Peripheral T-cell Lymphomas (PTCL)[1]

Note: Consider Clinical Trials as treatment options for eligible patients.

PATHOLOGIC DIAGNOSIS

ESSENTIAL:

- Hematopathology review of all slides with at least one paraffin block or 15 unstained slides representative of the tumor. Re-biopsy if consult material is nondiagnostic.
- Adequate morphology and immunophenotyping to establish diagnosis
  - Paraffin Panel: CD20, CD4, CD8, CD3 and/or other pan-T-cell markers (CD2, CD5, CD7, CD43) and Ki-67 **or**
  - Flow cytometry immunophenotypic studies: CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD16, CD25, CD26, CD14, CD45, CD52, CD56, CD57, CD94, TCRbeta and TCRgamma

OF USE IN CERTAIN CIRCUMSTANCES TO DETERMINE SUBGROUP:

- EBER *in situ* hybridization, CD56, CD57, cytotoxic proteins (TIA-1, granzyme B or perforin), (extranodal T/NK cell lymphomas, T-cell large granular lymphocytic leukemia)
- BetaF1, TCR gamma (gamma delta T-cell lymphomas and subcutaneous panniculitis-like T-cell lymphoma)
- CD10, BCL-6, PD1, CXCL13 (angioimmunoblastic T-cell lymphoma)
- CD30, CD15, ALK1, EMA (anaplastic T-cell lymphoma)
- CD103 (enteropathy-associated T-cell lymphoma)
- CD1a, CD34, TdT (T lymphoblastic lymphoma)
- TCL-1, FOXP3, CD25 (T-cell prolymphocytic leukemia and adult T-cell leukemia/lymphoma)
- Molecular studies to detect clonality of the *TCR* genes

STRONGLY RECOMMENDED:

- FNA or core biopsy for tissue array/banking by protocol

INITIAL EVALUATION

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Consider Dermatology consult for comprehensive skin assessment if cutaneous involvement is present or suspected
- Performance status
- B symptoms (Unexplained fever >38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss >10 percent of body weight ≤ 6 months of diagnosis)
- CBC with differential, BUN, creatinine, albumin, AST, bilirubin, serum calcium, alkaline phosphatase, uric acid, LDH
- Chest x-ray (AP & LAT)
- Lymphoma screening
- Unilateral or bilateral bone marrow biopsy with aspirate
- Calculation of International Prognostic Index[2]
- Muga scan or echocardiogram
- PET/CT
- Beta-2-microglobulin
- Screening for HIV 1 and 2, hepatitis B and C (HBcAb, HBaAg, HCVAb)
- HTLV 1/2 serology
- HLH work-up including EBV by PCR, ferritin, fibrinogen, triglycerides, and cytokine 12 profile including IL-2sR

OF USE IN SELECTED CASES:

- CT head or MRI
- Pregnancy test
- Stool guaiac, if anemic
- Lumbar puncture, if paranasal sinus, testicular, parameningeal, orbit, CNS, paravertebral, bone marrow or HIV lymphoma
- Serum immunoelectrophoresis (SIEP)
- Discuss fertility options and sperm banking for patients of child bearing potential

See Page 2: Induction therapy

[1] This algorithm contains the following subtypes: PTCL - not otherwise specified, angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma, ALK+ and ALK- and enteropatic associated T-cell lymphoma (EATL). The following subtypes are not included in this algorithm: primary cutaneous anaplastic large-cell lymphoma (ALCL) and all other cutaneous T-cell lymphoma.

[2] See Appendix A for International Prognostic Index

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Peripheral T-cell Lymphomas (PTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.

INDUCTION THERAPY

Stages I - IV →

- CD30-positive
  - CHP-Bv **or**
  - Clinical trial
- CD30-negative
  - EPOCH **or**
  - CHOEP **or**
  - CHOP **or**
  - Clinical trial
- NK/T cell lymphoma
  - Stage I/II: DeVIC with radiation therapy
  - Stage III/IV: DeVIC **or** SMILE
- CTL
  - Skin directed therapies: clobetasol, bexarotene, infectious prophylaxis
- Large cell transformation CTLC
  - Brentuximab (if CD30-positive) **or**
  - Denileukin diftitox **or**
  - Romidepsin **or**
  - Pralatrexate
- Hepatosplenic T-cell lymphoma
  - HCVAD **or**
  - EPOCH
- Anaplastic lymphoma kinase (ALK) and anaplastic large-cell lymphoma limited disease
  - CHOEP or CHOP plus radiation therapy

→ After 2-4 cycles, repeat all positive studies[1]

INTERIM RESPONSE

→ Complete or partial response[2, 3] →
- Complete current treatment
- See Page 3: Response, treatment and follow-up

→ No response or progressive disease → See Page 4: Refractory or relaspe therapy

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone
CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone
CHP-Bv = cyclophosphamide, doxorubicin, prednisone, brentuximab vedotin
EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
HCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
DeVIC = dexamethasone, etoposide, ifosfamide, carboplatin
SMILE = steroid, methotrexate, ifosfamide, L-asparaginase, etoposide

[1] PET scans should be used to assess residual abnormalities on CT scan, especially if done pretreatment
[2] Partial Response includes a biological measure of disease: positive PET scan, or ideally positive biopsy
[3] See Appendix B for Response Criteria for Lymphoma

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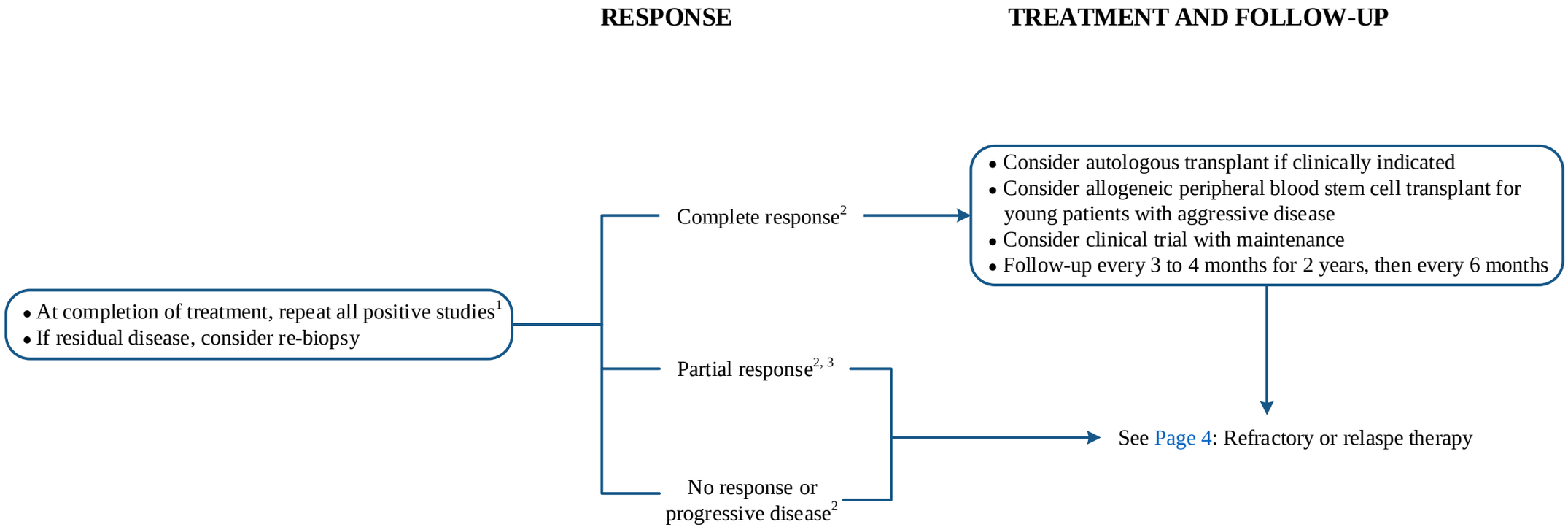
Peripheral T-cell Lymphomas (PTCL)

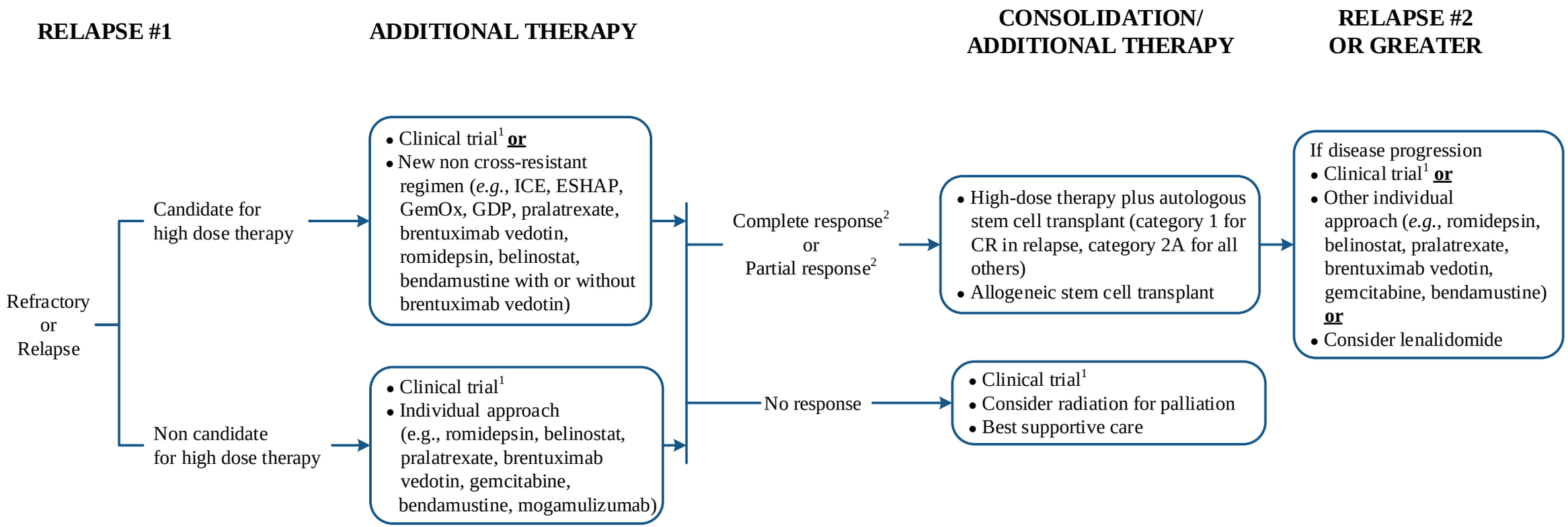
Note: Consider Clinical Trials as treatment options for eligible patients.



[1] PET scans should be used to assess residual abnormalities on CT scan, especially if done pretreatment
[2] See Response Criteria for Lymphoma (Appendix B)
[3] Partial Response includes a biological measure of disease: positive PET scan, or ideally positive biopsy

Peripheral T-cell Lymphomas (PTCL)

Note: Consider Clinical Trials as treatment options for eligible patients.



ICE = ifosfamide, carboplatin, etoposide
ESHAP = etoposide, methylprednisolone, high dose cytarabine, cisplatin
GemOx = gemcitabine and oxaliplatin
GDP = gemcitabine, dexamethasone, and cisplatin

[1] Clinical trials or individual regimens: patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval

[2] See Response Criteria for Lymphoma (Appendix B)

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APPENDIX A: International Prognostic Index for PTCL-U

Risk Factors	Prognostic Risk	Number of Risk Factors
• Age greater than 60 years • Serum LDH greater than 1 times normal • Performance status 2 – 4 • Bone marrow involvement	• Group 1 • Group 2 • Group 3 • Group 4	0 1 2 3 or 4

APPENDIX B: Response Criteria for Malignant Lymphoma

Response Category	Nodal Masses	Spleen, Liver	Bone Marrow
CR (Complete response: disappearance of all evidence of disease)	• FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative • Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, imunohistochemistry should be negative
PR (Partial response)	• Decrease of ≥ 50% in SPD of up to 6 largest dominant masses; no increase in size of other nodes ◦ FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site ◦ Variably FDG-avid or PET negative; regression on CT	Decrease of ≥ 50% in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD (Stable disease: failure to attain CR/PR or PD)	• FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET • Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapse or progressive disease (PD) (Any new lesion or increase by ≥ 50% of previously involved sites from nadir)	• Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis • New foci of FDG-avidity if FDG-avid lymphoma or PET positive prior to therapy	Increase of > 50% from nadir in the SPD of any previous lesions	New or recurrent involvement

FDG [^{18}F] = fluorodeoxy glucose
SDP = sum of the product of the diameters

Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067.

SUGGESTED READINGS

Advani, R., Horwitz, S., Zelenetz, A., & Horning, S. J. (2007). Angioimmunoblastic T cell lymphoma: Treatment experience with cyclosporine. *Leukemia & Lymphoma*, *48*(3), 521-525. doi:10.1080/10428190601137658

Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., … Eastern Cooperative Oncology Group. (2014). Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: The lugano classification. *Journal of Clinical Oncology*, *32*(27), 3059-3067. doi:10.1200/JCO.2013.54.8800

Chihara, D., Pro, B., Loghavi, S., Miranda, R. N., Medeiros, L. J., Fanale, M. A., … Oki, Y. (2015). Phase II study of HCVIDD/MA in patients with newly diagnosed peripheral T-cell lymphoma. *British Journal of Haematology*, *171*(4), 509-516. doi:10.1111/bjh.13628

Coiffier, B., Pro, B., Prince, H., Foss, F., Sokol, L., Greenwood, M., … Horwitz, S. (2010). Final results from a pivotal, multicenter, international, open label, phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy. *Blood*, *116*(21) 56-57.

Crump, M., Baetz, T., Couban, S., Belch, A., Marcellus, D., Howson-Jan, K., … Meyer, R. (2004). Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-hodgkin lymphoma: A phase II study by the national cancer institute of canada clinical trials group (NCIC-CTG). *Cancer*, *101*(8), 1835-1842. doi:10.1002/cncr.20587.

d'Amore, F., Relander, T., Lauritzsen, G. F., Jantunen, E., Hagberg, H., Anderson, H., … Umeå universitet. (2012). Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *Journal of Clinical Oncology*, *30*(25), 3093-3099. doi:10.1200/JCO.2011.40.2719

Dang, N. H., Pro, B., Hagemeister, F. B., Samaniego, F., Jones, D., Samuels, B. I., … Fayad, L. (2007). Phase II trial of denileukin diftitox for relapsed/refractory T-cell non-hodgkin lymphoma. *British Journal of Haematology*, *136*(3), 439-447. doi:10.1111/j.1365-2141.2006.06457.x

Horwitz, S., O'Connor, O. A., Pro, B., Illidge, T., Fanale, M., Advani, R., … Rossi, G., (2019). Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomized, phase 3 trial. *The Lancet*, *393*(10168), 229-240. doi: 10.1016/S0140-6736(18)32984-2.

Horwitz, S., O'Connor, O. A., Pro, B., Illidge, T., … ECHELON-2 Study Group. (2019). Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): A global, double-blind, randomized, phase 3 trial. *The Lancet*, *393*(10168), 229-240. doi:10.1016/S0140-6736(18)32984-2

Kim, Y. H., Bagot, M., Pinter-Brown, L., Rook, A. H., Porcu, P., Horwitz, S. M., … Sokol, L. (2018). Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): An international, open-label, randomised, controlled phase 3 trial. *The Lancet Oncology*, *19*(9), 1192-1204. doi:10.1016/S1470-2045(18)30379-6

López, A., Gutiérrez, A., Palacios, A., Blancas, I., Navarrete, M., Morey, M., … Rodríguez, J. (2008). GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: A phase II study. *European Journal of Haematology*, *80*(2), 127-132. doi:10.1111/j.1600-0609.2007.00996.x

National Comprehensive Cancer Network. *T-Cell Lymphomas* (NCCN Guidelines. Version 2.2019). Retrieved from: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf

O'Connor, O., Pro, B., Pinter-Brown, L., Popplewell, L., Bartlett, N., Lechowicz, M., … Horwitz, S. (2009). PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). *Journal of Clinical Oncology*, *27*(15). doi:10.1200/jco.2009.27.15_suppl.8561

Continued on next page

SUGGESTED READINGS - continued

Savage, K. J., Chhanabhai, M., Gascoyne, R. D., & Connors, J. M. (2004). Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. *Annals of Oncology*, *15*(10), 1467-1475. doi:10.1093/annonc/mdh392

Schmitz, N., Trümper, L., Ziepert, M., Nickelsen, M., Ho, A. D., Metzner, B., … Pfreundschuh, M. (2010). Treatment and prognosis of mature T-cell and NK-cell lymphoma: An analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood*, *116*(18), 3418-3425. doi:10.1182/blood-2010-02-270785

Talpur, R., Apisarnthanarax, N., Ward, S., & Duvic, M. (2002). Treatment of refractory peripheral T-cell lymphoma with denileukin diftitox (ONTAK®). *Leukemia & Lymphoma*, *43*(1), 121-126. doi:10.1080/10428190210183

Velasquez, W. S., McLaughlin, P., Tucker, S., Hagemeister, F. B., Swan, F., Rodriguez, M. A., … Cabanillas, F. (1994). ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: A 4-year follow-up study. *Journal of Clinical Oncology*, *12*(6), 1169-1176. doi:10.1200/JCO.1994.12.6.1169

Yamaguchi, M., Kwong, Y., Kim, W. S., Maeda, Y., Hashimoto, C., Suh, C., … Suzuki, R. (2011). Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: The NK-cell tumor study group study. *Journal of Clinical Oncology*, *29*(33), 4410-4416. doi:10.1200/JCO.2011.35.6287

Yamaguchi, M., Tobinai, K., Oguchi, M., Ishizuka, N., Kobayashi, Y., Isobe, Y., … Oshimi, K. (2009). Phase I/II study of concurrent chemoradiotherapy for localized nasal natural Killer/T-cell lymphoma: Japan clinical oncology group study JCOG0211. *Journal of Clinical Oncology*, *27*(33), 5594-5600. doi:10.1200/JCO.2009.23.8295

Zelenetz, A. D., Hamlin, P., Kewalramani, T., Yahalom, J., Nimer, S., & Moskowitz, C. H. (2003). Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-hodgkin's lymphoma. *Annals of Oncology*, *14*(1), i5-i10. doi:10.1093/annonc/mdg702

Zinzani, P. L., Baliva, G., Magagnoli, M., Bendandi, M., Modugno, G., Gherlinzoni, F., … Tura, S. (2000). Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: Experience in 44 patients. *Journal of Clinical Oncology*, *18*(13), 2603-2606. doi:10.1200/JCO.2000.18.13.2603

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