, with a mean Ki67 labeling index of 88%; the median survival rates were similar to those of BL [10•]. There are three distinct clinical and genetic subtypes of BL: endemic, sporadic, and immunodeficiency-associated [11]. Virtually 100% of endemic BL cases contain the Epstein-Barr virus (EBV) genome. Twenty percent to 35% of sporadic BL cases in Europe and North America are EBV-positive, increasing to 50% to 80% in South America and parts of the Middle East. Only 30% to 35% of immunodeficiency-associated BL cases are EBV-positive, despite the heavy EBV load in most patients with HIV [11]. The contribution of EBV to the oncogenesis of BL is unclear and reviewed elsewhere [12••]. BL is universally associated with translocation of the c-myc gene from chromosome 8 to the immunoglobulin (Ig) heavy chain region on chromosome 14 [t(8;14) (q24;q32)] or, less commonly, to light chain loci on chromosome 2 [t(2;8) (p12;q24)] or 22 [t(8;22) (q24;q11)] [12••]. Chromosome translocations lead to dysregulation with a high level of expression of the proto-oncogene, c-myc, a gene that normally plays a role in controlling cell proliferation, differentiation, and apoptosis [12••].

Pharmacologic treatment

- In the 1970s, initial treatments for African children with BL included single agent cyclophosphamide, which demonstrated response rates near 80% [13]. However, most children relapsed with systemic and CNS disease. Subsequent combination chemotherapy using cyclophosphamide, vincristine, and methotrexate demonstrated higher response rates and longer remissions of the disease. In patients with advanced BL, clinical trials in the United States in the 1970s demonstrated long-term survival rates of 30% to 40% [14]. Clinical trials for children over the next 20 years evaluated shorter, dose-intensified systemic chemotherapy regimens with routine CNS prophylaxis and treatment, which have demonstrated long-term disease-free survival (DFS) rates of 70% to 80% [15].
- The adult experience with BL treatment has been similar to that of children. Older regimens using traditional ALL chemotherapy protocols administered over 1 to 3 years or standard intermediate grade lymphoma regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and related protocols yielded poor long-term DFS rates [6,16–18]. There have been several effective chemotherapy regimens developed during the last decade for BL treatment in adults, which have modeled the protocols of

shorter duration, dose intense chemotherapy used for children. European and American organizations introduced treatment protocols for adults that included anthracyclines, vincristine, high-dose fractionated cyclophosphamide (or ifosfamide), intermediate- or high-dose methotrexate, cytarabine, and epipodophyllotoxins with early and repeated CNS treatment with intrathecal chemotherapy with or without cranial irradiation, which provided long-term DFS rates of 50% to 60% [19–23].

- More recently developed adult protocols are approaching similar therapeutic efficacy rates as those demonstrated in children [2•,24]. Magrath *et al.* [2•] and Adde *et al.* [3••] at the National Cancer Institute (NCI) developed protocol 89-C-41, consisting of two alternating multi-agent chemotherapy regimens (known as CODOX-M and IVAC) administered for a total of four cycles (Table 1). They treated 55 patients with BL/BLL and 11 patients with diffuse, large B-cell lymphoma (40 children and 26 adults). The median age of the adult patients treated in protocol 89-C-41 was 25 years; all patients were younger than 60 years. With a median follow-up of 48 months, 61 of 66 patients (92%) achieved a complete remission (CR). Two of 61 patients relapsed, but one is a long-term survivor after haplotype-mismatched BMT, yielding an overall event-free survival (EFS) rate at 1 year and later of 85%. In an updated report, there were no significant differences demonstrated between adults and children with respect to EFS (84% and 85%, respectively; $P = 0.92$). Twenty-two of 25 adults remained alive and disease free, with a median follow-up of 47 months [3••]. The previous NCI experience using the CODOX-M regimen alone (without IVAC) achieved long-term EFS of only 55%. The major toxicities in protocol 89-C-41 were hematologic (pancytopenia approaching 95%–100% incidence by last cycle of IVAC) and infectious (40%–60% infection rate with 20%–28% bacteremia rate). Neurologic toxicity ranged from mild to severe in 57% of the patients. In patients entering the 89-C-41 study before 1994, an unusual and severe atypical neuropathy was documented [25]. This neuropathy was usually of acute onset with symptoms of excruciating pain confined to the lower limbs, especially the soles of the feet, with concomitant motor weakness. This syndrome was found in 12 patients (seven adults and five children), with adults experiencing worse overall neuropathy ($P = 0.0006$) in addition to the severe atypical variant. Moreover, data analysis suggested a possible synergistic effect between administration of colony-stimulating factors and vincristine in the development of this neuropathy (10 of 11 patients received colony-stimulating factor) and a strong association with cumulative vincristine dose, especially in the first CODOX-M cycle. The day 15 vincristine dose in the first CODOX-M cycle has since been omitted from this protocol.
- The M. D. Anderson group has evaluated a protocol known as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), which uses alternating courses of chemotherapy for a total of eight cycles to treat patients with ALL FAB L-3 (Table 2) [5••]. Twenty-one of 26 patients (81%) achieved CR, with 12 of 21 patients in continuous remission at a median follow-up of 3.5 years. The overall 3-year survival rate was 49%, with age, anemia, and peripheral blasts identified as independent worse prognostic factors. The overall median age of patients in this trial was 58 years, with the median age of those younger than 60 years (14 patients; 54%) of 38 years. The 3-year survival rate for patients younger than 60 years of age was 77%, and for patients older than 60 years of age (12 patients; 46%) 17% ($P < 0.01$).
- Lee *et al.* [1••], for the cancer and leukemia group B (CALGB), reported the activity of a similar brief duration, high intensity chemotherapy protocol (Table 3). Twenty-four patients with ALL FAB L-3 and 30 patients with BL

Table 1. Treatment protocol 89-C-41 [2•,3••]

Agent	Dosage	Timing
Regimen A (CODOX-M), cycles 1 and 3		
Cyclophosphamide	800 mg/m^2 IV	Day 1
	200 mg/m^2 IV	Days 2 to 5
Doxorubicin	40 mg/m^2 IV	Day 1
Vincristine	1.5 mg/m^2 IV	Cycle 1, days 1 and 8 Cycle 2, days 1, 8, and 15
Methotrexate (MTX)	1200 mg/m^2 IV	Over 1 hour
	240 mg/m^2 per hour by CI	Over next 23 hours
Leucovorin	192 mg/m^2 IV	Begun 36 hours after start of MTX and continued every 6 hours until serum MTX is < 5 × 10^{-8} mol/L
Intrathecal therapy		
Cytarabine	70 mg	Days 1 and 3; if patient also has lymphomatous meningitis, give additional dose on day 5 in first cycle
MTX	12 mg	Day 15; if patient also has lymphomatous meningitis, give additional dose on day 17 in first cycle
Regimen B (IVAC), cycles 2 and 4		
Ifosfamide	1500 mg/m^2 IV	Days 1 to 5, with mesna uroprotection
Etoposide	60 mg/m^2 IV	Days 1 to 5, with mesna uroprotection
Cytarabine	2000 mg/m^2 IV	Days 1 and 2, every 12 hours (four total doses)
Intrathecal therapy		
MTX	12 mg	Day 5; if patient also has lymphomatous meningitis, give additional cytarabine 70 mg on days 7 and 9 for one cycle

CI—continuous infusion; IV—intravenously.

(overall median age 44 years) received a cytoreductive prephase with cyclophosphamide and corticosteroids in an attempt to ameliorate TLS. This was followed by alternating courses of chemotherapy for a total of seven cycles (Table 3). Overall, 43 of 54 patients (80%) achieved CR (18 of 24 patients with ALL and 25 of 30 patients with BL) with 28 patients alive (52%) and in continuous CR (median follow-up 5.1 years). Severe neurologic toxicity occurred in a large percentage of the patients, which was likely in part secondary to the aggressive prophylactic CNS intrathecal schedule that included cranial irradiation for all patients (Table 3). Neurologic toxicity included transverse myelitis, which was progressive and debilitating for five patients. Other neurologic toxicities included severe peripheral neuropathy (two patients) and central neurologic disease (transient aphasia/arm weakness and irreversible cortical blindness). CALGB has since modified their intrathecal therapy plan, reserving cranial irradiation for patients with marrow or CNS disease and dividing in half the total amount of intrathecal chemotherapy administered in the protocol.

- Relapsed or refractory BL/BLL or ALL FAB L-3 disease has not been well-studied. Drugs used for salvage have included high-dose methotrexate and high-dose cytarabine or etoposide and cisplatin. Atra *et al.* [26] reported on their experience of 26 children with progressed or relapsed ALL FAB L-3 or B-cell non-Hodgkin's lymphoma (NHL) after first-line short, intensive, multi-agent chemotherapy regimens. Second-line therapy resulted in remission in 30% of the patients, with 11% long-term survivors. Experience from the pediatric literature has suggested that patients with BL and primary refractory disease could be treated with salvage chemotherapy and BMT. Philip *et al.* [27]

Table 2. Treatment protocol of hyper-CVAD [5••]

Agent	Dosage	Timing
Odd cycles (1, 3, 5, 7)		
Cyclophosphamide	300 mg/m^2 IV	Days 1 to 3 every 12 hours (six total doses)
Mesna	600 mg/m^2 daily by CI	Days 1 to 3
Doxorubicin	50 mg/m^2 IV	Day 4
Vincristine	2 mg IV	Days 4 and 11
Dexamethasone	40 mg orally	Once daily on days 1 to 4 and days 11 to 14
Intrathecal therapy		
Methotrexate (MTX)	12 mg	Day 2 of each course*
Cytarabine	100 mg	Day 7 of each course*
Even cycles (2, 4, 6, 8)		
MTX	1000 mg/m^2 IV	Day 1 over 24 hours
Leucovorin	50 mg IV	Start 12 hours after MTX
	15 mg IV	Every 6 hours until serum MTX < 1×10^{-8} mol/L
Cytarabine	3000 mg/m^2 IV	Days 2 and 3 every 12 hours (four total doses)
Intrathecal therapy		
MTX	12 mg	Day 2 of each cycle*
Cytarabine	100 mg	Day 7 of each cycle*

*If patient has lymphomatous meningitis on diagnosis, increase intrathecal therapy to twice weekly until the cerebrospinal fluid cell count normalizes.
CI—continuous infusion; hyper-CVAD—hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IV—intravenously.

described the outcome of 27 pediatric patients with refractory BL from the SFOP 84 trial. Fifteen patients had a partial response to salvage therapy (etoposide, etoposide and high-dose cytarabine, or MIME) and were treated with high-dose therapy (one allogeneic). All patients without transplantation died, whereas four of the 15 patients with transplantation were alive and likely cured of their disease. In adult BL, reports of salvage chemotherapy followed by autologous BMT have demonstrated varied results, with some studies reporting few long-term survivors [28]. Sweetenham *et al.* [29] transplanted 70 patients in first remission and 47 patients with relapsed disease. The 3-year actuarial overall survival rate was 72% for patients transplanted in first CR, 37% for patients in chemosensitive relapse, and 7% for patients with chemoresistant relapse. Nademanee *et al.* [30] transplanted 10 patients with BL/BLL in first remission and reported 60% 3-year DFS rate. They also studied autologous BMT in refractory and relapsed disease and demonstrated 5-year DFS rate of 30% for patients transplanted in induction failure and 34% for relapsed patients [31].

- Allogeneic BMT has not been well-studied in the BL/BLL patient population, although there are reports of allogeneic transplantation in relapsed and refractory BL/BLL [32,33], including one report of successful nonmyeloablative transplantation in a patient with refractory BL [34]. Bureo *et al.* [35] reported on their experience with autologous and allogeneic transplantation in 46 pediatric patients with high-grade NHL transplanted in six Spanish centers. Fourteen patients underwent allogeneic BMT and 32 autologous BMT (46% lymphoblastic lymphoma, 41% BL, and 13% diffuse large cell lymphoma). More than 60% of the patients were in second or third CR, with 28% in first CR and 11% with active disease (four of five with active chemosensitive disease). The overall EFS rate was 58%, with a median follow-up of 33 months. The EFS was similar for patients with allogeneic or autologous BMT.

Table 3. Cancer and leukemia group B treatment protocol [1••]

Agent	Dosage	Timing
Cycle 1		
Cyclophosphamide	200 mg/m^2 intravenously (IV)	Days 1 to 5 (five total doses)
Prednisone	60 mg/m^2 orally	Days 1 to 7
Cycles 2, 4, and 6		
Ifosfamide	800 mg/m^2 IV	Days 1 to 5 (five total doses)
Mesna	200 mg/m^2 IV	At 0, 4, and 8 hours after ifosfamide
Methotrexate (MTX)	150 mg/m^2 IV	Over 30 minutes
	1350 mg/m^2 IV (total dose 1.5 g/m^2)	For 23.5 hours
Leucovorin	50 mg/m^2 IV	36 hours after MTX initiation
	15 mg/m^2 IV	Every 6 hours until MTX is < 10^{-8} M
Vincristine	2 mg IV	Day 1
Etoposide	80 mg/m^2 IV	Days 4 and 5
Dexamethasone	10 mg/m^2 orally	Days 1 to 5
Intrathecal therapy		
MTX	15 mg	Days 1 and 5 (each course)*
Cytarabine	40 mg	Days 1 and 5 (each course)*
Hydrocortisone	50 mg	Days 1 and 5 (each course)*
Cycles 3, 5, and 7		
Cyclophosphamide	200 mg/m^2 daily IV	Days 1 to 5
MTX	150 mg/m^2 IV	Over 30 minutes
	1350 mg/m^2 IV (total dose 1.5 g/m^2)	For 23.5 hours
Leucovorin	50 mg/m^2 IV	36 hours after MTX initiation
	15 mg/m^2 IV	Every 6 hours until MTX is < 10^{-8} M
Vincristine	2 mg IV	Day 1
Doxorubicin	25 mg/m^2 IV	Days 4 and 5
Dexamethasone	10 mg/m^2 orally	Days 1 to 5
Intrathecal therapy		
MTX	15 mg	Days 1 and 5 (each course)*
Cytarabine	40 mg	Days 1 and 5 (each course)*
Hydrocortisone	50 mg	Days 1 and 5 (each course)*
Cranial irradiation†	24 Gy	12 fractions given after cycle 3 (after day 4, cycle 3) and before cycle 4

*This part of the regimen has been modified secondary to neurotoxicity. Patients receive intrathecal therapy on day 1 for only cycles 2 to 7 (12 doses reduced to six doses).
†This part of the regimen has been modified secondary to neurotoxicity. Cranial irradiation is reserved for patients with marrow or central nervous system disease. Irradiation begins after chemotherapy is completed.

- The overall number of HIV-associated NHL cases is decreasing with improved HIV treatments, but the virus has led to an overall increase in BL cases [7••]. The NCI of Italy reported 131 cases of HIV-associated NHL over an 8-year period, of which 35% were BL [36]. Histology with HIV-associated NHL will be high grade in up to two-thirds of the cases. Immunoblastic and diffuse large cell histologies usually predominate in most series, with BL/BLL representing 10% to 30% of cases in HIV-associated NHL [37•,38•,39,40]. Several studies have examined varied therapeutic options in the HIV-positive NHL population, including standard dose chemotherapy protocols [38•,39] and reduced dose regimens. The complete response rates were 30% to 60%, with 5-year survival rates of less than 50%. Few reports have addressed the treatment of HIV-positive BL/BLL separately, although anecdotal case reports of aggressive chemotherapy plans yielding long-term survival have been reported. Spina *et al.* [36] reported that the CR rates were lower in HIV-

positive BL than in HIV-negative BL (40% and 65%, respectively; $P = 0.03$). The overall survival rate was worse in HIV-positive patients with BL (median 7 months vs not yet reached), whereas the DFS rate at 4 years was identical in the two groups. These rates resulted from a higher incidence of infection-related deaths in the HIV-positive BL group, but this group also received lower intensity chemotherapy when compared with their HIV-negative counterparts. Infusional chemotherapy (cyclophosphamide, doxorubicin, etoposide) with rituximab has been studied in phase I/II trials in HIV-associated NHL. Response rates have been encouraging at 90%, with 86% CR rate [41]. The integration of highly active antiretroviral therapy (HAART) into the treatment plan of HIV-positive NHL appears to have improved patient outcomes [42–44], although further prospective trials are warranted. Autologous BMT has been evaluated in patients with HIV-associated NHL, including relapsed disease [45]. Most reports have been small, but high-dose chemotherapy with stem cell reinfusion has proven feasible in this high-risk patient population and may improve the survival rate in selected patients [45–48]. There are only case reports of allogeneic BMT in HIV-positive patients with NHL [46]; further randomized trials are warranted. Adverse prognostic factors such as CD4 cell count fewer than 100×10^6/L, poor performance status, high lactic dehydrogenase (LDH), and immunoblastic histology have been identified, which should help determine subsets of patients in whom BMT would be feasible and advantageous [39,49,50].

- Prevention and treatment of TLS is an important component of medical care for patients with highly proliferating diseases such as BL/BLL. TLS is a metabolic complication of BL and other high-grade lymphomas that may lead to significant morbidity and can be fatal [51]. Hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia occur when normal renal excretion and buffering mechanisms of the kidneys become overwhelmed and cannot excrete the large amount of intracellular content (nucleic acids such as purine or phosphorus, and potassium). They are released after cytotoxic therapy or spontaneously [52]. Clinical factors that contribute to the incidence of acute renal failure (ARF) include intravascular volume depletion and compromised baseline renal function. The metabolic factors involved in the development of ARF include uric acid nephropathy with subsequent precipitation of uric acid crystals and calcium phosphate [51,53]. Early prevention and therapy of TLS includes aggressive hydration before and during cytotoxic therapy to attain adequate urine output, increasing ionization and subsequent solubility of uric acid and phosphorus through alkalinization (urinary pH > 7.0) through sodium bicarbonate or acetazolamide, correcting specific electrolyte disturbances, and decreasing uric acid and phosphorus concentrations using pharmacologic agents such as allopurinol [51,52,54]. Allopurinol is a xanthine analog that is converted into the pharmacologic active metabolite, oxipurinol, which in turn inhibits xanthine oxidase, the enzyme responsible for converting hypoxanthine to xanthine and xanthine to uric acid [55]. An intravenous preparation of allopurinol has been available on a compassionate use basis since 1969. Smalley *et al.* [55] reviewed the data from more than 1000 patients treated from 1969 to 1990 and demonstrated that intravenous allopurinol effectively prevented hyperuricemia in more than 90% and lowered plasma uric acid levels to control levels in 57% of adults and 88% of children. The toxicities were minimal. A novel approach to the prophylaxis and management of TLS includes the use of the recombinant urate oxidase agent, rasburicase, which has been demonstrated to be a safe and effective treatment option [56]. This agent catalyzes the enzymatic oxidation of uric acid into allantoin, which is a substance approximately five times more soluble than uric acid (the normal endpoint of purine metabolism in humans is uric acid).

Cyclophosphamide

Standard dosage	Varied, depending on protocol. Ranges from 200 to 800 mg/m^2, usually administered in a hyperfractionated fashion.
Contraindications	Severe renal insufficiency, hypersensitivity to drug, class, or compound. Use caution in patients with significant hepatic enzyme changes or damage.
Main drug interactions	Allopurinol may increase risk of bone marrow suppression. Doxorubicin may increase risk of hemorrhagic cystitis. Avoid succinylcholine use within 10 days because it may potentiate and prolong neuromuscular blockade (succinylcholine metabolism decreased). Avoid drugs that may cause bone marrow suppression.
Main side effects	Common: Myelosuppression (dose limiting; platelets usually spared; nadir usually reached in 10–14 days, with recovery by day 21). Nausea, vomiting, mucocutaneous effects (reversible alopecia, darkening of skin and nails, mucositis uncommon), bladder damage (hemorrhagic or nonhemorrhagic cystitis may occur in 5%–10%, usually reversible), amenorrhea, and azoospermia. Uncommon: Interstitial pulmonary fibrosis, secondary neoplasia, acute cardiotoxicity (pericardial effusion, congestive heart failure, myocardial infarction).
Special points	Administer in the morning, maintain adequate fluid intake, and have patient empty bladder several times daily to avoid cystitis. Intravenous concomitant mesna treatment may be administered to ameliorate bladder complications.
Cost effectiveness	Single IV dose of 1000 mg costs $30.00 to $39.99.

Doxorubicin

Standard dosage	Varied, depending on protocol. Ranges from 25 to 50 mg/m^2.
Contraindications	Prior anthracycline doses of 450 to 550 mg/m^2, congestive heart failure or cardiomyopathy, highly elevated bilirubin, hypersensitivity to drug, class, or compound. Use caution with concomitant radiation therapy.
Main drug interactions	Digoxin (may increase digoxin levels), mercaptopurine (may increase hepatotoxicity), phenobarbital (may decrease doxorubicin levels), phenytoin (may decrease phenytoin levels), verapamil (may increase risk of doxorubicin cardiotoxicity). Avoid drugs that may cause bone marrow suppression.
Main side effects	Myelosuppression (dose limiting; nadir white blood cell count and platelets usually reached in 10 to 14 days, with recovery typically by day 21). Nausea, vomiting, mucocutaneous effects (stomatitis can be dose limiting, reversible alopecia, recall of skin reaction due to prior radiotherapy is common, hyperpigmentation). Cardiotoxicity (potentially irreversible congestive heart failure from cardiomyopathy; incidence depends on cumulative dose, which should not exceed 550 or 450 mg/m^2 if previous chest radiotherapy or significant cardiac disease).
Special points	Careful calculation of prior anthracycline therapy and risk assessment of cardiac disease. Repeat measurements of ejection fraction often in patients at high risk of cardiac toxicity. Administer half dose for serum bilirubin of 1.2 to 3.0 mg/dL, and quarter dose for serum bilirubin greater than 3.0 mg/dL.
Cost effectiveness	Single IV dose of 70 mg costs $50.00 to $59.00.

Vincristine

Standard dosage	Varied, depending on protocol. Ranges from 1.5 to 2 mg^2.
Contraindications	Preexisting neurologic disease; hypersensitivity to drug, class, or compound; intestinal obstruction or paralytic ileus; pregnant or lactating patients.
Main drug interactions	Azole fungals, clarithromycins, cyclosporine, diltiazem, erythromycin, protease inhibitors, and verapamil may increase risk of neurotoxicity (hepatic metabolite inhibition). Avoid drugs that may cause bone marrow suppression.
Main side effects	Neurotoxicity, which is dose dependent and limiting. Mild paresthesias and decreased deep tendon reflexes. More severe peripheral neuropathies, severe constipation, or ileus are indications to reduce or hold therapy. Autonomic dysfunction with orthostatic hypotension or urinary retention may be seen.

Special points	Administer as slow intravenous push, avoiding extravasation. Because neurotoxicity is cumulative, neurologic evaluation should be performed before each dose and therapy decreased or stopped if severe paresthesias, motor weakness, or other severe abnormalities occur.
Cost effectiveness	Single IV dose of 2 mg costs $30.00 to $39.99.

Methotrexate

Standard dosage	Varied, depending on protocol. Ranges from 1000 to 1500 mg/m^2 over 24 hours.
Contraindications	Patients with extensive body cavity effusions or alcohol abuse history; pregnant or lactating patients. Avoid use or reduce dosage in patients with severe renal or liver insufficiency, or hypersensitivity to drug, class, or compound.
Main drug interactions	Oral anticoagulants (*eg*, warfarin) may be potentiated by methotrexate. Avoid sulfonamides, aspirin, phenytoin, tetracycline, and other protein-bound drugs that may displace methotrexate and cause an increase in free drug. Avoid drugs that may cause bone marrow suppression.
Main side effects	Common: Myelosuppression, with nadir at 6 to 10 days after a single intravenous dose; recovery is rapid. Nausea and vomiting (occasional), mucocutaneous effects (mild stomatitis is common and a sign that a maximum tolerated dose has been reached). Uncommon: Acute hepatocelluar injury, hepatic fibrosis, renal tubular necrosis.
Special points	Intrathecal methotrexate must be mixed in a buffered physiologic solution containing no preservatives.
Cost effectiveness	Single IV dose of 1500 mg costs $360.00 to $380.00.

Ifosfamide

Standard dosage	Varied, depending on protocol. Ranges from 800 to 1500 mg/m^2 daily for 5 consecutive days.
Contraindications	Severe renal insufficiency; hypersensitivity to drug, class, or compound.
Main drug interactions	Other drugs that may cause bone marrow suppression.
Main side effects	Myelosuppression is dose limiting. The platelets are usually spared; granulocyte nadir usually at 10 to 14 days, with recovery by day 21. Nausea and vomiting, mucocutaneous effects (alopecia common, mucositis rare). Hemorrhagic cystitis is common and dose limiting unless a uroprotective agent such as mesna is used; with mesna, the incidence of hemorrhagic cystitis is 5% to 10%. Infertility is common (as with other alkylating agents).
Special points	Must be used with mesna (Mesnex; Bristol-Myers Squibb, New York, NY) to prevent hemorrhagic cystitis. Mesna dose is at least 20% of ifosfamide dose administered immediately before (or mixed with) the ifosfamide dose and again at 4 and 8 hours after the ifosfamide to detoxify the urinary metabolites that cause hemorrhagic cystitis. Vigorous hydration is warranted with a minimum of 2 liters of oral or intravenous hydration daily; administer as slow intravenous infusion.
Cost effectiveness	Single IV dose of 3000 mg costs $250.00 to $260.00.

Etoposide

Standard dosage	Varied, depending on protocol. Ranges from 60 to 80 mg/m^2.
Contraindications	Impaired liver function, hypersensitivity to drug, class, or compound.
Main drug interactions	Cyclosporine (use alternative or reduce etoposide dose by 50%); combination may increase etoposide levels; risk of toxicity with high-dose cyclosporine (clearance decreased). Avoid drugs that may cause bone marrow suppression.
Main side effects	Myelosuppression; dose-limiting leukopenia and less severe thrombocytopenia have a nadir at 14 to 16 days, with recovery by day 21. Nausea and vomiting (mild to moderate), mucocutaneous effects (alopecia common, stomatitis uncommon).
Special points	Administer as 30- to 60-minute infusion to avoid hypotension; monitor blood pressure during infusion and avoid extravasation. Decrease dose by 50% for bilirubin levels of 1.5 to 3 mg/dL; decrease by 75% for bilirubin of 3 to 5 mg/dL; discontinue if bilirubin level is more than 5 mg/dL.
Cost effectiveness	Single IV dose of 100 mg costs $5.00 to $10.00.

Cytarabine

Standard dosage	Varied, depending on protocol. Ranges from 2000 to 3000 mg/m^2.
Contraindications	Prior anthracycline doses of 450 to 550 mg/m^2; highly elevated bilirubin level.
Main drug interactions	Avoid drugs that may cause bone marrow suppression.
Main side effects	Common: Myelosuppression is universal, with recovery by day 21. Neurotoxicity is usually mild and reversible, but can be permanent and fatal; cerebellar toxicity is common, particularly in the elderly and in patients with elevated creatinine. Conjunctivitis, nausea, vomiting, and diarrhea. Uncommon: Hepatic toxicity with cholestatic jaundice.
Special points	Administer in 1- to 3-hour infusion; longer infusion enhances toxicity. CNS toxicity is increased in patients with decreased creatinine clearance. Administer two drops hydrocortisone in each eye four times daily during and 48 hours after treatment.
Cost effectiveness	Single IV dose of 1000 mg costs $50.00 to $59.00.

Allopurinol

Standard dosage	Varied, depending on renal function. Ranges from 100 to 800 mg orally daily, in two to four divided doses. Use higher doses for 2 to 3 days after initial chemotherapy, with subsequent decrease in daily dosing. Intravenous formulation administered 40 to 150 mg/m^2 every 8 hours.
Contraindications	Hypersensitivity to drug, severe renal dysfunction.
Main drug interactions	Administer allopurinol 1 hour before antacids because combination may decrease allopurinol efficacy. Combinations of angiotensin-converting enzyme inhibitors, diuretics, and hydrochlorothiazide may increase risk of allopurinol hypersensitivity and decrease uricosuric effect. Didanosine combination may increase didanosine levels and risk of toxicity; renal excretion is decreased. Azathioprine combination may increase risk of azathioprine toxicity (metabolism inhibited). Amoxicillin/ampicillin may increase risk of amoxicillin/ampicillin rash. Leflunomide may increase uricosuric effects (additive effects). Decrease mercaptopurine dose by 75% because combination may increase risk of mercaptopurine toxicity (metabolism inhibited). Warfarin may increase International Normalized Ratio and risk of bleeding. Use probenecid for a therapeutic advantage because combination may increase uricosuric efficacy (synergistic effects).
Main side effects	Common: Rash, diarrhea, liver dysfunction, and pruritus. Uncommon: Agranulocytosis, aplastic anemia, thrombocytopenia, toxic epidermal necrolysis, exfoliative dermatitis, purpura, urticaria, and Stevens-Johnson syndrome.
Special points	For renal insufficiency, adjust dosing. For creatinine clearance 10 to 50, administer less than 400 mg orally daily every 12 to 24 hours for 2 to 3 days, with subsequent decrease in dosage to 100 to 200 mg daily. For creatinine clearance less than 10, administer less than 200 mg per dose every 48 to 72 hours. Patients should drink at least 2 to 3 liters of concomitant water daily. Consider concomitant urinary alkalinization (intravenous sodium bicarbonate at 20–40 mEq/L fluid or 2 ampules in 1 liter of D5W or 1 ampule in 1 liter of 0.45 normal saline).
Cost effectiveness	Approximate retail price for 30 300-mg tablets is $7.50.

Radiation therapy

- Radiation therapy has a minor role in the treatment of BL/BLL. Most of the controlled studies examining radiation for BL/BLL stem from the pediatric literature. One hundred twenty-nine pediatric patients with localized NHL were randomly assigned to receive chemotherapy (vincristine, cyclophosphamide, doxorubicin, prednisone, mercaptopurine, and methotrexate) with involved field irradiation (27 Gy) or chemotherapy without radiation. With a median follow-up of 38 months, the DFS was similar in both groups (87.3 ± 9.4% and 87.9 ± 8.8%, respectively; $P = 0.44$) [57]. Link *et al.* [58] then treated 340 pediatric patients with early stage NHL (54% BL, 15%

immunoblastic, 24% diffuse large cell) with a more dose-intensive 9-week chemotherapy plan and randomized the patients to involved-field radiation or no radiation. At 5 years and later, the rates of continuous CR were essentially the same in both groups, thereby revealing that radiation therapy was not beneficial in this patient population. Similar studies have not been duplicated in adults, although the practice in adult patients with BL with localized disease reflects these outcomes in the pediatric studies. Studies have not been done specifically addressing the benefits of radiation therapy to bulky sites for patients with advanced disease.

Surgery

- The main role of surgery with BL is a simple and safe procedure to obtain enough viable tumor for accurate diagnosis, which should be followed by prompt initiation of systemic chemotherapy. Aspiration techniques may be used for diagnosis, but in general, surgical biopsies are preferred for diagnosis of lymphoma to allow for proper examination of the architecture. More definitive surgery may be warranted if routine biopsy does not establish the histologic diagnosis, but the best outcomes in patients with BL are associated with prompt chemotherapy. Once BL has been diagnosed in adults, surgery rarely plays a role in the therapeutic management. This is in part because of the typically rapid response of BL to systemic chemotherapeutic agents and radiation therapy. There is some controversy in the pediatric literature regarding varied therapeutic surgical interventions for patients with BL, but most physicians will avoid surgical debulking or other invasive surgical therapeutic options once BL has been diagnosed [59,60]. In adults or children, there may be rare instances in which a solitary lesion is completely or almost completely resected for BL of extranodal sites, such as the thyroid, breast, skin, or head and neck region. However, BL tends to respond quickly and often completely to systemic chemotherapy and external beam radiation therapy, obviating the morbidity associated with invasive procedures [61]. Furthermore, surgical intervention may delay the administration of systemic chemotherapy, the definitive treatment for BL. Surgery may be warranted for various complications that can be related to BL, such as intestinal perforation, bleeding, or obstruction, refractory gastric outlet obstruction, or spinal cord instability [62,63].

Emerging therapies

- New therapies will need to continue including shorter duration, intensive chemotherapy regimens for most patients with BL/BLL. Monoclonal antibodies such as rituximab (or the recently approved radioimmunoconjugate, Zevalin [IDEC Pharmaceuticals, San Diego, CA]) may be added to these regimens in an attempt to improve response and long-term survival rates [41,64]. Thomas [65] studied rituximab in combination with hyper-CVAD in 19 patients with newly diagnosed BL/BLL (median age 50 years). In this single institution study, the complete response rate in 15 evaluable patients was 93%, with no difference noted between BL and BLL.
- Further study into the molecular biology of BL/BLL with attention to the role of c-myc dysregulation may aid in prognostic calculations and possibly translate into targeted therapies for this disease [12••,66]. The cellular and molecular events leading to c-myc dysregulation and the intermolecular interactions that determine c-myc function represent potential therapeutic targets in the treatment of BL. After varied position breakpoints involving immunoglobulin heavy or light chain loci and c-myc, there is juxtaposition of

DNA coding sequences of c-myc with immunoglobulin enhancer genes [6,68]. This leads to inappropriately high levels of c-myc DNA and protein expression with concomitant removal of the negative regulatory sequences of c-myc. The functional regulation of c-myc involves many protein-protein interactions such as the heterodimerization of c-myc with max leading to active transcription, which in part requires histone acetylation modification for activation [69,70] and the dimerization of competing inhibitory partners, max-max and mad-max, and various other proteins known to interact with c-myc [71,72]. The cell biologic consequences of c-myc dyregulation are pleiotropic [21]. They include promotion of cell cycle with subsequent increased proliferation, alteration of various metabolic pathways, and induction of apoptosis (which may underlie the "starry sky" appearance of the pale, phagocytic macrophages resulting from high rates of cell death). Furthermore, tumor cell immortalization may occur through activated oncogenes such as N-ras and expression of the enzyme telomerase. Down-regulation of cellular adhesion function may enable BL cells to escape immune surveillance.

- The expanding knowledge into the cellular and molecular mechanisms of BL oncogenesis needs to be validated in excised lymphomatous tissue. Prior limitations in tissue-based research may be averted through use of technology such as cDNA microarray [73•,74]. The identification and description of specific gene and protein expression with BL/BLL through the combination of gene expression profiling and advanced bioinformatics, similar to research by Shipp *et al.* [75•] for diffuse large, B-cell lymphoma, is warranted. This research may lead to more advanced BL/BLL tumor classification to allow accurate prediction of a patient's disease course, and may further elucidate the molecular oncogenesis of BL/BLL to develop patient-tailored therapy, including the discovery of molecular targeted therapy.

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