

Characteristics of Chronic Lymphocytic Leukemia Patients

Part II: Charting for Individuals

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Introduction

Currently, over 1,500 CLL patients around the world are participating in the collection and voluntary reporting of blood tests and treatment information at www.patientdatabases.org. Part I of our report contains demographic information and analyses, such as tabulation of geographic locations, age at diagnosis broken down by age ranges, gender, race, and education level. Time to treatment was also broken down by age and gender. While such demographic information is important in identifying general patient characteristics, there is interest on the part of many patients in seeing how their individual data may relate to disease aggressiveness. This report discusses the kinds of reports which can be generated.

Reports in the form of blood charts, calculation of lymphocyte doubling times, and measures of disease progression can be prepared and emailed to all participants upon request without charge. These charts graphically reveal the time series behavior of laboratory tests commonly reported to CLL patients and their physicians. These include Red Blood Cell Count (RBC), White Blood Cell Count (WBC), Hemoglobin (HGB), Hematocrit (HCT), Platelets (PLT), the percentage of WBC consisting of lymphocytes (LYM%) and the absolute lymphocyte count (LYMABS).

Charts of these blood test results over time are far more informative than other ways of reviewing test results, such as flipping through patient file records or looking at tables of numbers. Changes over time evidenced in the charts may give physicians early hints on individual disease progression or lack of same. Such changes or lack of same may give patients either reassurance or an early warning that they need to notify their physicians of any adverse trends. In an early pilot project which led directly to the creation of the Patient Databases web initiative, around 10% of the participants reported that their course of treatment was altered after their physicians viewed our charts. Individual participants are strongly encouraged to show their charts to their care providers.

Some patients may not have the ability or expertise to produce these charts for themselves. Most physicians do not formally prepare such charts. Provision of these charts to each individual patient is viewed as a benefit to patients and their health care providers as well as a form of "Thank You" to all participants.

Discussion of Charting

Charts appearing in this report have been constructed from actual patient reported data on www.patientdatabases.org. Individual patient anonymity is clearly preserved, as it will be always in any of our reports. The author strongly believes that charting of patient data for a number of chronic illnesses is of crucial importance for both patients and physicians. Unfortunately, in 2008, the 'charts' for most patients are in the form of papers in manila folders, a 19th Century tradition that surely must be eliminated.

The author of this report is a statistician and database analyst and not a physician. Therefore, no medical advice is being provided in the current report. However, some advice on the reading of the charts can be given, and we do so in what follows, using some representative but anonymous charts from our participants

to illustrate some points and the type of information that can be found. Any erroneous interpretations of these charts is solely my responsibility.

Chart Data and Formats

The database contains information on a lot of variables. Some data is provided by almost all patients; other data may be provided uniquely by one participant. The charts discussed here are for the most commonly collected data.

The first chart produced for each of the selected participants contains the most commonly reported blood tests for CLL patients. These include white blood cell count (wbc; normal range 5-10), red blood cell count (rbc; normal range 4.7-6.1), hemoglobin (hgb; normal range 14-18), hematocrit (hct; normal range 42-52%), and platelet counts (plt; normal range 150-400). Since looking at all these numbers in a single chart is useful for spotting associations, trends, etc. and since the scales of the various blood tests differ enormously in magnitude, we have produced these charts on a logarithmic scale to maximize separation between the individual series being plotted..

Currently, there are a number of sophisticated tests available for measuring aggressiveness of disease and prognostications for future progression of CLL. These include FISH for partial deletions of the 13q chromosome (low progression), normal Karyotype or 12q Trisomy (intermediate risk) and 11q or 17p chromosome deletion (high risk). Levels of CD38 cells also play a role in assessing risk, with higher percentages of leukemic cells expressing CD38 being associated with higher risk of disease progression. Other tests cited in the literature are IgVh gene mutation status, ZAP-70 expression, angiogenesis markers, and TK levels. Such tests are often expensive and available only at major CLL research and treatment centers. Such test results have been reported by only a handful of our patient participants.

One prognostic indicator which is inexpensive and available to all patients is lymphocyte doubling time (LDT). It is simply the estimated time for the absolute lymphocyte count to double. It is widely reported in the medical literature that an LDT less than one year is a poor prognosis, being an indicator of rapid disease progression and the early need for treatment. An LDT less than one year is directly translatable to a Progression Rate in absolute lymphocyte counts of approximately 0.002 per day, a 0.2% growth rate interpretable in the same way as in compound interest calculations.

Common blood tests performed on all CLL patients permit estimation of Progression Rate. Technically, this growth rate must be estimated from reported absolute lymphocyte counts. We have found in the database that absolute lymphocyte count is infrequently reported by patients. More commonly, the white blood cell count (WBC) is reported. Since a characteristic of CLL is that a high and relatively constant percentage of WBC consists of lymphocytes, we have found it useful to calculate Progression Rate based on WBC rather than absolute lymphocyte counts. The Progression Rate measured with WBC or absolute lymphocyte counts is very similar for all patients.

The second chart produced for each patient in our discussion is that of the Progression Rate measured over time. Since WBC fluctuates rapidly during and immediately after treatment, we have deleted such cases from our charts. Progression Rate is therefore reported only during times where active treatment was not being applied.

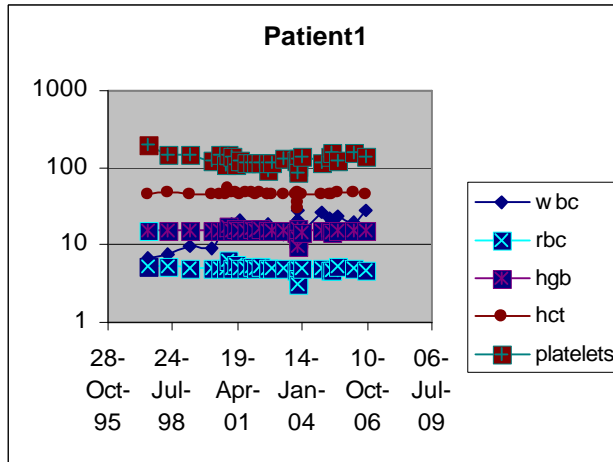
Beta-2 Microglobulin (B2M) has also been cited in the literature as a prognostic indicator, with B2M < 2.5 being considered a favorable prognostic indicator. Many patients have reported values of this test and these are discussed below where available.

Technical details on the production of our charts are given in the Appendix. Patients with suitable computer spreadsheet programs such as Excel can easily produce their own charts following the instructions given in the Appendix. As mentioned above, patients may also request that we prepare such charts for them at no charge. Please address such requests to Cogger@peakconsulting.com with 'CLL Charts' in the subject line of the email. Another option is to obtain an Excel template worksheet from the same source and simply plug in your data.

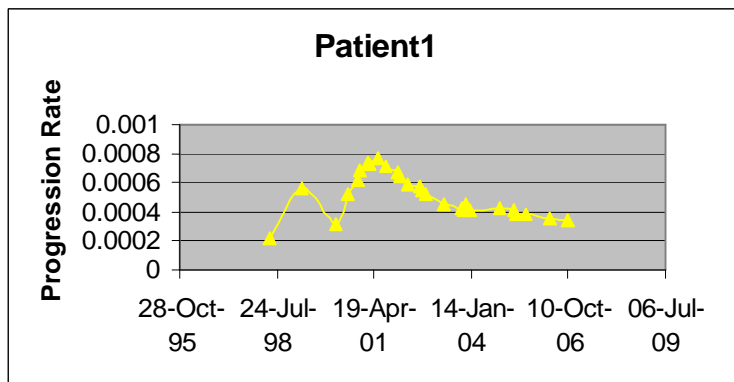
Representative Individual Charts

Ten patients were selected from the database and their charts reproduced and interpreted. They do not constitute any kind of random selection. Rather, they were chosen to represent a variety of disease situations. Some have had no treatment. Some have been treated several times. Some reveal rapid disease progression. Others are typical of 'smoldering' disease cited in the medical literature; such patients are commonly viewed as likely to not need treatment for a very long time, if ever.

Patient 1

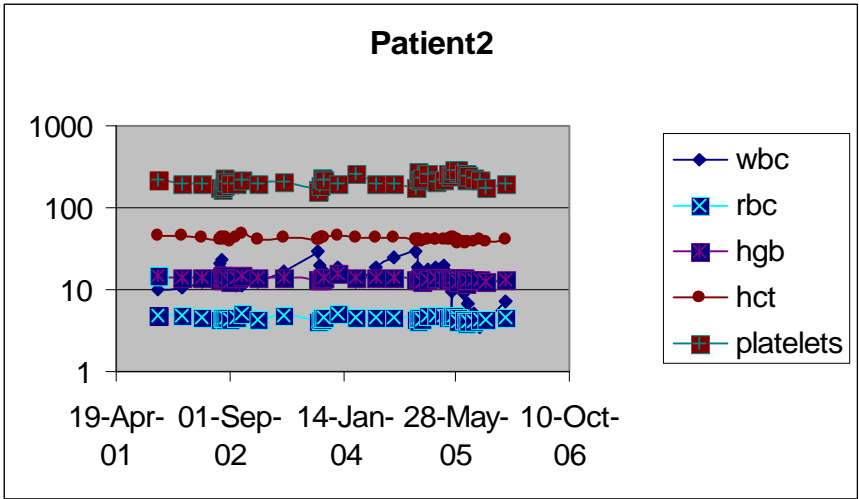


Patient 1 has not had treatment of any kind. B2M was reported at 1.8 on June 1, 2004. Such a low B2M is a favorable prognosis in the literature. All blood tests are within normal ranges except for WBC, which has increased relatively steadily from close to normal values at diagnosis (6.9 in July 1997) to nearly 28 in October, 2006, clearly outside normal ranges at the latter date. Except for the growth in WBC, there are no adverse trends in any of the blood tests.

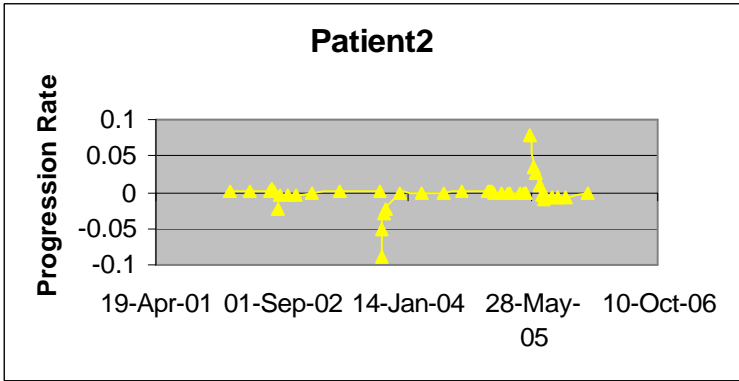


The Progression Rate for Patient 1 has varied some over this nearly ten year history, but all values are well below the benchmark value of 0.002 corresponding to an LDT of one year. This and the B2M value are both consistent with a favorable prognosis. In fact, for the past several years, the Progression Rate has actually decreased to 0.00034712 which implies an LDT of around 5.5 years.

Patient 2

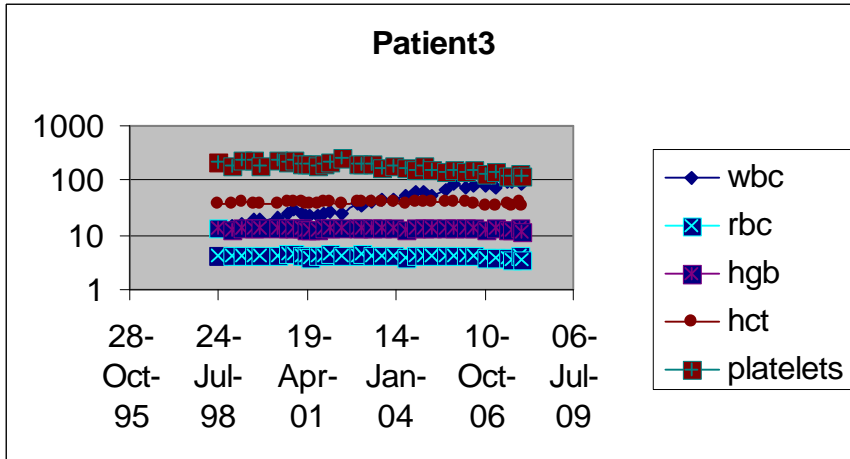


Patient 2 has been treated three times, in August 2002 and September 2003 with Rituxan, and May 2005 with Rituxan and Fludarabine, two commonly used CLL treatments. Downward movements in WBC corresponding to these treatment dates are clearly seen in this patient chart. This patient reported a B2M of 6.3 in 2003 and 7.8 in late 2004, both levels being above the normal limit of 2.5. This patient can be contrasted with Patient 1 in that both had comparable WBC levels but Patient 2 was treated. The B2M levels for Patient 2 are consistent with a more aggressive form of CLL.

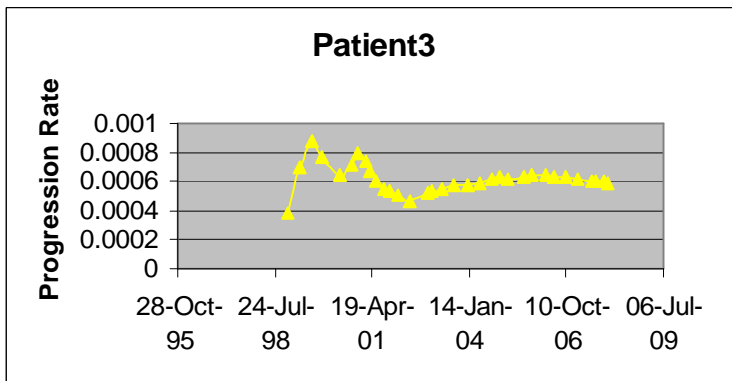


The Progression Rate for Patient 2 was very low until May 2005 when it reached a high of 0.08, consistent with a very short LDT. This patient's last treatment occurred shortly after this progression rate was observed. Downward movements in Progression Rate, clearly visible in this chart, all correspond to times of treatment. Since the last treatment, the Progression Rate has been zero or slightly negative, although WBC has risen in the last test.

Patient 3

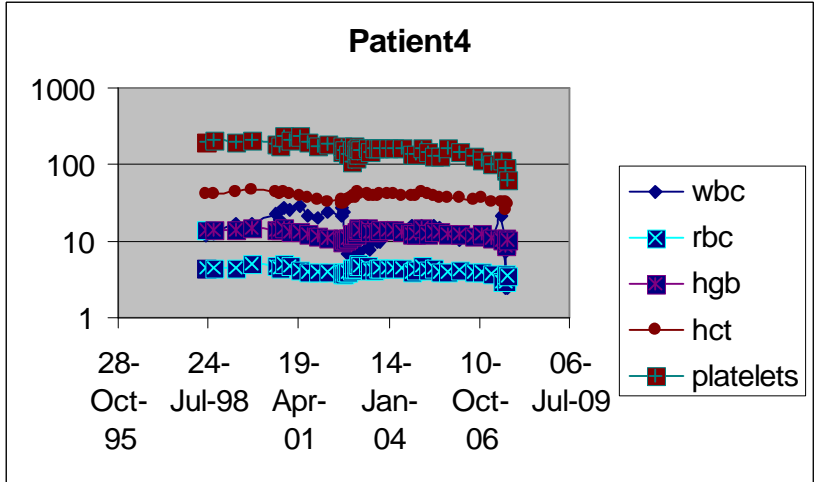


Patient 3 has not been treated for their CLL even though WBC has steadily climbed to more than 120. Most clinicians do not view WBC, alone, as a treatment indicator and this patient is illustrative of that fact. One adverse trend in this chart is the steady decline of platelets, which are at 118. All other counts are in normal ranges. Of note is that B2M was reported at 1.3 in 2006 and 1.6 in 2007, both being favorable indications and perhaps indicative of the lack of need for treatment.

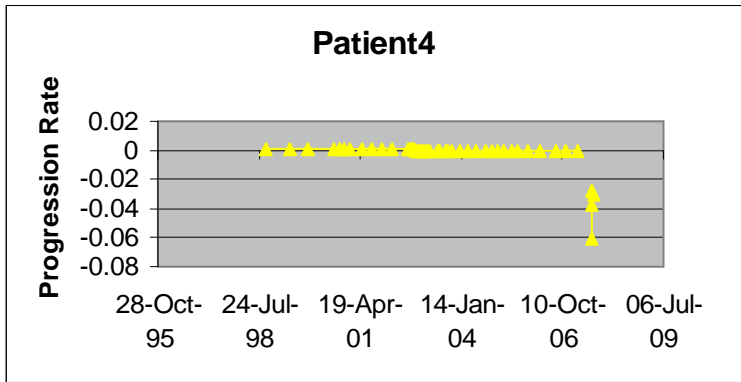


Another indication of the lack of aggressive change in this patient's CLL is the fact that the Progression Rate has remained well below the benchmark value of 0.002 and the recent stabilization at a rate of 0.00059338 corresponding to an LDT of more than three years.

Patient 4

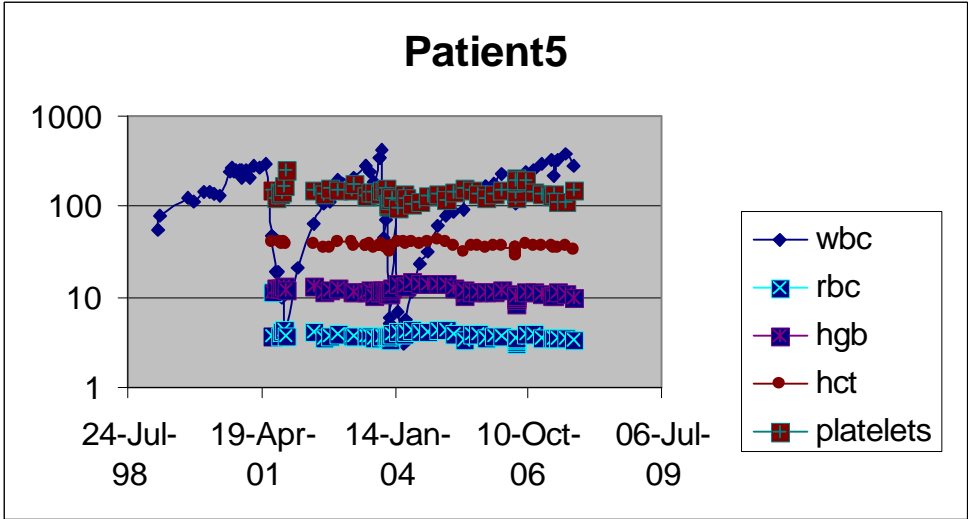


Patient 4 has been treated three times. A “Chinese” therapy was reported in May 2005 and in July 2007 treatment with Fludarabine was given, followed shortly by RFC treatment. Significant adverse trends in platelets, rbc, and hgb are observable in this chart.

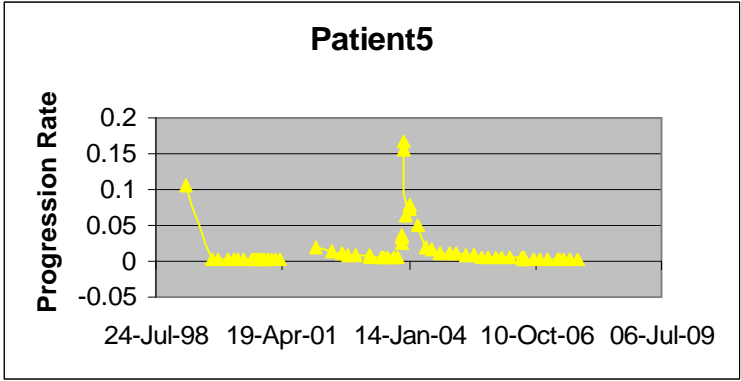


Patient 4 has not had large Progression Rates ever. The downward spikes in this chart correspond directly to the treatment dates indicated above. Only the F and RFC treatments are associated with these spikes. The “Chinese” therapy of 2005 is absent any associated changes in Progression Rate.

Patient 5

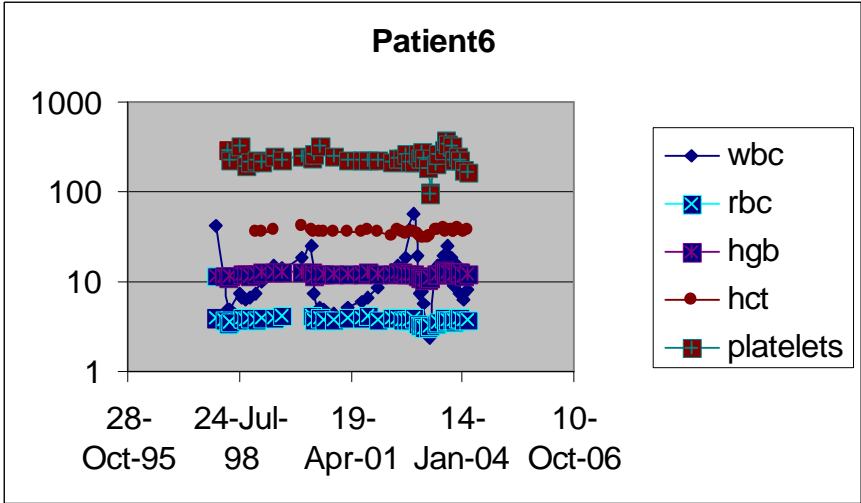


Patient 5 has had seven courses of treatment with Fludarabine. Dates are June, July, August, September, and October of 2001, October 2003, and February 2004. Downward spikes in wbc are clearly visible around these treatment times. Rapid growth of wbc to very high levels is observable prior to all of the treatment interventions.

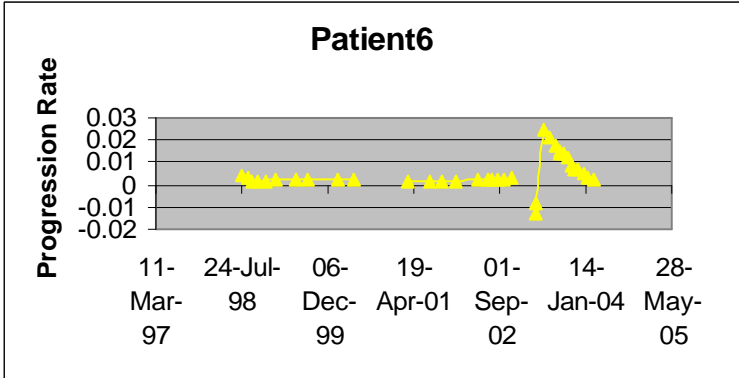


Progression Rate clearly started out at a very high level and then declined, but only to values around 0.002, consistent with an LDT of only one year. This relatively low LDT and relatively high growth rate may be consistent with the need for treatment. The last Progression Rates for this patient are well above 0.002 and this is consistent with the rapid increase in wbc notable in the first chart since the last Fludarabine treatment.

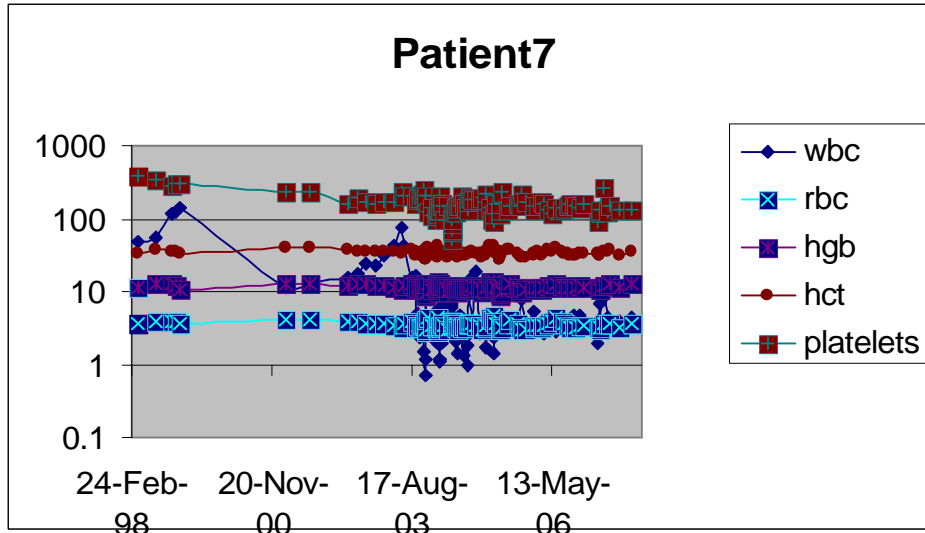
Patient 6



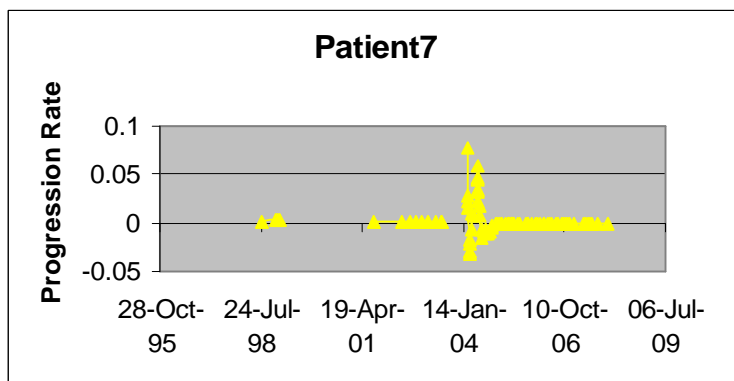
Patient 6 has had three courses of treatment extending over several months in early 1998, mid 2000, and mid 2003. These included fludarabine, and cytoxan plus fludarabine. Steroid supplemental therapy was also employed and IVIg started in mid 2003. Downward movements are observable in this chart for those treatment periods.



Patient 6 exhibits relatively constant Progression Rates except during times of treatment, which have been removed from calculation. Rates are around 0.003, however, indicating an LDT less than one year.
Patient 7

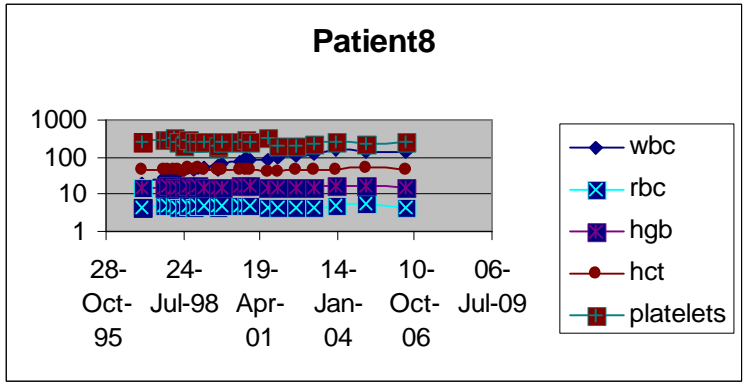


Patient 7 has been treated four times, in early 1999 with fludarabine, from August 2003 to October 2003 with Rituxan, with Cytosan plus Fludarabine from November 2003 to February 2004, and Fludarabine in April 2004. Declines and fluctuations in wbc are noted in the above chart during these periods of time. All blood counts are abnormal; plt, hct, hgb, and rbc are all below normal ranges.

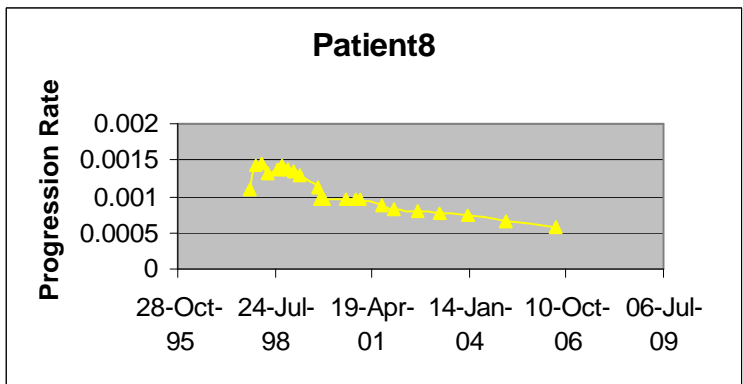


Progression Rates are dramatically high with very low LDT exhibited prior to treatment in late 2003 and early 2004. Since those treatments, progression rates have fallen to 0.00015 and a corresponding LDT of almost 13 years. Also, wbc has stayed in normal ranges since treatment.

Patient 8

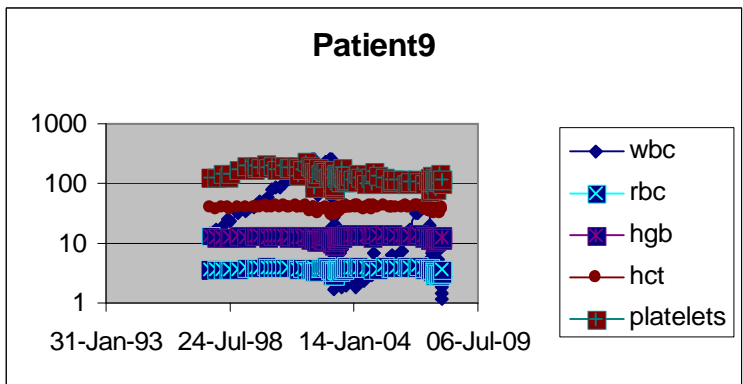


Patient 8 has not had treatment of any kind and has reported a B2M of 1.8, indicating a favorable prognostication on that measure of disease aggressiveness. In spite of this, wbc has steadily increased to over 100. However, all other blood counts are within normal ranges. No adverse trends are apparent in rbc, hgb, hct, or platelets.



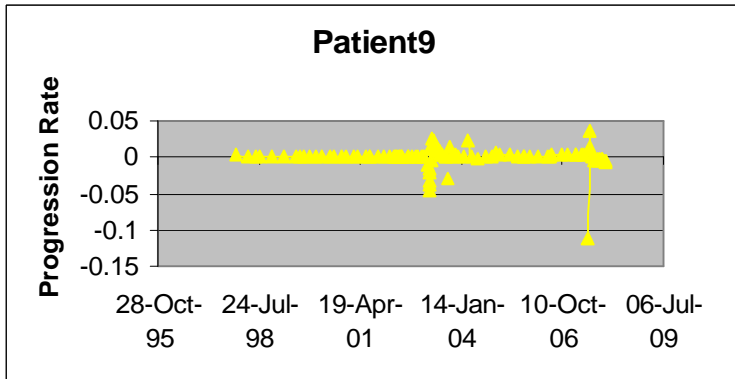
Progress Rate, after some initial fluctuations, has steadily declined to a value of less than 0.0006 and corresponding LDT of more than three years.

Patient 9



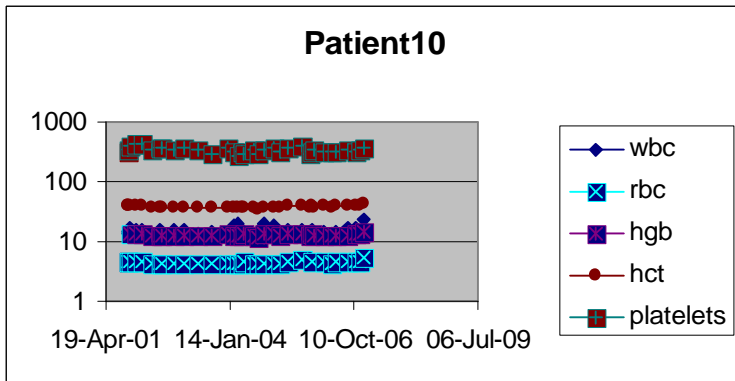
Patient 9 reports B2M values ranging from 2.4 to 4.1 suggesting an aggressive form of CLL. This patient has been treated four times, with fludarabine and rituxan in January 2003, with rituxan alone in August 2003, again with rituxan in February 2004, and with both fludarabine and rituxan in May 2007. These

treatment times correspond with the downward spikes in wbc visible in this chart. Plt, hct, hgb, and rbc are all below normal ranges, although no adverse trends are notable. The dramatic changes in this chart are in the wbc values.

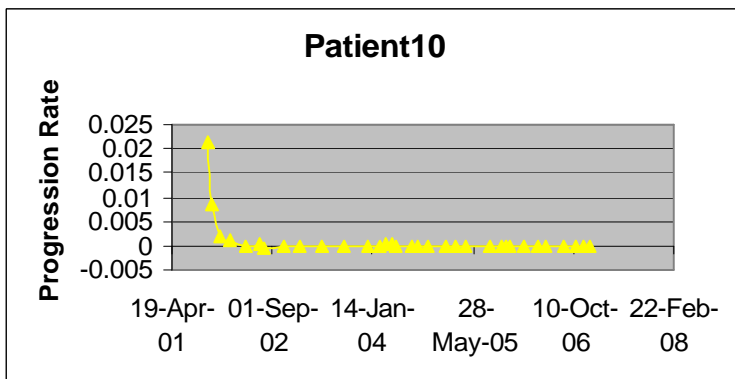


Progression rates for this patient fluctuate widely around the treatment points, as expected. Following the last treatment, the growth rate has declined into negative ranges, a possible residual effect from beneficial treatment. Prior to any treatment, growth rates were above 0.001 but below 0.002.

Patient 10



The last of our selected patients is a classic example of what might be termed 'smoldering CLL'. All blood counts are in normal ranges with the exception of wbc slightly on the high side. All series charted exhibit absolutely flat line behavior with no trends.



After an initially high Progression Rate, perhaps due simply to statistical anomalies associated with small numbers of tests and normal test variation, growth rates have steadily declined and are currently decreased to 0.0000368 which corresponds to an LDT of almost 52 years. This patient has not reported a B2M result, but it is likely this test would also be indicative of a very slowly progressing disease.

Concluding Remarks

The current Report indicates the types of charts that can be produced for individual patients participating in this project. A few exemplary charts have been included in this public report to indicate the types of information now available to individual patients. Potential insights into individual disease progress are possible from these charts and have not been previously available to CLL patients.

The SEER database on cancer statistics, for example, deals with statistical survival curves and mortality rates, but does not record patient information on an individual time dated manner. Through the use of individual charts for blood tests and CLL Progression Rate, new insights may be possible into individual disease progress and treatment. Alteration of treatment plans has been reported by patients who have shown these charts to their physicians.

Acknowledgments

This report and the work behind it would not have been possible without the efforts of many unpaid volunteers and, especially, our participants. Shelly Messenger, now deceased, had the original idea to survey CLL patients in 1998. His idea led directly to the current ongoing website project. Irene Murphy led the successful effort to establish a permanent organization to manage operations. Diane MacKinnon has been tireless in her assistance to me. The entire Board of Directors has been patient and supportive during the process of producing this report. The distinguished Advisory Committee has also been invaluable. I alone am responsible for any errors and mistakes in this report. None of the individuals named here are responsible for my errors in judgment or execution of the report. Finally, I must acknowledge “Granny Barb” Lackritz, deceased, who initiated so many projects beneficial to CLL patients and is remembered and revered, especially by those of us who personally met her.

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Appendix – Technical Information for Chart Production

The charts showing white blood counts (wbc), red blood cell counts (rbc), hemoglobin (hgb), hematocrit (hct), and platelets (plt) were prepared from basic worksheets containing these test measures along with their dates of measurement. In Excel, such charts are prepared by selecting all cells, with the date column being the first and, therefore, the horizontal axis. The Chart Wizard is then selected, with the XY-Scatter Plot option selected. Default options are then selected for production of the chart. Clicking on the chart to select it, on the main toolbar click on Chart and Options to insert a title for the chart if desired. The final

change to the default chart is to make the vertical axis of the chart appear in a logarithmic scale. This helps separate the plots of the five blood test results and make them more readable. To change this scale, simply right-click on the vertical axis numerical values, select Format Axis, select Scale, and click on logarithmic scale. Instructions for other spreadsheet programs may differ slightly.

The charts showing Progression Rate are more technical. First, start with the two columns (A and B) containing the dates and wbc values. The first row has text titles with the data in rows 2-8. Your data may have more or fewer rows.

eventdate	wbc
09-Oct-01	13.3
15-Oct-01	15.1
02-Nov-01	16.7
17-Dec-01	16.1
30-Jan-02	16.4
26-Apr-02	13.9
27-Jun-02	16.3

Insert two columns next to the date column A:

eventdate			wbc
09-Oct-01			13.3
15-Oct-01			15.1
02-Nov-01			16.7
17-Dec-01			16.1
30-Jan-02			16.4
26-Apr-02			13.9
27-Jun-02			16.3

Label column B as 'growthrate' and column C as 'ln(wbc)' :

eventdate	growthrate	ln(wbc)	wbc
09-Oct-01			13.3
15-Oct-01			15.1
02-Nov-01			16.7
17-Dec-01			16.1
30-Jan-02			16.4
26-Apr-02			13.9
27-Jun-02			16.3

In column C place formulas for calculating the natural logarithm function of values in column D:

eventdate	growthrate	ln(wbc)	wbc
09-Oct-01		=LN(D1)	13.3
15-Oct-01		=LN(D2)	15.1
02-Nov-01		=LN(D3)	16.7
17-Dec-01		=LN(D4)	16.1
30-Jan-02		=LN(D5)	16.4
26-Apr-02		=LN(D6)	13.9
27-Jun-02		=LN(D7)	16.3

Note that this table shows the formulas. Your worksheet will show the calculated values of the natural log function.

In column B, place formulas for the SLOPE function in Excel which calculates the slope of the regression function for the indicated ranges of x and y values. Since at least two values are needed to calculate a slope, the first formula entry is in row three:

eventdate	growthrate	ln(wbc)	wbc
09-Oct-01		=LN(D1)	13.3
15-Oct-01	=SLOPE(\$C\$2:C3,\$A\$2:A3)	=LN(D2)	15.1
02-Nov-01	=SLOPE(\$C\$2:C4,\$A\$2:A4)	=LN(D3)	16.7
17-Dec-01	=SLOPE(\$C\$2:C5,\$A\$2:A5)	=LN(D4)	16.1
30-Jan-02	=SLOPE(\$C\$2:C6,\$A\$2:A6)	=LN(D5)	16.4
26-Apr-02	=SLOPE(\$C\$2:C7,\$A\$2:A7)	=LN(D6)	13.9
27-Jun-02	=SLOPE(\$C\$2:C8,\$A\$2:A8)	=LN(D7)	16.3

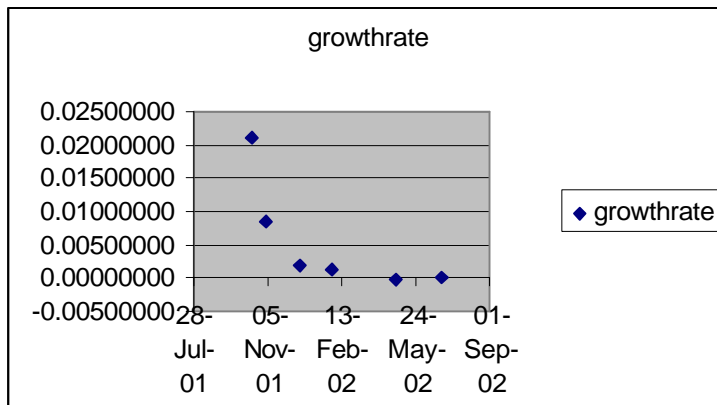
Again, this table shows the cell formula entries., not the calculated values. Instead of manually entering the necessary formulas, you may find it helpful to enter only the first formula and then copy and paste. Note the absolute reference in the SLOPE function to cells \$C\$2 and \$A\$2, which fixes the starting point of the regression. As formulas are pasted downward, the range of values will change reflecting the number of data points for which the regression slope is calculated.

The actual calculated values in this sample worksheet are as follows:

eventdate	growthrate	ln(wbc)	wbc
09-Oct-01		2.59	13.3
15-Oct-01	0.02115512	2.71	15.1
02-Nov-01	0.00858751	2.82	16.7
17-Dec-01	0.00201985	2.78	16.1
30-Jan-02	0.00120887	2.80	16.4
26-Apr-02	-0.00009754	2.63	13.9
27-Jun-02	0.00014173	2.79	16.3

Note that to calculate values in the correct format, column A must be formatted as a date value and columns B to D must be formatted as numerical values.

At this point, select all the cells in columns A and B including the first row with column headings. Choose the Chart Wizard with the XY Scatterplot option to produce the chart following:



This is the Progression Rate chart for Patient 10 for just the first six dates. The chart may be cleaned up a bit by deleting the legend, since only a single known series is being plotted. Also the title of the chart may be changed to, e.g., 'Patient1' and the vertical axis labelled as 'Progression Rate'.

If you are preparing such a chart where episodes of treatment are involved, it is advised that the growth rate cells be emptied during and immediately following treatment. Then, upon resumption of calculations, the formulas for growth rate should be reinitialized to start with the first two wbc values following treatment, fixing the first cell with the absolute referencing device.

The use of logarithms to estimate growth rates is a standard mathematical device when dealing with phenomenon with compound interest type exponential growth. If a measured number at time t is given by $y(t)$ and it grows at a rate g , then $y(t) = y(0) \cdot (1+g)^t$. This function is linearized, making it easier to analyze, if logarithms are taken: $\ln y(t) = \ln y(0) + t \cdot \ln(1+g)$. For small growth rates g , which is the case for disease progression, a nice property of natural logs is that $\ln(1+g)$ is approximately g . A plot of the linearized function $\ln y(t)$ versus t will have a slope = g . This is the reason for using the SLOPE function in Excel. Other spreadsheet programs usually have a function equivalent to SLOPE but perhaps with another name.

Lymphocyte doubling time for exponential functions can be expressed as $LDT = \ln(2)/g$. LDT and g are inversely related. In Excel as in most spreadsheets, dates are externally displayed in a recognized format such as 10-May-07, but are internally stored as numbers of days elapsed since some base date. Therefore g is a daily growth rate and LDT is measured in days. If LDT is calculated as $\ln(2)/g$, the often cited LDT of 6 months must be converted into days. So, 6 months is approximately 180 days giving a daily growth rate of $\ln(2)/180$ which is a bit less than 0.004.

Our choice of calculating g rather than LDT is also based on ease of interpretation. If a patient exhibits no growth in wbc, perhaps due to a cure, $g = 0$ and LDT is infinitely large. If a patient exhibits declining wbc, g will be negative and consequently LDT will be negative, but for such a patient LDT is also infinitely large since their wbc will never double. LDT is therefore misleading in situations of constant or declining wbc whereas the growth rate g can be consistently interpreted: high values of g are problematical and low values of g , even negative values, offer a favorable prognosis. For any kind of statistical analysis, we recommend the use of g rather than LDT.