

# Chronic Lymphocytic Leukemia (CLL)

At

## SwedishAmerican Hospital

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# CLL

CLL is the most common adult leukemia in Western countries, including the United States of America. According to the current World Health Organization (WHO) classification, B-cell CLL is considered to be identical (i.e. one disease at different stages) to the mature (peripheral) B-cell neoplasm small lymphocytic lymphoma (SCLL), one of the indolent non-Hodgkin's lymphomas. In the United States the estimated 8,190 new cases in 2004 and 4,800 deaths each year. It is estimated that more than 7,000 persons are newly diagnosed with CLL in the United States every year. CLL is more common in men than in women (1.7 to 1), with a steep age-specific incidence.

There are no known risk factors for CLL. Although, there are no clear genetic factors, an increased familial incidence has been reported.

The diagnosis of CLL requires a sustained increase in mature appearing lymphocytes in the peripheral blood to more than 5000/mm<sup>3</sup>. The majority of CLL cases are B-CLL and the cells predominantly express B-cell markers (CD19, CD20, and CD23), and CD5. The B-cells are monoclonal. The bone marrow usually is infiltrated by at least 30% lymphocytes. Whereas a bone marrow aspirate and biopsy are not needed to make the diagnosis, they are strongly recommended if cytopenias in other cell lines are present prior to starting therapy. Neither lymph node biopsy nor CT scanning is needed in the initial evaluation and should only be performed if clinically indicated.

At SwedishAmerican Hospital (SAH) 15 cases of CLL/ SCLL were diagnosed in year 2007. The incidence of CLL has almost been stable over the past ten years (1998 through 2007), and it favorably matches the data of the national cancer database (NCDB). The highest incidence was

in year 2007 (15 cases) and the lowest incidence has been reported in year 2000 and 2003 with 6 cases per year (**Table 1**). In our subsequent data, SCLL has not been incorporated in SAH statistical data.

The age distribution of CLL among diagnosed cases at SAH shows that 80% percent of cases between the years 1998 through 2007 are among patients older than 60 years old. The median age in this patient is 70 years old, which is well compared with the NCDB. This has been compared in **Table 2/ Figure 1**. Based on the NCDB about 10% to 15% of patients with CLL are younger than age 50, and 20% are younger than age 55. from secondary malignant disease non-CLL causes. Younger patient are more likely to die from CLL-related events, whereas older patients more often die

The sex distribution of CLL cases in SAH in 1998 - 2007 is also reported in **Table 3**. It shows that 37 cases have been diagnosed in men, versus 28 cases in women.

Several characteristics have been applied to stratify patients with CLL into groups according to different clinical outcomes that may require different therapeutic approaches. The five-stage Rai classification is most commonly used in the United States, and the Binet system is most often applied in Europe. Using the Rai staging system, **Figure 2** shows the stage of CLL diagnosed at SAH from years 1998 through 2007. As we see, 37% of the diagnosed cases fall into the earlier category, i.e. Stages 0 and 1, while 63% of the patients with CLL have more advanced stages, i.e. 2, 3, and 4.

Several prognostic factors separate patients into clinically meaningful risk groups even within a clinical stage. The outcome is poor for patients with CLL with unmutated heavy chain genes

and expression of CD38, regardless of clinical stage; the clinical course is more indolent for patients with mutated genes and no CD38 expression. CD38 and gene mutational status are independent factors. Favorable cytogenetic abnormalities tend to occur in patients with mutated immunoglobulin genes and patients who do not have expression of CD38; whereas unfavorable abnormalities occur with unmutated genes and expression of CD38. The data of different prognostic factors is not available either in the NCDB or SAH database system, however, given the above facts, it is recommended to be considered.

CLL is not curable with currently available therapies, with the exception of allogeneic hematopoietic cell transplantation, nor is there evidence that treatment of patients with early-stage disease (Rai 0-1 or Binet A) extends life expectancy. Therefore, asymptomatic patients with early-stage disease do not require any treatment. These patients should be monitored but not treated unless enrolled on a clinical trial. Radiation might be applied in some cases for local control, however, it is not considered as the main treatment, and it is only applied selectively. The data about the patients with CLL required radiation treatment at SAH is not available, however.

Early-stage patients with disease-related symptoms including B-symptoms; weight loss; pronounced fatigue; symptoms or complications from hepatomegaly, splenomegaly or lymphadenopathy; autoimmune anemia or thrombocytopenia; or recurrent infections may be candidates for treatment. A rapid lymphocyte doubling time (less than 6 months) also may support the decision to treat. Chemotherapy is usually considered as main treatment in these cases. The chemotherapy could be single agent or multi-agent. Based on our data, 80% of

the patients from year 1998 through 2007 did not receive any kind of chemotherapy, 12% received single agent chemotherapy and 8 percent received multi-agent chemotherapy (**Table 4, Figure 3**). The recorded chemotherapy given in patients with CLL at SAH has also been reported (**Table 5**).

Treatment is not necessarily needed for relapsed or refractory disease after initial therapy; treatment in this setting is based on the same indications as for initial treatment. The NCDB or SAH data of treatment in this setting (relapsed or refractory disease) is limited. Patients who relapse within 6 months of previous therapy should be switched to an alternative regimen. Patients initially treated with only alkylating agents should receive a fludarabine-containing regimen.

Initial trials of ablative allogeneic hematopoietic cell transplantation for refractory CLL showed substantial non-relapse mortality but prolonged disease-free survival for a significant proportion of patients. Given that the median age at diagnosis of CLL is older than 60, ablative transplantation for this disease has been limited to a minority of patients. The more recent advent of reduced-intensity transplantation has widened the possible application of transplantation. Supporting measures including splenectomy and leukapheresis has also been applied. The NCDB and SAH data regarding the above treatments is also limited.

Active participation in ongoing clinical trials is strongly recommended in order to improve the outcome of the disease and our understanding of CLL. Close monitoring of the disease (in earlier stages) and appropriate treatment of CLL is the key to a better outcome in the regional cancer center of SAH.

## TABLES and FIGURES

Table 1: Incidence of SCLL/ CLL from 1998 through 2007 at SAH

	<b>1998</b>	<b>1999</b>	<b>2000</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>Total</b>
SCLL	2	3	1	3	5	0	3	3	5	6	31
CLL	7	10	5	6	5	6	7	5	5	9	65
<b>Total</b>	9	13	6	9	10	6	10	8	10	15	96

Table 2: Age distribution in CLL patients at SAH (1998 through 2007)

<b>Age Group</b>	<b>98</b>	<b>99</b>	<b>2000</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>TOTAL</b>
40-49	0	0	0	0	0	1	1	0	0	0	2
50-59	2	1	0	2	1	2	0	1	0	2	11
60-69	1	3	1	1	0	1	2	1	2	3	15
70-79	2	4	3	2	2	1	4	1	2	3	24
80-89	2	1	1	1	2	1	0	2	1	1	12
90+	0	1	0	0	0	0	0	0	0	0	1
<b>TOTAL</b>	<b>7</b>	<b>10</b>	<b>5</b>	<b>6</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>5</b>	<b>5</b>	<b>9</b>	<b>65</b>

Table 3: Gender distribution in patients with CLL at SAH (1998-2007)

<b>Gender</b>	<b>1998</b>	<b>1999</b>	<b>2000</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>2008</b>
Male	5	7	0	4	2	3	7	1	3	6	38
Female	2	3	5	2	3	3	0	4	2	3	27
<b>Total</b>	<b>7</b>	<b>10</b>	<b>5</b>	<b>6</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>5</b>	<b>5</b>	<b>9</b>	<b>65</b>

Table 4: Treatment in patients with CLL at SAH (1998-2007)

<b>Treatment</b>	<b>98</b>	<b>99</b>	<b>2000</b>	<b>2001</b>	<b>2002</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>	<b>2006</b>	<b>2007</b>	<b>Total</b>
Chemotherapy Multi-agent	1	2	0	0	0	0	0	1	1	0	5
Chemotherapy Single agent	1	2	1	1	1	1	1	0	0	0	8
None	5	6	4	5	4	5	6	4	4	9	52
<b>Total</b>	7	10	5	6	5	6	7	5	5	9	65

Table 5: Recorded chemotherapy in patients with CLL (SAH: 1998-2007)

<b>YEAR</b>	<b>CHEMOTHERAPY</b>
1998	Leukeran
1999	Cytosan, Prednisone
1999	Fludarabine x 2, Mantle cell lymphoma Dx and switched to CHOP/ Rituxan
1999	Leukeran, Prednisone
1999	Oncovin, Cytosan
2000	Cytosan, Vincristine
2001	Fludarabine
2002	Chlorambucil
2003	No information on chemotherapy
2004	Rituxan
2004	Leukeran, Prednisone
2005	Cytosan, Vincristine
2006	Rituxan, Cytosan, Vincristine
2007	None

Figure 1: Age distribution in CLL patients at SAH (1998 - 2007)

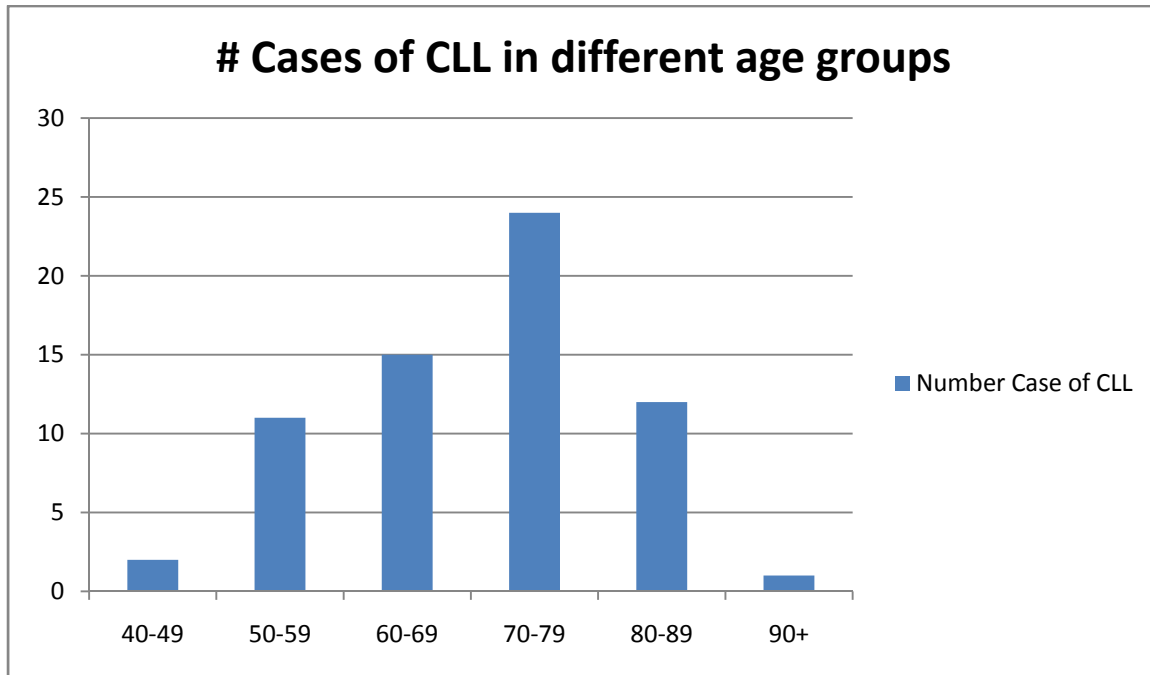


Figure 2: CLL patients distribution according to the stage (SAH: 1998-2007)

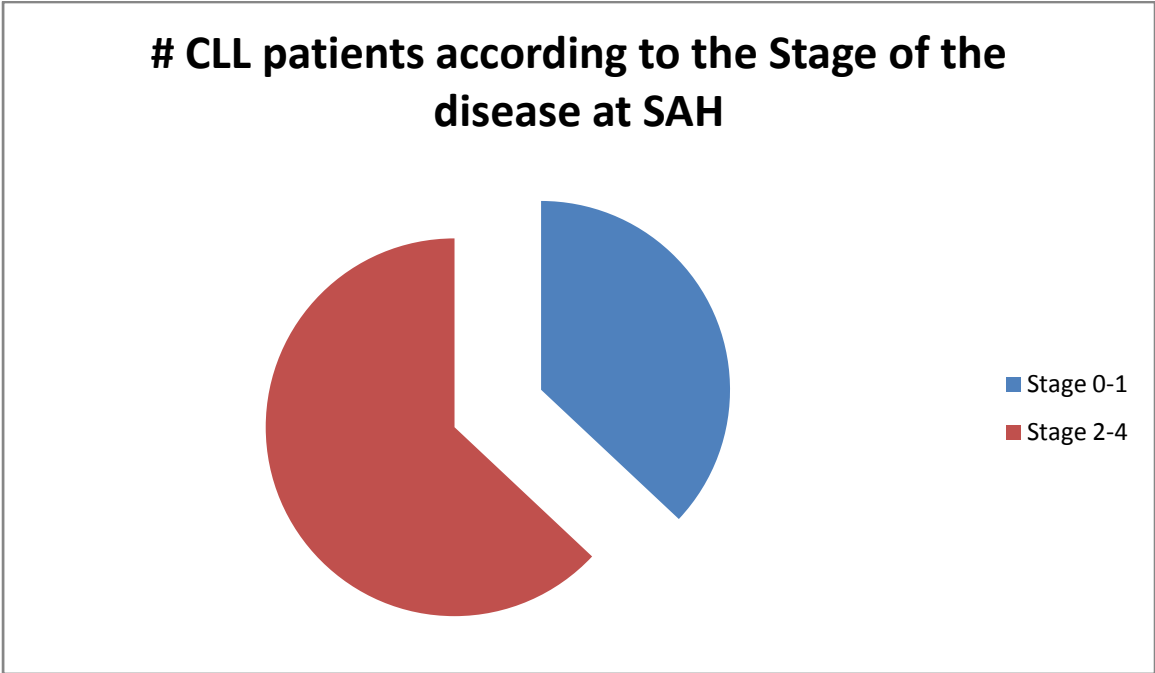


Figure 3: Treatment in patients with CLL (SAH: 1998-2007)

