

# BCCA Protocol Summary for Treatment of Chronic Lymphocytic Leukemia or Prolymphocytic Leukemia with Fludarabine and Rituximab

**Protocol Code** LYFLUDR

**Tumour Group** Lymphoma

**Contact Physician** Dr. Richard Klasa

## ELIGIBILITY:

- Chronic lymphocytic leukaemia or prolymphocytic leukemia, at time of initial need for systemic treatment
- A "Class II Drug Registration Form" must be submitted for Rituximab at the time of initiation of treatment. For other indications, or for more than 8 cycles, an Undesignated Indications Request" form must be approved.

## TESTS:

- Baseline (required before first treatment): CBC & diff, platelets, serum creatinine
- Baseline (required, but results do not have to be available to proceed with first treatment): HBsAg, HBcoreAb
- Before each treatment: CBC & diff, platelets, serum creatinine

## PREMEDICATIONS:

- No premedication is required for Fludarabine.
- For Rituximab Portion:  
Diphenhydramine 50 mg PO prior to Rituximab and then q 4 h during the IV infusion, if the infusion exceeds 4 h  
Acetaminophen 650 mg PO prior to Rituximab and then q 4 h during the IV infusion, if the infusion exceeds 4 h

## TREATMENT:

Drug	Dose	BCCA Administration Guideline
Fludarabine*	40 mg/m <sup>2</sup> /day x 5 consecutive days (Day 1-5) (round dose to nearest 10 mg)	PO Do not chew, break or crush the tablets.
Rituximab**	375 mg/m <sup>2</sup> on day 1 NOTE: Rituximab and PO Fludarabine to start on the same day.	IV in 250 mL NS over 90 minutes-8 hours*** (doses between 500-1000 mg can be prepared in either 250 mL or 500 mL NS)

\*If PO Fludarabine is not practical, substitute IV Fludarabine according to the following schedule:

Drug	Dose	BCCA Administration Guideline
Fludarabine	25 mg/m <sup>2</sup> /day x 5 consecutive working weekdays (day 1-5) (may skip Sat/Sun/holidays) NOTE: Rituximab to be given within 72 hours of IV Fludarabine.	IV in 50-100 mL NS over 20 to 30 minutes

Repeat every 28 days until maximum clinical benefit achieved, usually 4-6 cycles, to a maximum of 8 cycles. For further cycles, undesignated approval is required.

\*\* If the total WBC > 30 x 10<sup>9</sup>/L Rituximab should be omitted from the first cycle of treatment to avoid risk of massive cytokine release syndrome. Rituximab can be incorporated in subsequent cycles of treatment regardless of the level of the WBC count.

\*\*\*Start the Rituximab initial infusion at 50 mg/h and, after 60 minutes, increase by 50 mg/h every 30 minutes until a rate of 400 mg/h is reached. *For all subsequent treatments*, infuse 50 mL of 250 mL bag (or 100 mL of 500 mL bag) of the dose over 30 minutes then infuse the remaining 200 mL of 250 mL bag (or 400 mL of 500 mL bag) (4/5) over 60 minutes (total infusion time = 90 minutes). Development of an allergic reaction may require a slower infusion rate. See hypersensitivity below.

## DOSE MODIFICATIONS:

### 1. Hematologic:

<b>ANC (x 10<sup>9</sup>/L)*</b>		<b>Platelets (x 10<sup>9</sup>/L)*</b>	<b>Fludarabine and Rituximab</b>
< 1.2	OR	< 100	Delay until count recovery

\*No dose reduction if decreased counts are due to disease.

**2. Renal Dysfunction:** For any patient with a serum creatinine above normal and for all patients above the age of 60 years, a creatinine clearance should be measured or calculated using the following formula to determine the initial dose of Fludarabine.

Estimated creatinine clearance (in mL/minute) =

For men:  $[1.23 \times (140 - \text{age in y})(\text{weight in kg})] \div \text{serum creatinine in } \mu\text{mol/L}$

For women:  $[1.04 \times (140 - \text{age in y})(\text{weight in kg})] \div \text{serum creatinine in } \mu\text{mol/L}$

Creatinine Clearance (mL/min)	Dose	Fludarabine Actual Dose and Schedule (Note change in number of days)	
		PO	IV
> 70	100%	40 mg/m <sup>2</sup> /day x <b>5 days</b>	25 mg/m <sup>2</sup> /day x <b>5 days</b>
30 – 70	50%	32 mg/m <sup>2</sup> /day x <b>3 days</b>	20 mg/m <sup>2</sup> /day x <b>3 days</b>
< 30	DO NOT USE		

After the first cycle of Fludarabine it is not necessary to re-calculate the creatinine clearance or to re-adjust the Fludarabine dose unless the serum creatinine is above the normal range. If this occurs, use the above calculation and dose modification table.

If a reduced dose of Fludarabine was used for initial treatment and well tolerated it may be appropriate for the dose to be increased in subsequent cycles regardless of renal function. This decision must be individualized by the treating oncologist and cannot be reduced to a formula.

## PRECAUTIONS:

- Neutropenia:** fever or other evidence of infection must be assessed promptly and treated aggressively.
- Need for irradiated blood products:** potentially life-threatening transfusion-related graft-versus-host-disease has been described in patients actively receiving fludarabine. The Canadian Blood Service recommends that patients on fludarabine should receive irradiated blood products, effectively eliminating this risk.
- Hepatitis B.** The immunosuppression associated with fludarabine may increase the risk of re-activation of hepatitis B. Although the risk of this is probably small, fludarabine should be avoided in patients with known prior hepatitis B (HBsAg positive or anti-hepatitis B antibody positive) unless the clinical situation justifies this increased risk and this has been explained to the patient.
- Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with Lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with a hepatologist and consideration given to halting chemotherapy.
- Hypersensitivity:** Refer to BCCA Hypersensitivity Guidelines. Rituximab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, alarm, pruritus, sneezing, cough, fever or faintness. Patients are to be under constant visual observation during all

dose increases and for 30 minutes after infusion is completed. Vital signs are not required unless symptomatic. Because transient hypotension may occur during infusion, consider withholding antihypertensive medications 12 hours prior to Rituximab infusion. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. A reasonable guideline is as follows. After recovery of symptoms, restart Rituximab infusion at one infusion rate below the rate at which the reaction occurred and continue with escalation of infusion rates on the appropriate schedule above. If the infusion must be stopped a second time, restart after clearance of symptoms, at one infusion rate lower and continue at that rate without further escalation. Fatal cytokine release syndrome can occur (see below).

6. **Fatal Cytokine Release Syndrome** has been reported. It usually occurs within 1-2 hours of initiating the first Rituximab infusion. Initially, it is characterised by severe dyspnea (often with bronchospasm and hypoxia) in addition to fever, chills, rigors, urticaria and angioedema. Pulmonary interstitial infiltrates or edema visible on chest x-ray may accompany acute respiratory failure. There may be features of tumour lysis syndrome such as hyperuricemia, hypocalcemia, acute renal failure and elevated LDH. For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized. If the total WBC  $> 30 \times 10^9/L$  Rituximab should be omitted from the first cycle of treatment to avoid risk of massive cytokine release syndrome. Rituximab can be incorporated in subsequent cycles of treatment regardless of the level of the WBC count.
7. **Rare Severe Mucocutaneous Reactions:** (similar to Stevens-Johnson Syndrome) have been anecdotally reported. If such a reaction occurs, Rituximab should be discontinued.

**Call Dr. Richard Klasa or tumour group delegate @ (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

Date activated: 01 Nov 2004

Date revised: 01 Nov 2006 (clarified vital signs monitoring)

#### **References:**

1. Cheson B, et al. Fludarabine. J Clin Oncol 1991;9:175-88.
2. Johnson S, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukemia. Lancet 1996;347:1432-8.
3. Chin Yee, I et al. The role of fludarabine in intermediate- and high-risk chronic lymphocytic leukemia. Current Oncology 1999;6:90-102.
4. Boogaerts MA, et al. Activity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia. J Clin Oncol 2001; 22:4252-4258.
5. Byrd JC, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.