Initial treatment of advanced stage (III/IV) follicular lymphoma

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INTRODUCTION — Follicular lymphoma (FL, previously called follicle center lymphoma) is the second most common type of non-Hodgkin lymphoma (NHL). It is the most common of the indolent NHLs defined as those lymphomas in which survival of the untreated patient is measured in years. (See "Classification of the hematopoietic neoplasms".)

Treatment of FL depends upon the stage of disease at presentation (table 1). Patients with localized (stage I) disease are candidates for radiation therapy, which is curative in a percentage of patients. In contrast, the treatment of advanced (stage III/IV) disease is not curative and focuses largely on symptom control with chemoimmunotherapy with or without radiation therapy. Even so, patients with advanced stage FL generally have an excellent prognosis.

The management of patients with stage II FL is more variable, with some clinicians offering treatment similar to that used for stage I disease and others offering treatment similar to that used for advanced stage disease. (See "Initial treatment of limited stage (I/II) follicular lymphoma", section on 'Stage II FL'.)

The initial treatment of advanced stage (III/IV) FL is discussed here. The initial treatment of limited stage (I/II) FL and the management of relapsed or refractory FL are presented separately, as are the epidemiology, clinical presentation, pathologic features, diagnosis, and pathobiology of FL. Of importance, the recommendations presented here pertain to patients with histologic grade 1, 2, or 3a FL; patients with grade 3b FL are treated as aggressive lymphomas (eg, diffuse large B cell lymphoma). (See "Initial treatment of limited stage (I/II) follicular lymphoma" and "Treatment of relapsed or refractory follicular lymphoma" and "Clinical manifestations, pathologic features, diagnosis, and prognosis of follicular lymphoma" and "Pathobiology of follicular lymphoma", section on 'Introduction' and "Pathobiology of follicular lymphoma".)

PRE-TREATMENT EVALUATION — The initial evaluation of a patient with non-Hodgkin lymphoma (NHL) must establish the precise histologic subtype, the extent and sites of disease, and the performance status of the patient. These investigations are important for determining the treatment strategy and for predicting outcome with the Follicular Lymphoma International Prognostic Index (FLIPI) or one of its variants. General approaches to the diagnostic work-up and staging of NHL are presented separately (table 1). The pre-treatment evaluation for patients with advanced stage FL is the same as that of patients with limited stage FL. This is discussed in more detail separately. (See "Initial treatment of limited stage (I/II) follicular lymphoma", section on 'Pretreatment evaluation' and "Clinical presentation and diagnosis of non-Hodgkin lymphoma" and "Evaluation, staging, and response assessment of non-Hodgkin lymphoma".)

ADVANCED STAGE DISEASE

Therapeutic strategy — Advanced stage disease includes disease on both sides of the diaphragm (stage III) or diffuse involvement of one or more extralymphatic tissues (stage IV) (table 1). Seventy to 85 percent of patients present with advanced stage disease. Survival rates vary and can be estimated for the population

using the Follicular Lymphoma International Prognostic Index (FLIPI) score with five- and 10-year overall survival rates ranging from approximately 50 to 90 and 35 to 70 percent, respectively in the pre-rituximab era (table 2).

Patients with advanced stage disease are usually not cured with conventional treatment. While remissions can be attained, repeated relapses are common. Treatment focuses on the alleviation of symptoms, reversal of cytopenias, and improvement of quality of life. While not curative, modern therapy that incorporates rituximab prolongs survival. (See 'Immunotherapy-based treatment' below.)

The treatment of patients with advanced stage FL varies widely [1,2]. Whenever available, patients should be encouraged to participate in clinical trials. Asymptomatic patients can be observed initially. Once therapy is indicated, immunotherapy-based treatment (eg, chemotherapy plus rituximab) is preferred because it results in superior response rates, progression-free survival, and overall survival. Single agent rituximab may be considered for patients with comorbid conditions that make them poor candidates for chemotherapy. Single agent rituximab is also a reasonable alternative for those with a low tumor burden and/or disease that progresses slowly over years. Oral chemotherapy without rituximab (eg, low dose single agent chlorambucil or cyclophosphamide) may be used for the uncommon patient who cannot tolerate rituximab or who is not a candidate for more intensive intravenous chemotherapy [3]. Local radiation can be administered for the palliation of locally symptomatic disease.

Indications for treatment — As described above, patients with asymptomatic, stable FL do not require immediate treatment, but should be followed closely. The disease course is variable with some patients demonstrating stable disease for years and others progressing more rapidly. Rarely, patients may have spontaneous remissions lasting longer than one year.

Clinicians differ in the criteria that they use to initiate treatment. The two most commonly used systems are those proposed by the Groupe d-Etude des Lymphomes Folliculaires (GELF) [4] and the British National Lymphoma Investigation (BNLI) [5]. Our approach, described below, incorporates factors of each.

The following findings are clear indications for treatment:

- Local symptoms due to progressive or bulky nodal disease
- Compromise of normal organ function due to progressive or bulky disease
- Presence of systemic B symptoms (ie, fevers, weight loss, night sweats)
- Presence of symptomatic extranodal disease, such as effusions
- Cytopenias due to extensive bone marrow infiltration, autoimmune hemolytic anemia or thrombocytopenia, or hypersplenism
- An increase in disease tempo

These criteria are used as general indications for therapy because treatment of these factors is thought to improve quality of life. These are similar to the indications for therapy used in the trials comparing observation with initial therapy described in the previous section and most of the trials of chemotherapy for advanced stage disease.

Asymptomatic patients — Several randomized trials comparing chemotherapy regimens of different intensities with a watch-and-wait strategy followed by chemotherapy at the time of progression support the use of an initial period of observation for asymptomatic patients with low volume disease [4-10]. This approach does not jeopardize survival, and a prolonged treatment-free period may decrease the potential for drug resistance by avoiding exposure of the tumor to chemotherapy. In contrast, a large international randomized trial comparing watchful waiting versus initial treatment with rituximab suggested that initial

treatment with rituximab may improve quality of life (ie, decrease anxiety) and postpone cytotoxic chemotherapy [11].

In an international phase III trial, 379 patients with advanced-stage, asymptomatic, non-bulky FL were randomly assigned to initial management with one of three strategies: watchful waiting; rituximab induction (rituximab 375 mg/m^2 weekly for four doses); or rituximab induction followed by maintenance rituximab (administered every two months for two years) [11]. Poor accrual resulted in the early closure of the rituximab induction arm. Rituximab therapy was associated with improved ratings on quality of life measures, reflecting a decrease in anxiety. There was no difference in overall survival or rate of histologic transformation. There were 18 serious adverse events potentially related to rituximab therapy. As expected, watchful waiting resulted in a greater percentage of patients requiring subsequent interventions at three years (54 versus 12 and 22 percent). Surprisingly, the majority (91 percent) of patients in the watchful waiting group received chemotherapy upon progression, whereas four were treated with single-agent rituximab.

For asymptomatic, stable patients with advanced stage FL, we suggest initial observation. Immunotherapy-based treatment (eg, chemotherapy plus rituximab) is reserved for disease progression. This preference is largely based upon the prospective trials that have demonstrated no difference in overall survival with deferred therapy and the avoidance of cost, complications, and potential drug resistance. Alternatively, patients seeking immediate treatment may choose initial therapy with rituximab alone. (See 'Immunotherapy alone' below.)

We follow asymptomatic patients in clinic every three months for the first year and then every three to six months thereafter until progressive disease is noted. At these appointments we perform a history, physical examination, and laboratory studies including a complete blood count with differential, chemistries with liver and renal function and electrolytes, and lactate dehydrogenase (LDH). Imaging studies are repeated only if clinically indicated. Progressive disease is defined by an enlarging liver, spleen, or lymph node mass or by the development of new lesions, signs, or symptoms [12].

The progression of FL to the more aggressive variant diffuse large B cell lymphoma (DLBCL) occurs regardless of whether FL is treated aggressively or conservatively, at a rate of approximately 3 percent per year, depending upon the magnitude of the large cell component. Histologic transformation should be suspected if there is a rapid progression of lymphadenopathy, infiltration of extranodal sites, the development of systemic symptoms, or an elevated serum LDH. Biopsy of a suspicious area is indicated in such circumstances. In addition, we have a low threshold for obtaining a biopsy for all patients with FL at the time of progression. (See "Histologic transformation of follicular lymphoma".)

Immunotherapy-based treatment — Immunotherapy with monoclonal antibodies is a key component of the treatment of patients with FL; chemoimmunotherapy results in superior response rates, progression-free survival, and overall survival when compared to chemotherapy alone [13-19]. The anti-CD20 antibody rituximab was the first monoclonal antibody to be used successfully in FL. There are less data regarding the use of other anti-CD20 monoclonal antibodies (eg, obinutuzumab, ofatumumab) in previously untreated FL, although results from one randomized trial suggest that obinutuzumab-based induction and maintenance prolongs progression-free survival over that seen with rituximab-based therapy [20]. (See 'Choice of anti-CD20 antibody' below.)

Most studies have utilized intravenous administration. A subcutaneous formulation (rituximab-hyaluronidase) that uses a fixed dose and a shorter administration time is an acceptable alternative for patients who have tolerated at least one full dose of intravenous rituximab [21]. Randomized trials have demonstrated comparable efficacy and safety of the two formulations in patients with FL, diffuse large B cell lymphoma, and chronic lymphocytic leukemia [22-25].

The major toxicities of anti-CD20 antibodies include infusion reactions (ie, fevers, rigors, and hypotension) and infections related to immunosuppression. These agents also imposes a risk of hepatitis B reactivation among patients positive for hepatitis B surface antigen (HBsAg) or antibodies against hepatitis B core antigen

(anti-HBc). (See "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy", section on 'Rituximab' and "Secondary immunodeficiency induced by biologic therapies", section on 'Rituximab' and "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Prospective trials have also investigated the use of single agent rituximab and the use of radioimmunotherapy as consolidation therapy after initial combination chemotherapy. (See 'Immunotherapy alone' below and 'Radioimmunoconjugates' below.)

For patients with previously untreated FL who require therapy, we recommend treatment with an immunotherapy-based regimen rather than chemotherapy alone. We typically administer rituximab plus chemotherapy; we prefer this to rituximab alone, chemotherapy followed by rituximab, or chemotherapy followed by a radioimmunoconjugate, principally due to the greater clinical experience with this approach. Single agent rituximab is an acceptable alternative for patients with comorbid conditions that make them poor candidates for chemotherapy and for those with a low tumor burden and/or disease progressing slowly over years. (See 'Immunotherapy alone' below.)

Choice of anti-CD20 antibody — As described above, immunotherapy with an anti-CD20 antibody is a key component to the treatment of patients with FL. Rituximab was the first anti-CD20 monoclonal antibody to be used successfully in FL and is generally our preferred agent. There are less data regarding the use of novel anti-CD20 monoclonal antibodies (eg, obinutuzumab, ofatumumab) in previously untreated FL, although one randomized trial (GALLIUM) suggest that obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) over that seen with rituximab-based therapy; however, this impact on PFS may depend upon the chemotherapy backbone used.

The GALLIUM study was an international, open-label, randomized phase III trial comparing an obinutuzumab-based induction and maintenance strategy versus a rituximab-based induction and maintenance strategy in 1202 patients with previously untreated advanced stage FL [20]. Participating treatment centers selected one of the following chemotherapy regimens to use with the antibody for induction: bendamustine (57 percent), CHOP (33 percent), or CVP (10 percent). At a median follow-up of 34.5 months, the obinutuzumab-based strategy resulted the following:

- Similar estimated rates of overall response (89 versus 87 percent) and complete response (20 versus 24 percent)
- Superior PFS (80 versus 73 percent at three years; HR 0.66, 95% CI 0.51-0.85)
- Similar overall survival (OS) (94 versus 92 percent at three years; HR 0.75, 95% CI 0.49-1.17) and similar rates of histologic transformation
- Higher rates of grade 3 to 5 adverse events (75 versus 68 percent), infusion-related events (59 versus 49 percent), febrile neutropenia (6.9 versus 4.9 percent), and grade 3/4 infections (20 versus 15.6 percent)

Fatal adverse events were seen in 4 and 3.4 percent of patients receiving obinutuzumab and rituximab, respectively. Fatal adverse events were more common in patients receiving bendamustine plus obinutuzumab (5.6 percent) or rituximab (4.4 percent) when compared to those receiving CHOP or CVP (≤2 percent). This increased rate of fatal adverse events has not been seen when bendamustine is used in combination with rituximab in the absence of maintenance therapy.

These results suggest improved PFS with the use of an obinutuzumab-based induction followed by obinutuzumab maintenance. It is not known whether this will translate into a survival benefit in the future and the use of either antibody is reasonable at this time. When considering the choice of anti-CD20 antibody, the potential toxicities and the value of PFS as a clinical endpoint must be interpreted within the context of the disease course. Patients with advanced stage FL are not cured with conventional therapies. Most of these

patients are managed over decades with a focus on symptom control. Active treatment may be separated by several years without active therapy and asymptomatic progression does not require immediate therapy.

Chemoimmunotherapy — Anti-CD20 monoclonal antibodies can be administered either alone or in combination with chemotherapy. Many chemotherapy regimens have been combined with rituximab in prospective trials. A choice among these various regimens depends upon patient and tumor characteristics:

- In general, we prefer bendamustine plus rituximab (BR) given the fewer side effects associated with this regimen and trials that suggest increased efficacy when compared with R-CHOP.
- There is a paucity of data regarding the use of BR in patients with the more aggressive histologic grade 3a disease; R-CHOP may be preferred in this setting for fit patients with clinically aggressive disease.
- R-CVP is an alternative for patients who cannot receive anthracyclines, but is expected to result in a lower response rate and a shorter PFS. (See 'Patients with cardiac disease' below.)
- Fludarabine-based regimens are not used due to high toxicity in this population [26-28].

As described in more detail below, in two randomized trials, BR achieved at least equivalent response rates and was less toxic than R-CHOP or R-CVP [29,30]. In one of these trials, when compared with R-CHOP, BR demonstrated superior PFS and similar OS [29]. Importantly, the choice of initial therapy will impact the options for treatment at the time of relapse or histologic transformation. The following studies illustrate the efficacy and toxicity of these three regimens:

- Bendamustine **plus** rituximab **(BR)** (table 3) [29,30] – Bendamustine (90 mg/m^2 days 1 and 2) plus rituximab (375 mg/m^2 day 1) every 28 days for six cycles was compared with standard R-CHOP for six cycles in a randomized, phase III trial (StiL trial) of 514 patients with advanced follicular, indolent, and mantle cell lymphoma, and showed superior median PFS (69.5 versus 31.2 months, hazard ratio 0.58, 95% CI 0.44-0.74) for all histologic subtypes except marginal zone lymphoma with less toxicity, including lower rates of grade 3 and 4 neutropenia (29 versus 69 percent) and leukocytopenia (37 versus 72 percent), fewer infectious episodes (37 versus 50 percent), less paresthesia (7 versus 29 percent), less stomatitis (6 versus 19 percent), and no alopecia [29]. There was no difference in OS (70 versus 66 percent at 10 years) [31]. The number of second malignancies was similar between the two treatment arms (39 versus 47 cases).

  In the international phase III BRIGHT trial, 447 previously untreated patients with advanced stage follicular (n = 314 patients), mantle cell (n = 74 patients), or other indolent lymphoma were randomly assigned to six cycles of BR according to the same dose and schedule described above or to R-CHOP or R-CVP (as determined by the investigator prior to randomization) [30,32]. BR resulted in similar complete (31 versus 25 percent) and overall (97 versus 91 percent) response rates. BR was associated with higher rates of vomiting and drug hypersensitivity and lower rates of peripheral neuropathy/paresthesia and alopecia. The use of prophylactic antiemetics was not specified in the protocol and was more common among patients assigned to R-CHOP. Preliminary data suggest that BR resulted in improved PFS (66 versus 56 percent at five years) for the group as a whole, a finding that lost statistical significance when the patients with mantle cell lymphoma were removed from the analysis [33]. There was no difference in OS.

- Cyclophosphamide**,** doxorubicin**,** vincristine**, and** prednisone **plus** rituximab **(R-CHOP)** (table 4) [17,28,34] – Standard R-CHOP was compared with R-CVP and R-FM (rituximab, fludarabine, mitoxantrone) in a randomized trial of 534 patients with advanced stage FL [28]. When compared with R-CVP, R-CHOP and R-FM resulted in superior rates of three-year PFS (68 and 63 versus 46 percent) and time to treatment failure (59 and 62 versus 46 percent). A survival analysis was not performed. R-FM had higher rates of severe neutropenia and second malignancies. In the randomized trial of R-CHOP versus BR described above, the overall response rate was 91 percent with a median time to progression of 6.8 years and four-year OS rate of 83 percent [29]. Common side effects include severe neutropenia

(69 percent) and mild to moderate alopecia, nausea, vomiting, and infusion related reactions. There is a 1 to 2 percent treatment-related mortality rate.

Immunotherapy alone — Single agent rituximab is an acceptable initial treatment for patients with comorbid conditions that make them poor candidates for chemotherapy and for those with a low tumor burden and/or disease progressing slowly over years. Rituximab has a low toxicity profile and good response rates and has been shown to delay disease progression in these populations. Long-term follow-up is limited, and it is not known if survival is improved. However, a large international randomized trial comparing watchful waiting versus initial treatment with rituximab suggested that initial treatment with rituximab may improve quality of life (ie, decrease anxiety) and postpone cytotoxic chemotherapy [11]. (See 'Asymptomatic patients' above.)

The ideal dosing schedule of rituximab is not known. The following administration schedules were used in the randomized trials and are equally acceptable approaches:

- Rituximab 375 mg/m^2 IV per week for a total of four doses [35]
- Rituximab 375 mg/m^2 IV per week for four weeks followed by four additional doses administered every two months [36,37]

A subcutaneous formulation (rituximab-hyaluronidase) that uses a fixed dose and a shorter administration time is an acceptable alternative for patients who have tolerated at least one full dose of intravenous rituximab [21].

The following describes the largest trials evaluating single agent rituximab (375 mg/m^2 IV per week for a minimum of four consecutive weeks) as initial therapy in patients with FL [36,38-43]:

- An international trial of 202 patients with previously untreated or relapsed/refractory FL administered four weekly doses of single agent rituximab [36,37]. The 151 patients with responding or stable disease at week 12 were randomized to no further treatment or prolonged rituximab maintenance every two months for four doses. At a median follow-up of 35 months, patients who received the prolonged rituximab maintenance had a significantly longer median event-free survival (23 versus 12 months) when compared with those randomized to observation with no apparent increase in toxicity. This benefit appears to be maintained with long-term follow-up demonstrating 35 percent of responders still in remission at eight years [37]. Of note, 45 percent of newly diagnosed patients in this study were in remission at eight years with extended schedule rituximab.
- An international phase III trial compared rituximab induction followed by rituximab maintenance (administered every two months for two years) versus observation in 379 patients with advanced stage, asymptomatic, non-bulky FL [11]. Rates of overall and complete response after rituximab were 88 and 51 percent, respectively. Spontaneous remissions were seen in 6 percent of patients in the observation group. The two groups had similar estimated rates of overall survival at three years (94 versus 97 percent) and biopsy proven histologic transformation (11 versus 7 percent). There were 18 serious adverse events potentially related to rituximab therapy.
- In another multicenter trial (RESORT), 408 patients with low tumor burden previously untreated FL received four weekly doses of rituximab [35]. Of these, 299 (73 percent) patients achieved a complete or partial response and were randomly assigned to rituximab maintenance or to observation and retreatment with rituximab at the time of progression. Estimated overall survival at five years was similar in both groups (94 percent), and there was no difference in the rate of histologic transformation. Anxiety levels did not differ by assigned treatment (maintenance versus observation) [44].

These data suggest that single agent rituximab is associated with low toxicity and high response rates in patients with low tumor burden advanced stage FL. The use of maintenance rituximab is discussed in more detail separately. (See 'After immunotherapy' below.)

Radiation therapy — The role of radiation therapy in advanced stage FL is limited to the use of local palliative radiation for the treatment of locally symptomatic disease. Consolidation radiation therapy given after chemotherapy does not appear to improve outcomes and may result in secondary disorders.

Studies have failed to demonstrate improvements in relapse-free survival or overall survival when radiation therapy is added to conventional chemotherapy. Although myelodysplasia (MDS) and acute leukemia are uncommonly seen in patients with indolent lymphomas treated with chemotherapy alone, a 15-year cumulative incidence of MDS and secondary acute leukemia of 17 percent has been reported for the combination of low dose total lymphoid irradiation and cytotoxic chemotherapy [45]. This suggests that combined modality therapy increases the incidence of hematopoietic stem cell disorders. As such, we do not use combined modality therapy in this patient population.

Radioimmunoconjugates — Several prospective trials have investigated the use of anti-CD20 radioimmunoconjugates (eg, ibritumomab tiuxetan) in patients with previously untreated FL receiving chemotherapy without rituximab, which is also directed against CD20. Until more definitive data are available, we do **not** use radioimmunoconjugates as part of first-line therapy. Their use in relapsed or refractory disease is discussed separately. (See "Treatment of relapsed or refractory follicular lymphoma", section on 'Radioimmunotherapy'.)

Results from randomized trials of radioimmunoconjugates in patients who did not receive rituximab suggest that consolidation with a radioimmunoconjugate may improve the quality of remission by converting partial responses into complete responses [46-49]. This results in superior progression-free survival, but no difference in overall survival.

Based largely upon these trials, the US Food and Drug Administration approved the use of ibritumomab tiuxetan for the treatment of FL patients who have achieved a partial or complete response to first-line chemotherapy. However, this treatment approach is not used commonly since it is cumbersome and there is no clear benefit over initial chemoimmunotherapy alone.

Transplantation

Autologous HCT — Several prospective randomized trials have examined the use of high dose chemotherapy followed by hematopoietic cell transplantation (HCT) in the treatment of newly diagnosed FL [50-55]. While some have demonstrated improvements in progression-free survival, none has shown an overall survival benefit. As an example, a prospective, multicenter phase III study of 136 patients with newly diagnosed high-risk FL randomly assigned therapy to six courses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) followed by rituximab or rituximab-supplemented high-dose sequential chemotherapy with autologous HCT [55]. Patients were eligible if they had Ann Arbor stage III or IV FL and an age-adjusted International Prognostic Index (IPI) score ≥2. When compared with those who received R-CHOP alone, patients assigned to receive HCT had significantly higher rates of complete remission (85 versus 62 percent). At a median follow-up of 51 months, four-year overall survival rates were approximately 80 percent for both groups.

A 2012 Cochrane systematic review and meta-analysis of these trials found that high dose chemotherapy followed by autologous HCT resulted in significantly improved progression-free survival (hazard ratio [HR] 0.42; 95% CI 0.33-0.54) but similar overall survival (HR 0.97; 95% CI 0.76-1.24) when compared with combination chemotherapy or immunochemotherapy [56]. There was also no significant difference in the rates of treatment-related mortality and rates of secondary hematologic and solid cancers. Similar results were found in a second systemic review and meta-analysis performed by another group of investigators [57].

For patients with previously untreated advanced stage FL who require therapy, we recommend treatment with an immunotherapy-based regimen rather than chemotherapy alone or HCT.

Allogeneic HCT — Allogeneic HCT may cure a percentage of patients with advanced stage disease, but is associated with a treatment-related mortality rate of approximately 30 percent. Given this high mortality

rate, allogeneic HCT is reserved for young, highly motivated patients with relapsed or resistant FL. This is discussed in more detail separately. (See "Autologous hematopoietic cell transplantation in follicular lymphoma".)

SPECIAL SITUATIONS

Grade 3b FL — FL tumors are graded on a scale from 1 to 3 according to the number of centroblasts per high powered field. FL grade 3b (not 3a) is synonymous with what is often referred to as follicular large cell lymphoma. In contrast to lower grade FL, this histologic variant has a lesser tendency to involve the bone marrow or peripheral blood and often presents with larger lymphoid masses. Although the follicular architecture is preserved, the clinical presentation, behavior, and outcome with treatment more closely approximates that of the aggressive non-Hodgkin lymphoma (NHL) variant diffuse large B cell lymphoma (DLBCL). Grade 3b FL is treated according to protocols used for DLBCL. The treatment of DLBCL is presented in more detail separately. (See "Initial treatment of advanced stage diffuse large B cell lymphoma".)

Patients with hepatitis C — A number of reports, primarily from Europe, have indicated that treatment of a coexisting hepatitis C virus infection (HCV) with interferon and ribavirin has resulted in complete clinical remissions in some patients with indolent lymphoma, including FL [58-61].

One study evaluated the effect of treatment with interferon alpha, alone or in combination with ribavirin, in 18 patients with splenic marginal zone lymphoma (MZL), coexisting hepatitis C virus (HCV) infection, and mixed cryoglobulinemia [58]. Hematologic and virologic responses were correlated, in that all 14 patients (78 percent) who cleared HCV RNA had a sustained hematologic response. Monoclonal immunoglobulin gene rearrangement persisted after treatment regardless of response. Interferon was without effect in six patients with splenic MZL who were not infected with HCV [59].

Similar treatment results were noted in a series of 13 patients with HCV infection and various forms of indolent lymphoma, including follicular [61].

An initial trial of treatment directed at the hepatitis C virus infection may be indicated for patients with HCV who are asymptomatic from their lymphoma and would otherwise not require the initiation of chemotherapy directed at their lymphoma. (See "Extrahepatic manifestations of hepatitis C virus infection", section on 'Lymphoma'.)

Patients with cardiac disease — Patients with underlying cardiac disease may not be able to tolerate the use of an anthracycline (eg, doxorubicin) since these agents are toxic to cardiac cells. Anthracyclines should not be administered to patients with a baseline ejection fraction below 30 percent. Patients with an ejection fraction greater than 30 percent may require monitoring. (See "Clinical manifestations, monitoring, and diagnosis of anthracycline-induced cardiotoxicity" and "Prevention and management of anthracycline cardiotoxicity".)

Patients who are not candidates for anthracyclines may be treated with single agent rituximab or with R-CVP (cyclophosphamide, vincristine, and prednisone plus rituximab), depending upon the aggressiveness of disease and other patient characteristics. The use of single agent rituximab is discussed above. (See 'Immunotherapy alone' above.)

R-CVP is a non-anthracycline-containing chemoimmunotherapy regimen that has been used for patients with FL. When compared with BR and R-CHOP, R-CVP is expected to result in a lower response rate and a shorter progression-free survival [13,14,28]. Side effects are generally mild with gastrointestinal toxicities and peripheral neuropathy being most common. Severe (grade 3/4) neutropenia occurs in approximately 24 percent. Treatment-related deaths are uncommon. The overall response rate is 81 to 88 percent. Median time to progression is approximately 2.8 years with a three-year overall survival rate of 89 percent.

Histologic transformation — An integral part of the natural history of FL is progression to a higher grade histologic subtype, such as DLBCL. As is detailed separately, a subgroup of patients with FL who transform to a more aggressive histology may attain complete remission following treatment with CHOP-like chemotherapy and some may be cured by high dose chemotherapy followed by autologous hematopoietic cell transplantation. (See "Autologous hematopoietic cell transplantation in follicular lymphoma", section on 'Following histologic transformation' and "Histologic transformation of follicular lymphoma".)

EVALUATION OF RESPONSE TO THERAPY — After completion of initially planned treatment of FL, patients should be evaluated to determine the disease response to treatment and should be followed longitudinally for relapse. The response evaluation of patients with advanced stage FL is the same as that of patients with limited stage FL. This is discussed in more detail separately. (See "Initial treatment of limited stage (I/II) follicular lymphoma", section on 'Evaluation of response to therapy'.)

LONG-TERM MANAGEMENT

Maintenance therapy — Maintenance therapy refers to the prolonged administration of agents with low toxicity profiles in an attempt to prevent progression of disease. Several trials have investigated the use of maintenance rituximab after chemoimmunotherapy, after immunotherapy alone, and after chemotherapy alone. While the goal of treatment is a complete remission (CR), many patients only obtain a partial remission (PR) with induction chemotherapy. There has been an increasing interest in using maintenance therapy after induction therapy in order to convert some of the PRs into CRs. This is principally because patients who attain a CR demonstrate longer remissions and a trend towards increased overall survival. Even though maintenance therapy is designed to have a low toxicity profile, a decision regarding the use of maintenance therapy in an individual patient must take into consideration both the potential benefit from attaining a deeper response and the likelihood that this patient will tolerate the prolonged therapy.

After chemoimmunotherapy — For patients with newly diagnosed FL who have had at least a partial response to initial therapy with R-CVP or R-CHOP, we suggest maintenance rituximab rather than observation. In contrast, we do not advocate the use of rituximab maintenance after other chemoimmunotherapy regimens (eg, BR) for most patients. When administering maintenance rituximab, it is important to use one of the established regimens, such as that used in the PRIMA study (rituximab every two months for a total of two years) described below [62,63]. There are no published data regarding the safety or efficacy of therapy extending beyond this; as such rituximab maintenance should **not** exceed two years. Rituximab also imposes a risk of hepatitis B reactivation among patients positive for hepatitis B surface antigen (HBsAg) or antibodies against hepatitis B core antigen (anti-HBc). (See "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy", section on 'Rituximab' and "Secondary immunodeficiency induced by biologic therapies", section on 'Rituximab' and "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

The largest trial to address this was the Primary Rituximab and Maintenance (PRIMA) phase III intergroup trial in which 1019 patients with previously untreated FL who had demonstrated an initial response to chemoimmunotherapy were randomly assigned maintenance with rituximab (375 mg/m^2 every eight weeks for 24 months) or placebo [62,63]. At a median follow-up of 36 months from randomization, patients assigned to rituximab maintenance demonstrated the following significant findings:

- Higher rates of progression-free survival at 36 months (75 versus 58 percent)
- Higher percentage of patients in complete response (CR) or unconfirmed CR at 24 months (72 versus 52 percent)
- Higher overall rate of severe (grade 3/4) adverse events (24 versus 17 percent)
- Higher rate of infections (39 versus 24 percent), the majority of which could be treated in the ambulatory setting (grade 2)

- Similar survival and quality of life ratings

Further data with a median follow-up of six years, 463 patients had relapsed, 40 of which represented histologic transformation [64]. Most cases of histologic transformation occurred in the first year with a median time to transformation of 9.7 months.

PRIMA was included in a meta-analysis of seven trials evaluating rituximab maintenance after chemotherapy or chemoimmunotherapy in 2315 patients with FL [65]. For the group as a whole, maintenance rituximab improved progression-free survival (hazard ratio 0.57; 95% CI 0.51-0.64) and overall survival (HR 0.79; 95% CI 0.66-0.96), although the absolute improvement in median overall survival was small (12 versus 11.5 years). Maintenance rituximab was associated with a greater risk of adverse events, most commonly infections (34 versus 24 percent). On subset analysis, a survival benefit was **not** seen when maintenance rituximab was given after rituximab-containing induction.

It is not clear whether these results can be safely extrapolated to patients treated with other initial chemotherapy regimens, such as bendamustine plus rituximab (BR) or rituximab, fludarabine, mitoxantrone, and dexamethasone (R-FND). The universal applicability of rituximab maintenance was questioned by the results of a randomized phase III trial that evaluated the use of rituximab or observation after initial therapy with R-FND in 234 older adults (age 60 to 75 years) with previously untreated advanced stage FL [66]. After induction, the overall response rate was 86 percent (69 percent complete). After a median follow-up of 42 months, the estimated rates of progression-free survival and overall survival at three years were 66 and 89 percent, respectively. Rituximab maintenance was associated with a trend towards improved progression-free survival at two years (81 versus 69 percent), which did not reach statistical significance, and a higher rate of severe (grade 3/4) neutropenia (14 versus 1 percent). Variation in the benefit from rituximab maintenance by induction regimen was also suggested on a subset analysis of the PRIMA trial, in which there didn't appear to be a benefit following rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) [62,63]. As such, we do not advocate the use of rituximab maintenance after initial therapy with regimens other than R-CVP or R-CHOP. A subset of patients may select to proceed with maintenance after discussion of the potential harms and benefits. Such patients place a higher value of a potential yet unknown benefit extrapolated from the PRIMA study and a lower value on the potential harms.

After immunotherapy — For patients initially treated with single agent rituximab, we recommend a finite schedule of rituximab rather than continuing rituximab until progression (maintenance rituximab). Rituximab maintenance has not been shown to improve overall survival and is associated with potential toxicity, including progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation. (See "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy", section on 'Rituximab' and "Secondary immunodeficiency induced by biologic therapies", section on 'Rituximab' and "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

The following administration schedules were used in the randomized trials and are equally acceptable approaches:

- Rituximab 375 mg/m^2 IV per week for four weeks followed by four additional doses administered every two months [36,37,67]

- Rituximab 375 mg/m2 IV per week for a total of four doses [35]

The prolonged dosing schedule is supported by a randomized trial, described above, which evaluated the use of a prolonged rituximab schedule after initial treatment with single agent rituximab [36,37]. After demonstrating response or disease stabilization at week 12 after four weekly doses of single agent rituximab, patients randomly assigned to continue with rituximab maintenance (every two months for four doses) had a significantly longer median event-free survival (24 versus 13 months) when compared with those randomized to observation. There was no apparent increase in toxicity, and those patients who had not received chemotherapy before had an even more pronounced improvement in median event-free survival with

prolonged rituximab therapy (36 versus 19 months) when compared with observation. (See 'Immunotherapy alone' above.)

In contrast, using rituximab as maintenance until progression is associated with greater toxicity and does not improve event-free or overall survival. In the SAKK 35/03 trial, 270 patients with FL were treated with four weekly doses of rituximab [67]. The 165 patients achieving at least a partial response were randomly assigned to receive rituximab every two months for four additional doses or to rituximab every two months for a maximum of five years. Those assigned to long-term maintenance had improved progression-free survival (median 7.4 versus 3.5 years) but were more likely to experience toxicities (at least one adverse event 76 versus 50 percent). There was no statistically significant difference in event-free survival, the primary study endpoint.

The shorter schedule (weekly rituximab for four total doses) was used in the multicenter RESORT trial evaluating maintenance rituximab. In this trial, 408 patients with low tumor burden previously untreated FL received four weekly doses of rituximab [35]. Patients achieving a complete or partial response were randomly assigned to rituximab maintenance (375 mg/m^2 every three months until progression) or to observation and retreatment with four weekly doses of rituximab at the time of progression. Rituximab therapy was well tolerated with the maintenance arm receiving approximately three times as much rituximab than the observation arm (18 versus 4 doses). When compared with observation and retreatment, maintenance rituximab resulted in a similar median time to treatment failure (3.9 versus 4.3 years) and similar health related quality of life and anxiety ratings. There was no difference in the estimated rates of overall survival at five years (94 percent) and histologic transformation. One patient in the maintenance rituximab arm died after developing progressive multifocal leukoencephalopathy.

Surveillance for relapse — Following the completion of therapy, restaging, and documentation of complete or partial remission, patients are seen at periodic intervals to monitor for treatment complications and assess for progression. This is discussed in more detail separately. (See "Initial treatment of limited stage (I/II) follicular lymphoma", section on 'Surveillance for relapse'.)

CLINICAL TRIALS — Often there is no better strategy to offer a patient than enrollment onto a well-designed, scientifically valid, peer-reviewed clinical trial. Additional information and instructions for referring a patient to an appropriate research center can be obtained from the United States National Institutes of Health (www.clinicaltrials.gov).

PROGNOSIS — Patients with FL generally have an excellent prognosis; however, there are groups of patients who have more as well as less favorable survival. The Follicular Lymphoma International Prognostic Index (FLIPI) (table 2) was developed specifically for patients with FL, since the International Prognostic Index, which was developed in patients with aggressive non-Hodgkin lymphoma (NHL), resulted in conflicting results, due in large part to a low number of patients with indolent lymphoma (approximately 10 percent) belonging to the higher risk groups.

This subject is discussed in detail separately. (See "Clinical manifestations, pathologic features, diagnosis, and prognosis of follicular lymphoma", section on 'Follicular lymphoma IPI (FLIPI)'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5^{th} to 6^{th} grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10^{th} to 12^{th} grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Follicular lymphoma (The Basics)")
- Beyond the Basics topics (see "Patient education: Follicular lymphoma in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma. Treatment of FL depends upon the stage of disease at presentation (table 1).
- A pretreatment evaluation both determines the extent of the disease and provides information about the individual's comorbidities that are likely to have an impact on treatment options. Enrollment in clinical trials should be encouraged. (See "Initial treatment of limited stage (I/II) follicular lymphoma", section on 'Pretreatment evaluation'.)
- Advanced stage disease includes disease on both sides of the diaphragm (stage III) or diffuse involvement of one or more extralymphatic tissues (stage IV). Advanced stage FL is not curable with conventional treatment. Thus, in contrast to patients with curable aggressive lymphomas, the major indication for treatment is alleviation of symptoms and most patients with asymptomatic disease may defer therapy. (See 'Indications for treatment' above.)
- For patients with previously untreated advanced stage FL who require therapy, we recommend treatment with an immunotherapy-based regimen rather than chemotherapy alone or hematopoietic cell transplantation (**Grade 1A**). A choice among the various regimens depends upon patient characteristics and physician comfort. While we generally prefer rituximab-based combinations, obinutuzumab-based regimens are an acceptable alternative. We suggest bendamustine plus rituximab (BR) rather than other regimens (**Grade 2B**). This preference is based upon our experience with the regimen and the improved progression-free survival rates and less toxicity when compared with R-CHOP. R-CHOP may be preferred for fit patients with clinically more aggressive histologic grade 3a disease. R-CVP would be an acceptable alternative in patients who are not candidates for anthracyclines (eg, those with underlying cardiac disease). Single agent rituximab would be an acceptable alternative in patients with comorbid conditions that make them poor candidates for chemotherapy and for those with a low tumor burden and/or disease progressing slowly over years. (See 'Immunotherapy-based treatment' above.)
- Patients are evaluated after treatment with laboratory studies and a computed tomography, in addition to a history and physical examination, to determine response to therapy. Patients attaining a complete or partial remission are followed at periodic intervals for disease progression. Patients who fail to achieve a partial remission are treated as refractory disease. (See "Initial treatment of limited stage (I/II) follicular lymphoma", section on 'Evaluation of response to therapy'.)
- The efficacy of rituximab maintenance (versus no maintenance) in patients with advanced FL after initial induction of response may be dependent upon the choice of initial therapy.
    - For most patients with newly diagnosed FL who have had at least a partial response to initial therapy with BR, we suggest observation rather than maintenance rituximab (**Grade 2C**). In contrast, for patients with newly diagnosed FL who have had at least a partial response to initial therapy with R-CVP or R-CHOP, we suggest maintenance rituximab rather than observation (**Grade 2B**). When administering maintenance rituximab, it is important to use one of the established regimens, such as that used in the PRIMA study (rituximab every two months for a total of two years). There are no published data regarding the safety or efficacy of therapy extending beyond this; as such rituximab maintenance should **not** exceed two years. (See 'After chemoimmunotherapy' above.)
    - For patients initially treated with rituximab therapy alone, we recommend a finite schedule of rituximab rather than continuing rituximab until progression (maintenance rituximab) (**Grade 1B**). Rituximab (375 mg/m^2 IV) is administered as four weekly doses followed either by observation or by

the same dose of rituximab every two months for four additional doses. (See 'After immunotherapy' above.)

- The vast majority of patients treated for FL will have an initial response with approximately half demonstrating a complete response. Unfortunately, therapy for FL is not curative and virtually all of these patients will ultimately develop progressive disease. The treatment of relapsed or refractory disease is presented separately. (See "Treatment of relapsed or refractory follicular lymphoma".)

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Topic 83847 Version 32.0

GRAPHICS

Revised staging system for primary nodal lymphomas (Lugano classification)

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

Extent of disease is determined by positron emission tomograph/computed tomography (PET/CT) for avid lymphomas and CT for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

* Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014; 32(27):3059-67. Reprinted with permission. Copyright © 2014 American Society of Clinical Oncology. All rights reserved.

Graphic 97479 Version 3.0

Follicular lymphoma international prognostic index (FLIPI)

• Age >60 years
• Serum lactate dehydrogenase concentration above normal
• Hemoglobin level <12.0 g/dL
• Ann Arbor stage III or IV
• Number of involved nodal areas >4
One point is given for each of the above characteristics present in the patient with FL, for a total score ranging from zero to five. When applied to an international study of long-term survival in 4167 patients with FL diagnosed between 1985 and 1992 and treated without rituximab, the following three risk groups and their corresponding five- and 10-year OS were, as follows[1]:

Score	Risk group	Five-year OS, percent	10-year OS, percent
0 to 1	Low risk	91	71
2	Intermediate risk	78	51
3 or more	High risk	52	36

This same score was applied to 2192 patients diagnosed between 2004 and 2007, the majority of whom (68 percent) received rituximab in the initial management, with the following results[2]:

Score	Two-year OS, percent	Two-year PFS, percent	Median PFS, months
0 to 1	98	84	84
2	94	72	70
3 or more	87	65	42

FL: follicular lymphoma; OS: overall survival; PFS: progression-free survival.

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Graphic 55987 Version 4.0

Bendamustine and rituximab for non-Hodgkin lymphoma[1,2]

Cycle length: 28 days.

Drug	Dose and route	Administration	Given on days
Rituximab	375 mg/m^2 IV	Dilute in normal saline (NS) or 5% dextrose in water to a final concentration of 1 to 4 mg/mL. Initial infusion: Start at 50 mg/hour; escalate in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour, as tolerated. In the absence of an initial infusion reaction, patients without clinically significant cardiovascular disease may receive subsequent infusions over 90 minutes.* For the 90-minute infusion, administer 20% of the total dose over the first 30 minutes and the remaining 80% over 60 minutes, as tolerated[3].◇	Day 1
Bendamustine	90 mg/m^2 IV	Dilute¶ in 500 mL NS or 2.5% dextrose/0.45% sodium chloride to a final concentration of 0.2 to 0.6 mg/mL.Δ Administer over 60 minutes.	Days 1 and 2

Pretreatment considerations:

Emesis risk	▪ MODERATE. ▪ Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults".
Prophylaxis for infusion reactions	▪ Premedicate with acetaminophen and diphenhydramine, with or without an H2 receptor blocker, 30 minutes prior to at least the first and second infusions of rituximab.[4] There is no standard premedication for the initial bendamustine dose. Consider premedication with antihistamines, antipyretics, and corticosteroids for patients with a previous grade 1 or 2 infusion reaction to bendamustine.[5-7] ▪ Refer to UpToDate content on "Infusion reactions to therapeutic monoclonal antibodies used for cancer therapy".
Vesicant/irritant properties	▪ Bendamustine is an irritant with vesicant-like properties; ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation (particularly by avoiding use of closed system transfer devices, adapters, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene [ABS] with Treanda injection solution¶); monitor IV site for redness, swelling, or pain. ▪ Refer to UpToDate content on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants".
Infection prophylaxis	▪ The specific incidence of febrile neutropenia was not reported, however, the incidence of grade 3 or 4 neutropenia was 29 to 49% and the incidence of grade 3 or 4 infection was 7 to 12%.[1,2] Primary prophylaxis with hematopoietic growth factors should be considered on an individual basis. ▪ Refer to UpToDate content on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation".
Dose adjustment for baseline liver or renal dysfunction	▪ Treanda should not be used in patients with a creatinine clearance <40 mL/min. Bedenka should not be used in patients with a creatinine clearance <30 mL/min. Bendamustine should be used with caution in patients with mild hepatic and renal impairment. Bendamustine should not be used in patients with moderate to severe (AST or ALT >2.5 times the ULN and total bilirubin >1.5 times the ULN) hepatic impairment.[5-7] ▪ Refer to UpToDate content on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease" and "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency".
Hepatitis screening	▪ Patients should be screened for hepatitis B and C prior to starting rituximab, and if positive, considered for antiviral prophylaxis.

	▪ Refer to UpToDate content on "Hepatitis B virus reactivation associated with immunosuppressive therapy".
Monitoring parameters:	
▪ Obtain CBC with differential weekly (initially).[5-7]	
▪ Assess electrolytes and liver and renal function prior to each treatment.	
▪ Carriers of hepatitis B or C virus should be monitored for clinical and laboratory signs of active infection during and following completion of therapy. Rituximab should be discontinued if reactivation occurs. ▪ Refer to UpToDate topic on "Hepatitis B virus reactivation associated with immunosuppressive therapy".	
▪ Monitor IV infusion site for redness, swelling, pain, infection, and necrosis during and after the bendamustine infusion.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ Delay treatment if absolute neutrophil count <1000/microL, platelet count <75,000/microL, or if there is an active infection.[4-7] If grade 4 hematologic toxicity occurs, reduce dose to 60 mg/m^2 on days 1 and 2 of each cycle.[2,5-7] Further dose reductions or dose re-escalation may be done at the discretion of the physician.
Other toxicity	▪ For grade 3 or greater nonhematologic toxicity, reduce bendamustine dose to 60 mg/m^2 on days 1 and 2 of the treatment cycle.[5-7] If toxicity resolves, doses may be cautiously re-escalated on subsequent cycles. Further dose reductions or dose re-escalation may be done at the discretion of the physician.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; CBC: complete blood count.
* In the absence of an initial reaction, an alternative schedule for subsequent rituximab infusions is to start at 100 mg/hour and escalate in 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour as tolerated.[4] If there is an infusion reaction to any dose, follow the initial infusion guidelines described above.
¶ Standard bendamustine solution (Treanda injection[5]) is not compatible with closed system transfer devices, adapters, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS), since these plastics can dissolve upon contact.
Δ Concentration and infusion length recommendations for Treanda are for lyophilized powder, which is available as 25 mg/vial or 100 mg/vial.[6] If using Treanda injection solution (which is available as a 45 mg/0.5 mL or 180 mg/2 mL solution), the recommended final concentration is 0.2 to 0.7 mg/mL, infused over 60 minutes.[5] If using Bendeka 25 mg/mL solution, dilute in 50 mL NS to a final concentration 1.85 to 5.6 mg/mL and infuse over 10 minutes[7].
◇ A subcutaneous formulation (rituximab-hyaluronidase) that uses a fixed dose and a shorter administration time is an acceptable alternative for patients who have tolerated at least one full dose of intravenous rituximab[8]. Dosing varies by histology and clinicians should refer to the US Prescribing Information for details.

References:

1. *Flinn IW, et al. Blood 2014; 123:2944.*
2. *Rummel MJ, et al. Lancet 2013; 381:1203.*
3. *Sehn LH, et al. Blood 2007; 109:4171.*
4. *Rituximab injection. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on December 1, 2016).*
5. *Treanda (bendamustine hydrochloride) injection, concentrate. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on December 1, 2016).*
6. *Treanda (bendamustine hydrochloride) injection powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on December 1, 2016).*
7. *Bendeka (bendamustine hydrochloride) injection solution, concentrate. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on December 1, 2016).*
8. *Rituximab and hyaluronidase human injection for subcutaneous use. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on June 30, 2017).*

Graphic 111141 Version 4.0

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP21) for non-Hodgkin lymphoma[1]

Cycle length: 21 days.

Drug	Dose and route	Administration	Given on days
Rituximab	375 mg/m^2 IV	Dilute in normal saline (NS) or 5 percent dextrose in water (D5W) to a final concentration of 1 to 4 mg/mL. Initial infusion: start at 50 mg/hour; escalate in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour, as tolerated[2]. For subsequent infusions, administer 20 percent of the total dose over the first 30 minutes and the remaining 80 percent over 60 minutes, as tolerated. The 90-minute infusion schedule should NOT be used in patients who have clinically significant cardiovascular disease or have a circulating lymphocyte count ≥5000/microL.*	Day 1
Cyclophosphamide	750 mg/m^2 IV	Dilute in 250 mL NS or D5W and administer over 30 minutes.	Day 1
Doxorubicin	50 mg/m^2 IV	Dilute in 50 mL NS or D5W and administer over three to five minutes.	Day 1
Vincristine	1.4 mg/m^2 IV (max dose 2 mg)	Dilute in 50 mL NS or D5W and administer over 15 to 20 minutes.	Day 1
Prednisone	100 mg orally	Administer 30 minutes prior to chemotherapy on day 1, then every 24 hours on days 2 to 5.	Days 1 to 5

Pretreatment considerations:

- **Emesis risk:** MODERATE. Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults".
- **Prophylaxis for infusion reactions:** Premedicate with acetaminophen and diphenhydramine, with or without an H2 blocker, 30 minutes prior to at least the first and second infusions of rituximab[2]. Refer to UpToDate topic on "Infusion reactions to therapeutic monoclonal antibodies used for cancer therapy".
- **Vesicant/irritant properties:** Doxorubicin and vincristine are vesicants; avoid extravasation. Refer to UpToDate topic on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants".
- **Infection prophylaxis:** The risk of febrile neutropenia with this regimen is 10 to 20 percent[1]; primary prophylaxis with hematopoietic growth factors should be considered on an individual basis, particularly for high-risk patients such as those with preexisting neutropenia, advanced disease, poor performance status, or patients age 65 years or older. Refer to UpToDate topic on the "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation".
- **Dose adjustment for baseline liver or renal dysfunction:** Adjustment of initial cyclophosphamide,

doxorubicin, and vincristine doses may be needed for preexisting liver dysfunction[3-5]. In addition, dose adjustment of cyclophosphamide may be required for renal dysfunction. Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease" and "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency".
• **Hepatitis screening:** Patients should be screened for hepatitis B and C prior to starting rituximab, and if positive, considered for antiviral prophylaxis. Refer to UpToDate topic on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease".
• **Cardiac screening:** LVEF should be evaluated prior to initiation of therapy. Dose alterations should be considered for LVEF <50 percent, and doxorubicin therapy is contraindicated in patients with LVEF <30 percent at initiation. Infusion times and schedule may be adjusted to decrease the risk of cardiotoxicity in individuals at high risk for its development. Refer to UpToDate topic on "Cardiotoxicity of anthracycline-like chemotherapy agents".
• **Neurotoxicity:** Vincristine may cause constipation, and in severe cases, paralytic ileus. A routine prophylactic regimen against constipation is recommended in all patients receiving vincristine. Refer to UpToDate topic on "Overview of neurologic complications of non-platinum cancer chemotherapy".
Monitoring parameters:
• CBC with differential and platelet count weekly during treatment.
• Assess basic metabolic panel (creatinine and electrolytes) and liver function prior to each subsequent treatment cycle.
• LVEF should be evaluated periodically based on LVEF at initiation of therapy and cumulative dose of doxorubicin. Refer to UpToDate topic on "Cardiotoxicity of anthracycline-like chemotherapy agents".
• Carriers of hepatitis B or C should be monitored for clinical and laboratory signs of active infection during and following completion of therapy. Rituximab should be discontinued if reactivation occurs. Refer to UpToDate topic on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease".
Suggested dose modifications for toxicity:
• **Myelotoxicity:** Treatment should be delayed until ANC is greater than 1500/microL and platelet count is greater than 100,000/microL. If a patient develops grade 4 (ANC <500) neutropenia or febrile neutropenia with any cycle, G-CSF support is added to the regimen for subsequent cycles. If grade 4 neutropenia or febrile neutropenia occurs despite G-CSF support, or if the patient develops grade 3 (25,000 to 50,000 platelets) or 4 (<25,000 platelets) thrombocytopenia with any cycle, the doses of cyclophosphamide and doxorubicin should be decreased by 50 percent for subsequent cycles.
• **Neuropathy:** Dose adjustment of vincristine may be necessary if the severity of neuropathy persists or worsens. No specific guidelines are available for dose adjustments.
If there is a change in body weight of at least 10 percent, dose should be recalculated for all drugs.

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy. The clinician is expected to use his or her independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; LVEF: left ventricular ejection fraction; CBC: complete blood count; ANC: absolute neutrophil count; G-CSF: granulocyte colony-stimulating factor.
* A subcutaneous formulation (rituximab-hyaluronidase) that uses a fixed dose and a shorter administration time is an acceptable alternative for patients who have tolerated at least one full dose of intravenous rituximab[6]. Dosing varies by histology and clinicians should refer to the US Prescribing Information for details.

References:

1. *Coiffier B, et al. N Engl J Med 2002; 346:235.*
2. *Rituximab injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on October 23, 2012).*
3. *Cyclophosphamide injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on October 23, 2012).*
4. *Doxorubicin hydrochloride injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on October 23, 2012).*
5. *Vincristine sulfate injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on October 23, 2012).*
6. *Rituximab and hyaluronidase human injection for subcutaneous use. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on June 30, 2017).*

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Contributor Disclosures

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