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Treatment strategies of CLL

Strategia leczenia przewlekłej białaczki limfatycznej

INTRODUCTION

The approach to patients with CLL is determined by the stage of the disease. A small proportion of patients with low-risk disease are classified as having "smoldering CLL" on the basis of a haemoglobin level > 12 g/L, lymphocyte count < 30 x 10^9 / L, platelet count > 150 x 10^9 / L and a non-diffuse pattern of BM involvement with fewer than 80% of lymphocytes. These patients are ulikely to experience disease progression and may live a normal life span without requiring therapy.

However, the outlook has not improved significantly over past few decades for those with advanced disease. Moreover, there is no plateau of the survival curve demonstrating that currently available therapies are not curative. Therefore, the decision as to the optimal time to initiate therapy is important (Fig. 1).

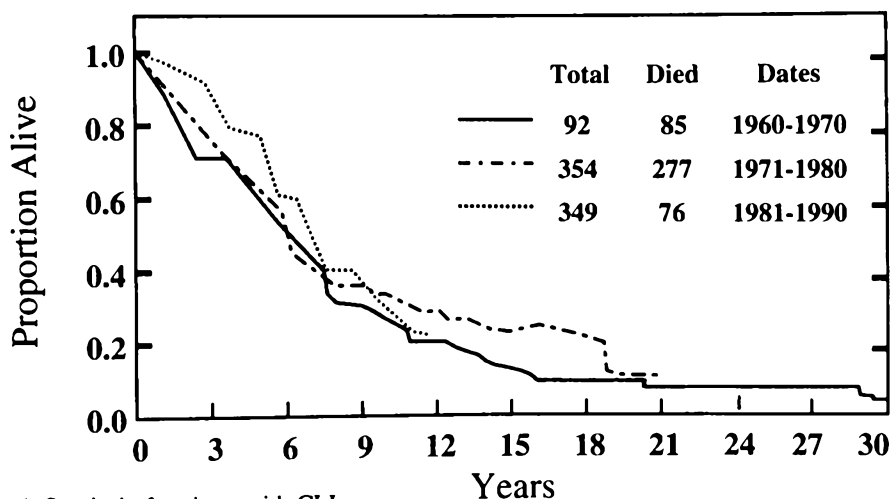

Fig. 1. Survival of patients with CLL

The current recommendation for patients with early stage CLL is that treatment should not be initiated without specific indications, which include disease related symptoms (e.g. fevers, chills, body weight loss, pronounced fatigue), increasing BM failure with anaemia or thrombocytopenia, massive or progressive hepatosplenomegaly or lymphoadenopathy, or recurrent infections.

Although the absolute number of lymphocytes is not determinant for starting therapy, a rapid lymphocyte doubling time (< 6 months) may support decision to treat.

Before making a decision on the employment of treatment to CLL patients some factors associated with poor prognosis should also be taken into consideration.

IMMEDIATE VERSUS DEFERRED TREATMENT OF EARLY-STAGE DISEASE

The question of the benefit of early intervention with the treatment involving chlorambucil, either alone or with steroids, was addressed by Dighiero et al. and identified in collaborative meta-analysis of six randomized trials in chronic lymphocytic leukaemia (Table I).

Table. I. Patients survival in the trials immediate versus deferred treatment with chlorambucil (Chl) for early stage chronic lymphocytic leukemia (CLL)

No of patients	Mode of teatment	Survival	
		Immediate	Deferred
2000 early CLL	Chl *vs* Chl plus steroid	44% (10 yrs)	47% (10 yrs)
840 CLL	CHOP *vs* Chl (+/– steroid)	48%	48%
760 CLL	COP *vs* Chl (+/– steroid)	48%	48%

Br. J. Haemat (102, No. 1, 277, 1998)

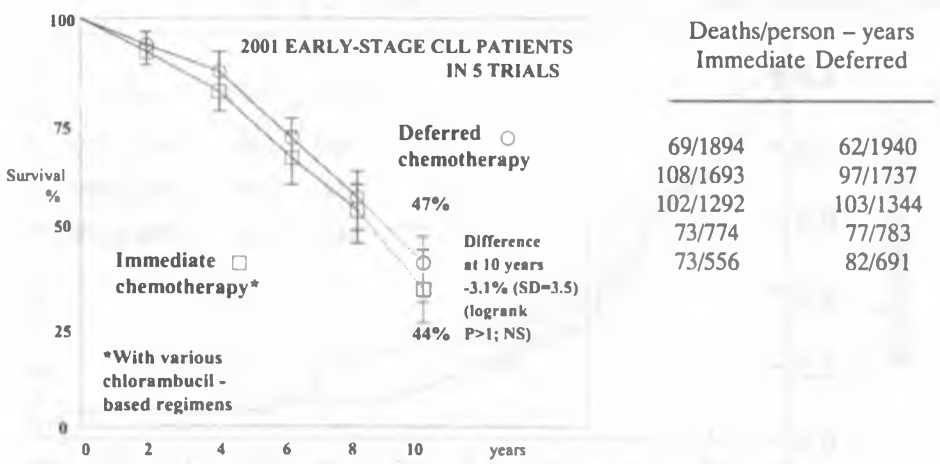

Fig. 2. Survival rates in trials of immediate versus deferred treatment for chronic lymphocytic leukemia (CLL)

In all the 10-year survival was slightly worse (but not statistically significant) with immediate chemotherapy (44% versus 47% survival; difference — 3%; 95% confidence interval (CI) = –10% to 4%), (Fig. 2).

Consensus was reached to accept that the different randomized trials and the meta-analysis results clearly demonstrate that conventional schedules containing chlorambucil do not prolong survival in these patients. Since, deferring therapy until it is required by disease progression to stages B or C does not compromise survival of these patients, therapy should be deferred until progression is observed.

SINGLE AGENT VERSUS COMBINATION CHEMOTHERAPY

There was another group of 2022 patients in 9 trials of combination chemotherapy versus chlorambucil, with or without prednisone / prednisolone. The 5-year survival was 48% in both cases (difference = 0%; 95% CI = –6% to 5%).

A subgroup of six of these 9 trials involved an anthracycline-containing regimen but again overall survival appeared not better than with chlorambucil (anthracycline-based regimen: 325 deaths among 627 patients; death rate ratio = 1. 07; 95% CI = 0.91 – 1.25; not statistically significant). In terms of survival, these trials support a conservative treatment strategy for CLL, i.e., no chemotherapy for most patients with early-stage disease, and single-agent chlorambucil as the first line of treatment for most patients with advanced disease, with no evidence of benefit from early inclusion of an anthracycline.

PURINE ANALOGS

Fludarabine (2–fluoro–ara–AMP)

Following intravenous administration, fludarabine is rapidly dephosphorylated, enters by a carrier-mediated transport mechanism, and undergoes intracellular rephosphorylation to F–ara–ATP by deoxycytidine kinase. F–ara–ATP is incorporated into DNA and inhibits DNA synthesis and affects other enzymes important in DNA synthesis and repair.

So far, Fludarabine seems to be the most active agent for the treatment of CLL (Table II).

When fludarabine is used as the initial treatment 70% of patients respond, including a complete response rate of about 30%.

Two randomized trials have compared fludarabine with alkylating agent- or antracycline-based regimens. The CALGB, *Southwest Oncology Group* (SWOG), ECOG and *National Cancer Institute of Canada Clinical Trials Group* (NCIC–CTG) collaborated to randomize 544 untreated patients with advanced stage active disease to either fludarabine (25 mg/m^2/day for 5 days), chlorambucil (40 mg/m^2 single dose) or a combination of the 2 agents (fludarabine 20 mg / m^2 day 1) every 4 weeks for up to 12 months. Patients who failed to respond to one single agents were crossed over to receive alternative drug. The 167 patients in the fludarabine group had an overall

Table II. Purine Analogs in Chronic Lymphocytic Leukemia

	No. of Patients	Prior Therapy	Response Rate (%) CR	PR
Fludarabine				
Grever et al.	32	+	3	9
Keating et al.	78	+	14 (24)	19
O'Brien et al.	169	+	37	15[c]
Keating et al.	35	–	37 (37)	6[c]
O'Brien et al.	95	–	63	16[c]
Sorenson et al.	655	+	4	29
Whelen et al.	15	+	0	20
Hiddemann et al.	20	+	20	35
Puccio et al.	42	+	0	52
CDA				
Saven et al.	90	90	4	40
Juliusson and Liliemark	18	18	39[c]	28
DCF				
Grever et al.	25	25	4	16
Spiers et al.	29	NS	3	21
Dillman et al.	39	26	3	23
Ho et al.	26	26	0	27

response rate of 70%, including 27% complete remissions, which was significantly higher than the results with chlorambucil (43% responses, 3% complete remissions: p. < 0.0001). The duration of response was 32 months with fludarabine versus 18 months with chlorambucil (p. = 0.0002), with a median progression-free survival of 27 months for fludarabine and 17 months for chlorambucil (p. < 0.0001), respectively. At the point of this analysis there was no apparent prolongation of survival, which may be related in part to the crossover design of the study; half of the patients who failed to respond to chlorambucil subsequently responded to fludarabine. The combination arm was terminated during the trial because it was more toxic with no advance of providing better results than fludarabine alone (Table III).

Table III. Results of comparative studies with fludarabine in previously untreated CLL

Accrual Period:	European Study may 1990 to July 1992			North American Study October 1990 to December 1994		
	Fludarabine	CAP	P	Fludarabine	CAP	P
N Patients	52	48		166	173	
CR (%)	23	17		27	3	
PR (%)	48	43		43	40	
CR + PR (%)	71	60	0.26	70	43	0.0001
Median remission duration (yrs)	2.8+	0.57	<.001	2.75	1.4	0.0002
Median overall survival (yrs)	5.0.+	4.35	0.087	5.0	4.7	0.21

Abbreviations: CAP = cyclophosphamide, doxorubicin, prednisone

The French Cooperative Group on CLL and international collaborators randomised 196 patients with Binet stage A (2 patients), stage B (105 patients) stage C (89 patients) to either fludarabine or 1 to 2 antracycline-based regimens [*cyclophosphamide*, *doxorubicin* and *prednisone* (CAP) or CHOP]. A higher response rate was attained with fludarabine in both treated and untreated patients, although the difference was only significant in the pretreated patients. Although the remission duration and survival in pretreated patients were longer with fludarabine, the differences were not significant. In the untreated patients, the advantage for fludarabine was significant for remission duration with a trend towards a survival advantage (p. = 0.087).

In a subsequent trial by the *International Working Group for CLL* (IWCLL) including 468 stage B and 209 stage C patients, a complete haematological remission was observed in 37% of the fludarabine group, 28% of the CHOP group and 13% of the CAP-treated patients. The differences were significant between fludarabine and CAP and between CHOP and CAP (p.= 0001) in response and survival, but not between fludarabine and CHOP (p.= 0.15). Nevertheless, there were fewer deaths in the fludarabine group, resulting in a significant survival advantage (p. = 0.05).

A number of combinations of fludarabine with other agents are being developed, including alkylating agents, anthracyclines or related compounds, cytarabine, and interferon–alpha. The addition of prednisone to fludarabine in the treatment of either previously treated or untreated patients did not improve the response rate; however, it was associated with increased opportunistic infections, including Listeriosis.

2–Chlorodeoxyadenosine

CDA is an ADA–resistant purine analogue with in vitro toxicity toward lymphocytes and monocytes. Deoxycytidine kinase mediates the intracellular phosphorylation to chlorodeoxy adenosine triphosphate (CldATP), which inhibits DNA synthesis in replicating cells. The activity of this agent appears to correlate with intracellular levels of deoxycitidine kinase and 5'–nucleotidase. Cytotoxicity in nonreplicating cells may be mediated by activation of apoptosis.

In a large Polish (Robak et al.) study with intermittent 2-hour infusions of 2–chlorodeoxyadenosine in the treatment of 110 patients with refractory or previously treated patients with CLL was assessed by Swedish authors who presented the following outcome (Table IV).

Table IV. Intermittent 2–hours intravenous infusion of 2–Chlorodeoxyadenosine in the treatment of 110 patients with refractory or previously untreated B–cell chronic lymphocytic leukemia

No of patients	Mode of treatment	Response rate	
110 CCL	2–CDA, 0,12 mg/kg, 5 days *i.v.* 1–10 courses (median 2,5)	CR 8 (7,3%)	PR 35 (31,8%)
		Overall 39.1%	

Leukemia–Lymphoma, 1996, V.22, N. 5–6, 509–514

CDA appears to display activity in CLL. Saven et al. Reported 4 percent complete responses and 40 percent partial responses of 90 relapsed and refractory patients with CLL, with a median duration of response of 4 months. Juliusson et al. Reported 18 previously treated patients with a 39 percent complete and 28 percent partial response.

Response correlated with clinical stage, number of previous treatment regimens, blood lymphocyte count, and lymphocyte halflife following the first cladribine course. The projected overall survival was 80% at three years for CR patients, and the median survival 28 months for PR patients and 4 months for non responding patients.

Although the respnse rate with fludarabine in chlorambucil failures is high, patients who are refreactory to fludarabine rarely respond to other conventional agents. Conflicting results have been achieved in fludarabine failures treated with CDA. Such therapy has been associated with significant thrombocytopenia, life threatening infections, and treatment related toxicities.

2'–Deoxycoformycin

DCF (pentostatin) is a potent inhibitor of the enzyme ADA that is widely distributed in mammalian cells, with particularly high levels in lymphocytes, especially in T cells. Children with severe combined immunodeficiency (SCID) are deficient in ADA. These observations led to the development of DCF as an ADA inhibitor for use against lymphoid malignancies. DCF achieves responses in 25 to 30 percent of previously treated or untreated patients with CLL, although few of these responses are complete or durable.

HIGH-DOSE CHEMOTHERAPY

High dose chemotherapy with transplantation of hematopoietic progenitor cells is another alternative to control the disease. E. Monserrst (Barcelona) summarized the results of an international project comparing patients (most of them stage Binet B) receiving either allo- or autotransplantation of hematopoietic progenitor cells.

The CR rate after autologous transplantation was higher (81%) than with allogenic cells (61%). Importantly the treatment related mortality was significantly lower for patients receiving autologous stem cells (8% vs. 39%). The number of long-term survivors was higher after allogenic transplantation, reflecting the lower relapse rates in this group (40% vs. 15%). Both procedures are feasible, but opportunistic infections have to be taken into account. In conclusion, the role of transplantation is not yet established in randomized trials.

Bone marrow transplantation was initially developed as a means to deliver supralethal doses of chemotherapy and radiation for treatment of malignancies. The transplant per se was considered a supportive-care modality to restore hematopoesis. Over the last decade, however, it has become clear that the high-dose therapy does not eradicate the malignancy in many patients and that the therapeutic benefit of allo-

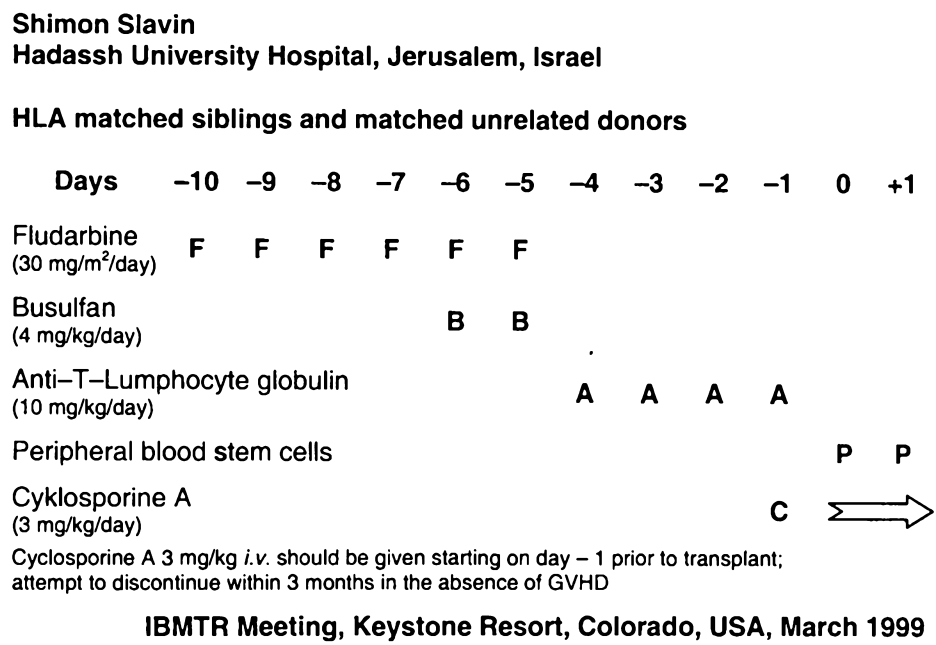

Fig. 3. Alogeneic nonmyeloablative blood stem cell transplantation for malignant and nonmalignant disease

genic marrow transplantation is largely related to an associated immune-mediated graft-versus-malignancy effect. These concept is supported by intensive clinical and experimental data. These include a reduced risk of relapse in transplant recipients with leukemia and chronic graft-versus-host disease and a higher risk after syngeneic bone marrow transplantation.

First pioneering studies in purely experimental settings were performed by Reiner Storb et al., at the early 1980s.

T-cell-depleted allotransplants are also associated with an increased risk of relapse, particularly in patients with chronic myelogenous leukemia.

The malignant cells are eliminated in most patients who receive unmodified marrow transplants during the first 6 months after transplantation. The most direct evidence of this graft versus-malignancy effect, however, is the finding that many patients who relapse after transplantation can be reinduced into remission by simply infusing additional donor lymphocytes after transplantation, presumably because of the graft-versus-leukemia (GVL) effect.

These observations are suggesting an alternative strategy, using a low-dose, nonmyeloablative, preparative regimen designed not to eradicate the malignancy but to provide sufficient immunosuppresion to achieve engraftment of an allogenic blood stem and development of a graft-versus-malignancy effect.

Some pilot studies in patients who were considered ineligible for high-dose myeloablative preparative regimens because of advanced age or comorbidities.

Indolent lyphoid malignancies (including CLL) are of particular interest because these disorders typically affect older and often debilitated patients. The optimal intensity of preparative regimen depends on several factors, including its susceptibility to graft-versus-malignancy effects, the aggressiveness of the underlying malignancy, immunocompetence of the host, and genetic disparity between donor and recipient. Immunocompromised patients, such as those with CLL, require less intensive immunosuppression therapy to achieve engraftment than a fully immunocompetent recipient.

Fludarabine is active against leukemic llnesses, and is markedly immunosuppressive, allowing in many cases the engraftment of allogeneic transplants.

One of the most commonly used regimens for nonmyeloablative transplantation is that proposed by Shimon Slavin (Fig. 3).

BIOLOGIC THERAPY

Biologic therapy for CLL has met with only limited success. The largest experience has been with IFN–alpha. Most of the studies were conducted in previously treated patients, and occassional brief partial responses were achieved. Responses are limited to previously untreated patients with early-stage disease, one-fourth to one half of whom may achieve a partial response, with a rare "complete response", but with no evidence for a favourable influence on outcome. Some data suggest benefit from IFN–alpha maintenance following a response to induction chemotherapy.

Cells from approximately 50% of cases of CLL express CD. 25 (IL–2 receptor), stimulating evaluation of IL–2 therapy in patients with CLL.Activity has been modest, generally characterized by transient decreases in circulating lymphocytes and a reduction in splenomegaly, but with considerable toxicity, including treatment-related deaths.

The characteristic phenotype of CLL cells provides an excellent target for the use of monoclonal antibody therapy (mAb). Unconjugated mAbs, such as those of CAMPATH family, have demonstrated activity. Another well known product is Rituximab, a chimeric anti CD–20 monoclonal antibody.

CD 20 is a B–cell antigen expressed during late pre–B stage until differentiation into the plasma cell and may function as a calcium channel. Rituximab has human IgG1, constant regions with murine anti–CD. 20 binding regions. The human Fc portion augments human complement (complement mediated lysis) and antibody-dependent cell-mediated cytotoxicity effector mechanisms.

Campath–1H is a humanized anti–CD52 mAb. The antigen is expressed on B and T lymphocytes, and the mAb strongly induces complement lysis. Early clinical studies demonstrated elimination of tumor cells in blood and bone marrow, and to a lesser extent the spleen, but with minimal effect on lymph node masses.

Radiolabeled monoclonal antibody therapy has been explored to augment the effect of unconjugated mAbs. Most studies have used iodine 131 or yttrium 90. A po-

tential advantage of radioimmunotherapy includes the killing of antigen-negative variant cells in close proximity to target cells. Undesirable antigen characteristics for radioimmunotherapy include modulation, secretion, or shedding of antigen, and all studies have reached dose-limiting toxicity because of radiation to normal organs.

FUTURE DIRECTIONS FOR THERAPY

The potential role of apoptosis as a mechanism of drug resistance in CLL limits the rationale for pursuing new cytotoxic regimens and the role of high-dose meyloablative chemotherapy. Progress in therapy for this disorder will require an application of the insights developed in the laboratory and to new clinical approaches.

The most appropriate treatment for patients with CLL who relapse after, or are refractory to, initial treatment is referral to a clinical research study. For patients who are not eligible for or are unwilling to participate in clinical research, salvage treatment is determined by the choice and response to initial treatment programme.

Patients who have experienced a response to an alkylating agent can often be successfully retreated. However, the quality of the response and its duration will be less than during initial treatment. Response rates with each of the same combinations used as initial treatment regimens are significantly lower in relapsed and refractory patients, and complete responses are uncommon.

Fludarabine has become the standard agent for patients initially treated with an alkylating agent based regimen. Patients who received fludarabine as their initial treatment and experienced a response lasting at least a year may be sucessfully retreated: about 67% will achieve a second response, although with a greater likelihood of mylosuppression.

Few effective therapeutic options exist for patients whose disease is refractory to fludarabine, and they should be referred to clinical trials. Cladribine in patients who do not respond to fludarabine has been associated with few responses, but significant thrombocytopenia, life-threatening infections and other treatment-related toxicities.

New Approaches

A number of newer cytotoxic drugs have been tested in patients with CLL, mostly in heavily pretreated patients. It has been reported that the taxanes, paclitaxel and taxotere, lack activity. In a single study, no activity was observed with topotecan.

Newer agents currently under investigation include the protein kinase C inhibitors bryostatin and UCN–01, and the cyclin inhibitor flavopiridol. Bryostatin alters the morphological appearance and phenotype of B–CLL cells in vitro to resemble hairy cells. Combinations of this agent with a purine analoge are in development. Flavopiridol exhibits sequence specific synergy with cycle-active agents, and includes apoptosis in CLL cells.

Nelarbine a prodrug for guanine arabinoside (ara–G), is a new purine analogue with activity against a variety of T cell and B cell malignancies. Responses have been seen even in patients who fail to respond to fludarabine.

Gene Therapy

A goal of genetic approach to CLL would be to modify the B–CLL phenotype so that it is capable of stimulating T cells to respond to presented CLL antigens. The interaction of CD 40 and its ligand CD40L on activated T cells plays a key role in . B cell activation, survival and differentiation.

OTHER THERAPEUTIC MEASURES

Splenectomy

Splenectomy may provide important palliation for patients with CLL who have failed to respond to systemic treatment and have persistent splenomegaly or who have cytopenias precluding chemotherapy. Thrombocytopenia is most likely to respond. When performed by an experienced surgeon, the mortality of the procedure is under 10%.

Radiation Therapy

Radiation therapy has limited role in the management of CLL alone or combined with chemotherapy. Splenic irradiation to palliate symptoms or treatment of autoimmune hemolytic anaemia achieves only brief responses.

CONCLUSIONS

1. Many aspects of treatment of CLL are not covered by well recognized treatment standards, yet. This holds true mainly for younger patients as well as poor responders to classical chemotherapy. In these cases experimental approach, mainly high dose chemotherapy supported by PBSCT or BMT or "minitransplantation" with nonmyeloablative conditioning.
2. In the last 10 years purine analogs, especially fludarabine phosphate, established its key role in the treatment of CLL. However, chlorambucil as the oral form of treatment, as well as combined chemotherapy for poor responders to other kinds of treatment.
3. Both radiotherapy and surgery are being used on purpose basis and should be considered mainly as an strategies additional to systemic treatment.

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STRESZCZENIE

Leczenie przewlekłej białaczki limfocytarnej nie zawsze może być ujęte w ramy standardowego postępowania obejmującego mono– lub polichemioterapię z zastosowaniem leków alkilujących, antymetabolitów lub antracyklin. Dotyczy to zwłaszcza pacjentów młodych oraz tych, którzy źle reagują na podaną chemioterapię. W takich przypadkach stosowana może być wysokodawkowana chemioterapia wspomagana komórkami macierzystymi szpiku lub transplantacją poprzedzoną niemieloablacyjnym kondycjonowaniem.

W ostatnich 10 latach szczególne uznanie zyskały analogi puryn, a zwłaszcza fosforan fludarabiny, który zalicza się obecnie do standardowego postępowania terapeutycznego.

Radioterapia oraz leczenie chirurgiczne są stosowane jako leczenie uzupełniające do chemioterapii systemowej.