Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Contents

Dose-Adjusted EPOCH-R Guidelines

The first cycle of DA-EPOCH-R (dose level 1) was administered as previously described[1] (Figure S1)(mg/m^2/day): rituximab (rituxan; Genentech) 375 as 3-hour infusion day 1; doxorubicin (generic) 10, etoposide (generic) 50 and vincristine (generic) 0.4 (no cap) as a continuous infusion on days 1, 2, 3, 4 (96-hour total); cyclophosphamide (generic) 750 as a 2-hour infusion on day 5; and prednisone (generic) 60 twice daily (120 mg/m^2/day) on days 1, 2, 3, 4, 5. Patients received filgrastim (neupogen; Amgen) 300 μg on day 6 through absolute neutrophil count (ANC) > 5000 cells/μl (5.0 x 10^9 cells/l) past the nadir. Subsequent cycles were dose adjusted every cycle based on the neutrophil nadir, which was monitored with twice-weekly complete blood counts (Figure S2). If the ANC nadir was ≥ 500 cells/μl (0.5 x 10^9 cells/l), the doses were increased 20%; if the nadir ANC was < 500 cells/μl (0.5 x10^9 cells/l) the doses were not changed; or if the platelet nadir was < 25,000/μl (25.0 x 10^9cells/l) the doses were reduced 20% from those on the previous cycle (Figure S3). Dose adjustments above dose level 1 applied to etoposide, doxorubicin and cyclophosphamide, and adjustments below dose level 1 only applied to cyclophosphamide. Deviations from the adjustment paradigm were only made in the event of a critical illness on the previous cycle. Vincristine was reduced 25% or 50% for grade 2 or 3 motor neuropathy, respectively, and reduced 50% for grade 3 sensory neuropathy. All patients (with negative CSF cytology and flow cytometry) received prophylactic intrathecal methotrexate 12 mg on day 1 and 5 of cycles 3-6. Patients with positive CSF at diagnosis received intrathecal or intraventicular methotrexate starting on day 1 of cycle 1 as outlined in the manuscript.

The agents in DA-EPOCH-R are administered per manufacturer guidelines except for infusional vincristine, etoposide and doxorubicin[1,2]. The daily dose (i.e., 24 hour supply) of vincristine, doxorubicin, and etoposide will be admixed together in 0.9% Sodium Chloride Injection. The diluent volume will be based on the etoposide dose for a 24 hour treatment: If etoposide ≤150 mg per 24 hours, dilute drugs in 500 mL and if etoposide >150 mg per 24 hours, dilute drugs in 1000 mL 0.9% Sodium Chloride Injection. The chemotherapy will then be administered with a suitable infusion pump via a central venous access device. Temporary PICC lines or permanent lines may be used. The bag will be exchanged daily for each of the four days to complete the 96 hour infusion. Stability studies conducted by the Pharmaceutical Development Service, Pharmacy Department, NIH Clinical Center, have demonstrated that admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, USP at concentrations, respectively, of 1, 25, and 125 μg/mL; 1.4, 35, 3 and 175 μg/mL; 2, 50, and 250 μg/mL; and 2.8, 70, and 350 μg/mL are stable for at least 36 hours at room temperature when protected from light[3]. Also, admixtures containing vincristine, doxorubicin, etoposide concentrations of 1.6, 40, and 200 μg/mL are stable for at least 30 hours at 32°C. Extravasation of these diluted agents has not caused local tissue damage due to their low concentrations in the diluent. Pegfilgrastim is not a recommended replacement for daily filgrastim due to its unpredictable pharmacokinetics. There was no maximum number of dose escalations except as limited by the number of cycles.

All patients should receive the following prophylactic medications on all cycles:

• Bactrim (sulphametoxazole and trimethoprim) DS 1 tablet TIW (equivalent if allergic)
• Omeprazole 20 mg PO QD daily (or equivalent)
• Docusate and senna 2 tablets PO BID as necessary for constipation
• Lactulose 20 gms Q6 PO as necessary for constipation.
• Hepatis B surface Ag+ patients should receive anti-viral therapy daily until 8 weeks past chemotherapy completion.

Short Course EPOCH-RR Guidelines

The first cycle of SC-EPOCH-RR was administered as previously described[4] (Figure S4)(mg/m^2/day): rituximab (rituxan; Genentech) 375 as 3-hour infusion day 1 and day 5; doxorubicin (generic) 10, etoposide (generic) 50 and vincristine (generic) 0.4 (no cap) as a continuous infusion on days 1, 2, 3, 4 (96-hour total); cyclophosphamide (generic); 750 as 2-hour infusion on day 5; and prednisone (generic) 60 once daily (60mg/m^2/day) on days 1, 2, 3, 4, 5. Patients received filgrastim (neupogen; Amgen) 300 μg on day 6 through absolute neutrophil count (ANC) > 5000 cells/μl (5.0 x 10^9 cells/l) past the nadir. The neutrophil nadir was monitored with twice-weekly complete blood counts. If the ANC was less than 500/mm^3 for 2 to 4 days or platelets less than 25,000/mm^3 for 2 to 4 days, on the subsequent dose, reduce cyclophosphamide by 187 mg/m^2 (i.e. 25% of full dose). If the ANC was less than 500/mm^3 for 5 days or more or platelets were less than 25,000/mm for 5 days or more, reduce cyclophosphamide by 375 mg/m^2 (i.e. 50% of full dose). In the event that the cyclophosphamide dose had been reduced on the previous cycle, it may be increased on the next cycle if the following criteria are met: if ANC >500/mm^3 and platelets > 25,000/mm^3, then increase cyclophosphamide by 187 mg/m^2 each cycle, up to full dose (i.e. 750 mg/m^2). All patients (with negative CSF by cytology and flow cytometry) received prophylactic intrathecal methotrexate 12 mg on day 1 and 5 of cycles 3-5. Patients with positive CSF (by cytology or flow cytometry) at diagnosis received intrathecal or intraventicular methotrexate starting on day 1 of cycle 1 as outlined in the manuscript.

The agents in SC-EPOCH-RR are administered per manufacturer guidelines except for infusional vincristine, etoposide and doxorubicin[1,2]. The daily dose (i.e., 24 hour supply) of vincristine, doxorubicin, and etoposide will be admixed together in 0.9% Sodium Chloride Injection. The diluent volume will be based on the etoposide dose for a 24 hour treatment: If etoposide ≤150 mg per 24 hours, dilute drugs in 500 mL and if etoposide >150 mg per 24 hours, dilute drugs in 1000 mL 0.9% Sodium Chloride Injection. The chemotherapy will then be administered with a suitable infusion pump via a central venous access device. Temporary PICC lines or permanent lines may be used. The bag will be exchanged daily for each of the four days to complete the 96 hour infusion. Stability studies conducted by the Pharmaceutical Development Service, Pharmacy Department, NIH Clinical Center, have demonstrated that admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, USP at

concentrations, respectively, of 1, 25, and 125 μg/mL; 1.4, 35, 3 and 175 μg/mL; 2, 50, and 250 μg/mL; and 2.8, 70, and 350 μg/mL are stable for at least 36 hours at room temperature when protected from light[3]. Also, admixtures containing vincristine, doxorubicin, etoposide concentrations of 1.6, 40, and 200 μg/mL are stable for at least 30 hours at 32°C. Extravasation of these diluted agents has not caused local tissue damage due to their low concentrations in the diluent. Pegfilgrastim is not a recommended replacement for daily filgrastim due to its unpredictable pharmacokinetics.

All patients should receive the following prophylactic medications on all cycles:

- Bactrim (sulphametoxazole and trimethoprim) DS 1 tablet TIW (equivalent if allergic)
- Omeprazole 20 mg PO QD daily (or equivalent)
- Docusate and senna 2 tablets PO BID as necessary for constipation
- Lactulose 20 gms Q6 PO as necessary for constipation.
- Hepatis B surface Ag+ patients should receive anti-viral therapy daily until 8 weeks past chemotherapy completion.

References

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4. Dunleavy K, Little RF, Pittaluga S, et al. The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. Blood 2010;115:3017-24.

	Dose mg/m^2/day	Treatment Days
Infusional Agents		
Etoposide	50	
Vincristine	0.4 (No cap)	Days 1 to 4
Doxorubicin	10	
Bolus Agents		
Cyclophosphamide	750	Day 5
Prednisone	60 bid	Days 1 to 5
Biologic Agents		
Rituximab	375	Day 1
G-CSF	5 (μg/kg)	Days 6 ➔ANC recovery

Figure S1. Dose-Adjusted EPOCH-R Regimen. Doses for the first cycle (dose level 1) are shown. Rituximab is infused as per manufacturers guidelines. Immediately after completion of rituximab, the infusional agents should be administered using a portable infusion pump through a central venous device. After completion of the infusions (on day 5), cyclophosphamide should be administered on the same day as per manufacturers guidelines. All treatment may be administered outpatient. Repeat cycles every three weeks. Patients with an ANC < 1000/μl on day one of the next cycle should receive one dose of filgrastim and treated the following day if the ANC > 1000/μl. Patients with platelet counts < 75,000/μl should be observed for up to one week and treated when the platelets are > 75,000/μl. Patients with bone marrow involvement by lymphoma should be treated on time irrespective of the ANC and platelet counts if safe. Patients should receive 6 cycles of treatment. If the tumor masses shrink > 20% between the end of cycle 4 and 6, administer two additional cycles.

- Dose adjustments above level 1 apply to etoposide, doxorubicin and cyclophosphamide
- Dose adjustments below level 1 apply to cyclophosphamide only.
- Measurement of ANC nadir based on twice-weekly complete blood counts.
- These drug doses are based on previous cycle ANC nadir as follows:

  - If Nadir ANC ≥ 500/μl : ↑ 1 dose level above last cycle
  - If Nadir ANC < 500/μl: Same dose level as last cycle

Or

  - If nadir platelet < 25,000/μl: ↓ 1 dose level below last cycle.

Figure S2. Pharmacodynamic Dose-Adjustment Paradigm for DA-EPOCH-R. Dose adjustment above level 1 apply to etoposide, doxorubicin and cyclophosphamide, and adjustments below level 1 only apply to cyclophosphamide (Figure S3). The pharmacodynamic dose adjustment is based on the previous cycle absolute neutrophil nadir. This is monitored by obtaining twice weekly complete blood counts. As shown, if the ANC nadir is ≥ 500/μl, the doses are increased one dose level, whereas if the ANC < 500/μl, the doses are unchanged. Only reduce by one dose level if the nadir platelet < 25,000/μl. On rare occasions, patients may develop prolonged neutropenia < 500/μl for over seven days or life threatening infections associated with organ failure or prolonged morbidity. In these cases, physicians should use their clinical judgment regarding reduction by one dose level. Doses should not be reduced for non-life threatening infections. Doses should not be reduced for neutropenia or thrombocytopenia in patients with bone marrow compromise due to marrow involvement by lymphoma unless life-threatening complications occur.

Drugs	Drug Doses per Dose Levels							
	-2	-1	1	2	3	4	5	6
Doxorubicin (mg/m^2/day)	10	10	10	12	14.4	17.3	20.7	24.8
Etoposide (mg/m^2/day)	50	50	50	60	72	86.4	103.7	124.4
Cyclophosphamide (mg/m^2/day)	480	600	750	900	1080	1296	1555	1866

Figure S3. Drug Dose Levels for DA-EPOCH-R. The drug dose escalation for doxorubicin, etoposide and cyclophosphamide are shown for each dose level. The doses are escalated 20% above the last cycle. The dose 20% dose escalation is based on the previous doses (i.e. compounded dose escalation). Only cyclophosphamide is adjusted when reducing below level 1.

	Dose mg/m^2/day	Treatment Days
Infusional Agents		
Etoposide	50	
Vincristine	0.4 (No cap)	Days 1 to 4
Doxorubicin	10	
Bolus Agents		
Cyclophosphamide	750	Day 5
Prednisone	60 od	Days 1 to 5
Biologic Agents		
Rituximab	375	Days 1 and 5
G-CSF	5 (μg/kg)	Days 6 ➔ANC recovery

Figure S4. SC-EPOCH-RR regimen. Doses for the first cycle are shown. Rituximab is infused as per manufacturers guidelines. Immediately after completion of rituximab, the infusional agents should be administered using a portable infusion pump through a central venous device. After completion of the infusions (on day 5), cyclophosphamide should be administered on the same day as per manufacturers guidelines. All treatment may be administered outpatient. Repeat cycles every three weeks. Patients have a CBC twice weekly and at least 3 days apart. Cyclophosphamide is reduced 25% for a nadir absolute neutrophil count (ANC) less than 0.5 x 10^9/L (500/mm^3) or platelet count less than 25.0 x 10^9/L (25000/mm^3) lasting 2 to 4 days and 50% if the nadir ANC was less than 0.5 x 10^9/L (500/mm^3) or platelet count less than 25.0 x 10^9/L (25000/mm^3) lasting for 5 or more days, based on twice weekly blood counts. Patients have at least 3 cycles with 1 cycle beyond CR as determined by combined CT and FDG-PET criteria[4].