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SUGGESTED TREATMENT REGIMENS^{1,2}
(in order of preference)

First-line therapy
• Frail patient with significant comorbidity (not able to tolerate purine analogs)
• Obinutuzumab + chlorambucil (category 1)
• Rituximab (category 1)
• Obinutuzumab + chlorambucil
• Rituximab + chlorambucil
• Obinutuzumab (category 2)
• Rituximab (category 3)
• Chlorambucil (category 3)

First-line therapy
• Age ≥65 and younger patients with significant comorbidities
• Obinutuzumab + chlorambucil (category 1)
• Rituximab (category 1)
• Obinutuzumab + chlorambucil
• Rituximab + chlorambucil
• Bendamustine (70 mg/m²) in cycle 1 with escalation to 90 mg/m² if tolerated ± rituximab³
• Obinutuzumab (category 2)
• Chlorambucil (category 3)
• Rituximab (category 3)

First-line therapy
• Age <65 without significant comorbidities
• Chemotherapy
• FCR (fludarabine, cyclophosphamide, rituximab) (category 1)⁴
• FR⁵ (fludarabine, rituximab) (category 1)⁶
• FCR (pentostatin, cyclophosphamide, rituximab)
• Bendamustine ± rituximab⁷
• Ibrutinib⁸

See Suggested Regimens for Relapsed/Refractory Therapy for CLL/SLL without del(17p)/TP53 mutation (2 of 5)

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)
See monoclonal antibody and viral reactivation (See CSLL-C)
See Suggested Regimens for CLL/SLL with del(17p) (3 of 5)

See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
See Supportive Care for Patients with CLL/SLL (CSLL-C).
See Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Venetoclax) (CSLL-F).
Data from the CLL1b study confirm the superiority of FCR over BR in younger patients.
For patients ≥65 y, the outcome was similar for both regimens with less toxicity for BR. Entry for a second course of therapy should be based on clinical judgment, performance, and is associated with fewer myelosuppressive toxicities.
See Discussion for further information on oral fludarabine.
Not for del(17p).

Autotransfuse hemolytic anemia (AHA) should not preclude the use of combination therapy containing fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those with a history of fludarabine-associated AHA if suspected.
See Discussion for further information on oral fludarabine.
Not for del(17p).

CSLL-D
1 OF 5

CLL/SLL WITH DEL(17p)/TP53 MUTATION

FIRST-LINE THERAPY^{1,2}

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)
See monoclonal antibody and viral reactivation (CSLL-C)

CLL/SLL with del(17p)/TP53 mutation^{1,4,7}

- Clinical trial
- Del(17p)/TP53 mutation is associated with low response rates with chemotherapy
- See Suggested Regimens (CSLL-D 3 of 5)

RESPONSE TO THERAPY

Response^{1,1}

- Complex karyotype present → Consider allogeneic stem cell transplant or Clinical trial or Observe → Progression → Relapsed/Refractory Therapy²
- Complex karyotype not present → Progression → Relapsed/Refractory Therapy²

No response → Relapsed/Refractory Therapy²

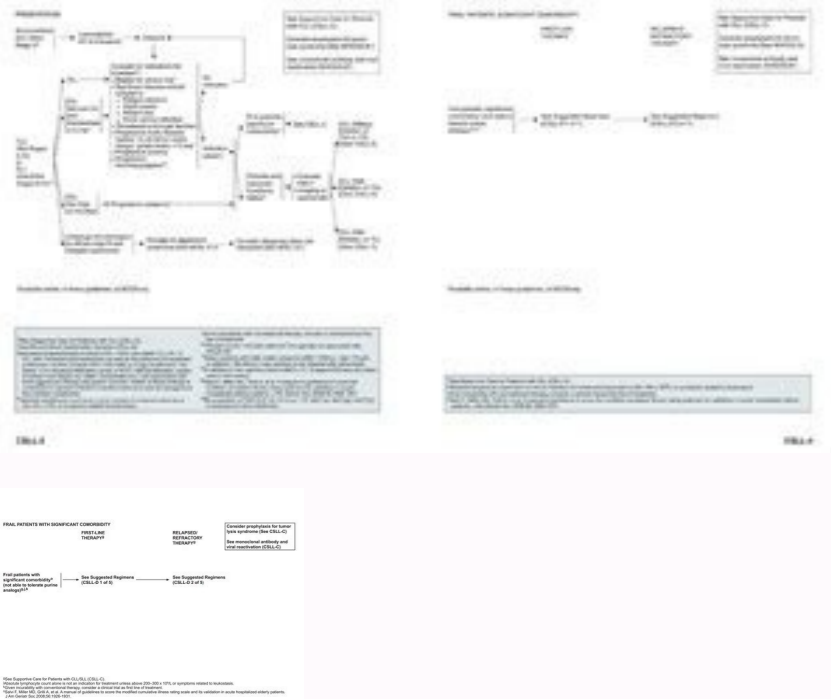
Relapsed/Refractory Therapy²

Clinical trial or See Suggested Regimens/Refractory Regimens (CSLL-D 3 of 5)

See Supportive Care for Patients with CLL/SLL (CSLL-C).
Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 × 10⁹/L or symptoms related to leukostasis.
FCR-stimulated karyotype is useful to identify high-risk patients, particularly for Bruton's tyrosine kinase (BTK) inhibitor therapy.
Patients with low positivity should be retested due to chance of false-positive results.
See Response Criteria: CLL/SLL (CSLL-E).
For patients with complex karyotype (≥3 abnormalities) in remission after BTK-inhibitor therapy, consider discussion of allogeneic transplant although data available do not support this as highly effective (Jagrowski et al. Br J Haematol 2012;159:82-87).

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CSLL-6



Nccn guidelines for cll/sll. Nccn treatment guidelines for cll.

Chronic lymphocytic leukemia (CLL) is a typically slow-growing cancer that begins in the bone marrow and spreads into the blood. Often, it is first suspected in a person who has no symptoms, during routine blood work. Additional testing helps to confirm the diagnosis and classify CLL into groups by low-risk to high-risk. Often, CLL does not cause any symptoms for at least a few years and does not require immediate treatment. Once treatment is needed, there are many options to help control the disease. Jose Luis Pelaez Inc/Getty Images This cancer develops in a type of white blood cells called B cells or B-lymphocytes. In fact, some of the therapies used in the treatment of different types of B-cell lymphoma are also used in CLL. An unexplained high white blood cell (lymphocyte) count is the most common clue that leads a healthcare provider to consider a CLL diagnosis. Often, a person has no symptoms related to CLL at the time of diagnosis. People with more aggressive types of CLL and those with more advanced disease may show any number of signs and symptoms, including any one or a combination of the following: Fatigue, feeling run down, less able to exercise Swollen lymph nodes Frequent infections Pain, pressure or fullness in the abdomen Bleeding problems Systemic symptoms are also possible, including what are sometimes referred to as "B symptoms": Fever/chills Night sweats Weight loss None of the above symptoms is specific to CLL, however. The diagnostic process begins with an appointment with your healthcare provider. You may be having symptoms, or signs of CLL may appear in your routine blood work and warrant further work-up. During a complete medical history, your practitioner will ask about symptoms, possible risk factors, family medical history, and your general health. During the physical exam, your healthcare provider will look for possible signs of CLL and other health problems, especially enlarged lymph nodes, any abdominal findings that might suggest an enlarged spleen, and other areas that might be affected. The complete blood count (CBC) measures the different cells in your blood, such as red blood cells, white blood cells, and platelets. Having more than 10,000 lymphocytes per cubic millimeter of blood is suggestive of CLL, but other tests are needed to know for certain. If your blood count is suggestive of CLL, you may be referred to a hematologist (a specialist in blood disorders) for additional testing to confirm the diagnosis and determine the risk group of your CLL. CLL is usually diagnosed with blood tests rather than bone marrow tests because the cancerous cells are easily found in the blood. Flow cytometry uses a machine that can distinguish different kinds of cells to help determine what types of cells are in a samples, and how many of specific kinds of cells. Flow cytometry can be done using blood samples, samples from the bone marrow, or other fluids. A bone marrow biopsy is usually not needed to diagnose CLL, but it is done in certain instances, such as before starting CLL treatment, or when there has been a major change in the progression of the disease or certain other instances. Your medical team may use other blood tests to help find liver or kidney problems that might influence the choice of treatment. They may also test your blood immunoglobulin (antibody) levels to help determine how well you can fight infections, especially if frequent infections are part of your medical history. They might do other blood tests to determine the characteristics of your CLL. Each of our cells normally has 46 chromosomes, 23 from each parent, that contain many genes. Each chromosome has a number, and the genes within each chromosome are named. For CLL, many different chromosomes and genes are important, including chromosomes 13, 11, and 17, and genes such as TP53 and IGHV. Sometimes CLL cells have chromosome changes as a result of part of the chromosome being missing or deleted. Deletions in parts of chromosomes 13, 11, or 17 are associated with CLL. The deletion of part of chromosome 17 is linked to a poor outlook. Other, less common chromosome changes include an extra copy of chromosome 12 (trisomy 12) or translocation (swapping) of DNA between chromosomes 11 and 14. Some studies look at chromosomal changes, whereas others look for changes in specific genes. Certain tests that look for chromosomal changes require that the cancer cells start dividing in the laboratory, so the whole process can take quite some time before you get results. Fluorescent in situ hybridization (FISH) testing uses fluorescent dyes that attach to specific chromosomes to look for changes. It's faster than methods that require growing cells in a lab. Additional markers of importance in CLL include IGHV and TP53 mutation status: Immunoglobulins are antibodies made by your immune system to help your body fight infections. Leukemia cells use immunoglobulin heavy chain variable (IGHV) genes, and unmutated IGHV genes are associated with a poorer prognosis than mutated IGHV genes. Abnormalities in the TP53 gene, which is a tumor suppressor, are also important in guiding treatment decisions. People with TP53 mutations are unlikely to do well on standard chemotherapy than with nonchemotherapeutic therapies. This information from genetic and molecular testing may be helpful to determine a person's outlook, but it needs to be looked at along with other factors making decisions about treatment. Staging refers to the extent to which the CLL has progressed, or the amount of CLL cells in the body and the impact of that burden. Staging is used in CLL (e.g., the Rai and Binet systems), but the outcome for a person with CLL also depends on other information, such as the results of lab tests and imaging tests. The treatment chosen will depend on many factors and the stage of CLL. CLL is a slow-growing cancer, and there isn't good evidence to support treating people in the early stages of CLL who have no symptoms and aren't at high risk. For these people, a period of no treatment—referred to as watch and wait, watchful waiting, active monitoring, or active surveillance—is considered the best option. Watchful waiting is not synonymous with foregoing treatment and does not worsen outcomes. Instead, blood counts are done fairly regularly, and treatment is initiated if constitutional symptoms (fever, night sweats, fatigue, weight loss greater than 10% of body mass), progressive fatigue, progressive bone marrow failure (with a low red blood cell or platelet count), painfully enlarged lymph nodes, a significantly enlarged liver and/or spleen, or a very high white blood cell count arise. A select group of patients (young, fit, with mutated IGHV, without TP53 mutations or deletions in chromosomes 11 or 17) has traditionally been viewed to benefit the most from a defined course of therapy with fludarabine, cyclophosphamide, and rituximab, the combination known as FCR, which achieves durable remissions for many patients. Biological agents such as ibrutinib, acalabrutinib, or venetoclax (rather than chemotherapy) in regimens with or without monoclonal antibodies (such as rituximab or obinutuzumab) are also among the options in some cases. The most effective initial therapy for fit, older adults (age over 65 years) with CLL has not been established definitively. For frail older adults, ibrutinib alone is often considered when there are no other health conditions that would preclude or cause concerns about its use. Approved options now include novel agents such as ibrutinib and novel agent combinations with anti-CD20 directed monoclonal antibodies. Both ibrutinib and venetoclax can be used in combination with anti-CD20 directed monoclonal antibodies. The efficacy and safety of ibrutinib alone have been established in previously untreated patients age 65 years or older with CLL, and data support continuous ibrutinib use in the absence of progression or toxicity. The role of the addition of a monoclonal antibody (that targets the CD20 marker on CLL cells) to ibrutinib continues to be explored. The introduction of novel targeted therapies that inhibit important pathways in the CLL disease process has changed the landscape of the treatment of the disease. Biological agents such as ibrutinib, idelalisib,

and venetoclax have had excellent outcomes, including in patients with a high-risk disease such as TP53 mutation or deletions on chromosome 17. However, issues of residual disease, acquired resistance, and lack of a nice, long response in patients with high-risk disease remain concerns. Additionally, despite this considerable progress, much is unknown regarding best treatment selection and sequence of therapies for different groups of people. In short, tremendous progress has been made in recent years, but there is still room for improvement. Get our printable guide for your next doctor's appointment to help you ask the right questions. Experts provide information and answer questions about chronic lymphocytic leukemia to help patients and caregivers compare, discuss, and select treatment options with their doctor.Please note that this is a not an accredited activity. The Know What Your Doctors Know: Chronic Lymphocytic Leukemia webinars occurred in April 2021. This informational program was created in conjunction with the recently updated NCCN Guidelines for Patients® for Chronic Lymphocytic Leukemia.The NCCN Guidelines for Patients sheets are available to read and download for free online and via the NCCN Patient Guides for Cancer mobile app. Printed editions can be ordered from Amazon.com for a small fee. NCCN Guidelines for Patients DO NOT replace the expertise and clinical judgment of the clinician. SupportersThis webinar is supported through the NCCN Foundation and by a contribution from our corporate supporter: AstraZeneca. The webinar is further supported by an independent educational grant from AbbVie.Our corporate supporters do not participate in the development of the NCCN Guidelines for Patients and Know What Your Doctors Know webinars and are not responsible for the content and recommendations contained therein.

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