

COMPENDIA TRANSPARENCY TRACKING FORM

DRUG: Cisplatin

INDICATION: Non-Hodgkin lymphoma, Relapsed or refractory, as part of the DHAP or ESHAP chemotherapy regimen

| COMPENDIA TRANSPARENCY REQUIREMENTS | |
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| 1 | Provide criteria used to evaluate/prioritize the request (therapy) |
| 2 | Disclose evidentiary materials reviewed or considered |
| 3 | Provide names of individuals who have substantively participated in the review or disposition of the request and disclose their potential direct or indirect conflicts of interest |
| 4 | Provide meeting minutes and records of votes for disposition of the request (therapy) |

EVALUATION/PRIORITIZATION CRITERIA: A, C

*to meet requirement 1

| CODE | EVALUATION/PRIORITIZATION CRITERIA |
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| A | Treatment represents an established standard of care or significant advance over current therapies |
| C | Cancer or cancer-related condition |
| E | Quantity and robustness of evidence for use support consideration |
| L | Limited alternative therapies exist for condition of interest |
| P | Pediatric condition |
| R | Rare disease |
| S | Serious , life-threatening condition |

Note: a combination of codes may be applied to fully reflect points of consideration [eg, therapy may represent an advance in the treatment of a life-threatening condition with limited treatment alternatives (ASL)]

EVIDENCE CONSIDERED:

*to meet requirements 2 and 4

| CITATION | STUDY-SPECIFIC COMMENTS | LITERATURE CODE |
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| <p>Velasquez WS, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing ymphoma: a 4-year follow-up study. J Clin Oncol.1994 Jun;12(6):1169-76.</p> | <p><u>Study methodology comments:</u> This was an open-label, randomized, comparative trial that terminated early. An interim analysis showing significantly greater efficacy with ESHAP (32 patients) compared with ESHA (31 patients) resulted in discontinuing the ESHA arm. Subsequent analyses included 122 patients who received ESHAP.</p> <p>A major strength of the study was that the effect of many potential confounding factors on outcomes was controlled through statistical analyses. Other strengths included 1) had inclusion criteria; 2) defined response; 3) defined tumor burden; 4) had a control group; and 5) randomized patients to study groups. Weaknesses included 1) no exclusion criteria; 2) open-label design without the use of independent reviewers; 3) absence of a power analysis; 4) did not present 95% confidence intervals; 5) did not discuss the method of randomization; and 6) possible selection bias since the patients were not recruited in a random or consecutive manner.</p> | <p>S</p> |
| <p>Rodriguez-Monge EJ, et al. Long-term follow-up of platinum-based lymphoma salvage regimens. The M.D. Anderson Cancer Center experience. Hematol Oncol Clin North Am. 1997 Oct;11(5):937-47.</p> | <p><u>Study methodology comments:</u> This paper provided long-term results of the studies reported in Velasquez WS et al. 1988 and Velasquez WS et al. 1994.</p> | <p>S</p> |

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| <p>Soussain C, et al. Intensive chemotherapy with hematopoietic cell transplantation after ESHAP therapy for relapsed or refractory non-Hodgkin's lymphoma. Results of a single-centre study of 65 patients. Leuk Lymphoma. 1999 May;33(5-6):543-50.</p> | <p><u>Study methodology comments:</u> This was an open-label, time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of potential confounding factors on outcomes. Additional weaknesses included 1) open-label design without the use of independent reviewers; 2) absence of a power analysis; 3) did not present 95% confidence intervals; and 4) possible selection bias since the patients were not recruited in a random or consecutive manner. An additional caveat of the study was that the authors examined the effect of potential confounding factors on outcomes but did not present the data or specify which statistical tests were conducted. Interpret these results with caution. Strengths of the study included 1) defined response; 2) had inclusion and exclusion criteria; 3) a complete response was confirmed at 4 weeks; and 4) the use of a within subject design to control for confounding effects of patient characteristics.</p> | <p>S</p> |
| <p>Olivieri A, et al. Salvage therapy with an outpatient DHAP schedule followed by PBSC transplantation in 79 lymphoma patients: an intention to mobilize and transplant analysis. Eur J Haematol. 2004 Jan;72(1):10-7.</p> | <p><u>Study methodology comments:</u> This was an open-label, time-series trial. A major weakness of the study was the absence of a control group which would have controlled for the effect of potential confounding factors on outcomes. Additional weaknesses included 1) no exclusion criteria; 2) open-label design without the use of independent reviewers; and 3) absence of a power analysis. A major strength of the study was that the effect of potential confounding factors on outcomes was statistically examined and controlled. Other strengths included 1) reduced selection bias by enrolling consecutively presenting patients; 2) defined response; 3) analyzed the intent-to-treat population; 4) had inclusion criteria; 5) presented 95% confidence intervals; and 6) the use of a within subject design to control for confounding effects of patient characteristics.</p> | <p>S</p> |

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| <p>Philip T, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995 Dec 7;333(23):1540-5.</p> | <p><u>Study methodology comments:</u> This was an open-label, randomized, comparative trial that compared convention therapy with four additional cycles of DHAP with autologous bone marrow transplantation. The results should be interpreted with caution. Strengths of the study included 1) randomized to treatment; 2) had both inclusion and exclusion criteria; 3) examined the effect of some potential confounding factors; 4) defined event; and 5) made statistical adjustments to preserve the type I error rate in the interim analyses.</p> <p>There were three major caveats of the study. First, the study was terminated early due to a low accrual rate. Second, the authors did not discuss the hypothesized effect size or power requirements. Third, 18 patients in the conventional treatment group later received HDCT and BMT. It is unclear how they were handled in the overall survival analyses. Additional weaknesses included 1) partial explanation of randomization procedure; 2) absence of a power analysis; 3) open-label design without the use of independent reviewers; 4) unclear on the intent of the second interim analysis; 5) did not define complete or partial response; 6) did not present 95% confidence intervals for OS and PFS to convey precision of results; 7) unclear if controlled for type I error rate in final analyses; and 8) possible selection bias since patients were not recruited in a random or consecutive manner.</p> <p>It should be noted that additional information on the study methodology and statistical analyses was obtained from a printed correction. The correction discussed 1) the statistical hypothesis and power analysis; 2) results of a cox proportional hazards analysis that included all the main prognostic factors; 3) age and Karnofsky scores of participants; 4) intent of second interim analysis; and 5) type I error rate. In addition, the authors presented the 95% confidence intervals for relative risk which indicated a lack of precision in the results.</p> | <p>S</p> |
| <p>Velasquez WS, et al. Effective salvage therapy for lymphoma with cisplatin in combination with highdose Ara-C and dexamethasone (DHAP). Blood. 1988 Jan;71(1):117-22.</p> | <p><u>Study methodology comments:</u> This was an open-label, time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of potential confounding factors on outcomes. Additional weaknesses included 1) no inclusion or exclusion criteria; 2) open-label design without the use of independent reviewers; 3) absence of a power analysis; and 4) did not present 95% confidence intervals. Strengths of the study included 1) reduced selection bias by enrolling consecutively presenting patients; 2) defined response; 3) responses had to be sustained for 4 weeks; 4) analyzed the intent-to-treat population; 5) examined the effect of potential confounding factors on outcomes; and 6) the use of a within-subject design to control for confounding effects of patient characteristics.</p> | <p>S</p> |

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| <p>Josting A, et al. High-dose sequential chemotherapy followed by autologous stem cell transplantation in relapsed and refractory aggressive non-Hodgkin's lymphoma: results of a multicenter phase II study. <i>Annals of Oncology</i> 2005 Aug;16(8):1359-65. Epub 2005 Jun 6.</p> | <p><u>Study methodology comments:</u> This was an open-label time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for many potential confounds. Additional weaknesses included 1) absence of a power analysis; 2) open-label study without the use of independent reviewers; 3) did not present 95% confidence intervals; 4) no exclusion criteria; and 5) possible selection bias since the patients were not recruited randomly or in a consecutive manner. The between-group comparisons between the progressive and relapse patients should be interpreted with caution. The authors did not discuss which statistical tests were conducted for these comparisons.</p> <p>Strengths included 1) confirmed diagnosis; 2) had inclusion criteria; 3) defined response; 4) responses were confirmed at 1 (CR) and 3 (PR) months; 5) defined primary and secondary endpoints; 6) examined the effect of some potential confounding factors on outcomes; and 7) the use of a within-subject design to control for confounding effects of patient characteristics.</p> | <p>S</p> |
| <p>Philip T, et al. Parma international protocol: pilot study of DHAP followed by involved-field radiotherapy and BEAC with autologous bone marrow transplantation. <i>Blood</i>. 1991 Apr 1;77(7):1587-92.</p> | <p><u>Study methodology comments:</u> This was an open-label, time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of potential confounding factors. Additional weaknesses included 1) no inclusion or exclusion criteria; 2) open-label design without the use of independent reviewers; 3) absence of a power analysis; 4) did not present 95% confidence intervals; 5) did not examine the effect of potential confounding factors on outcomes; and 6) possible selection bias since the patients were not recruited randomly or in a consecutive manner. Strengths of the study included 1) defined response; 2) histologic slides were assessed centrally by a single pathologist; and 3) the use of a within-subject design to control for confounding effects of patient characteristics.</p> | <p>2</p> |

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| <p>Oztürk MA, et al. Modified ESHAP as salvage chemotherapy for recurrent or refractory non-Hodgkin's lymphoma: results of a single-center study of 32 patients. Modified etoposide, methylprednisolone, cytarabine and cisplatin. Chemotherapy. 2002 Dec;48(5):252-8.</p> | <p><u>Study methodology comments:</u> This was a retrospective cohort study that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of potential confounding factors on outcomes. Additional weaknesses included 1) open-label design without the use of independent reviewers; 2) absence of a power analysis; 3) did not present 95% confidence intervals; 4) no inclusion or exclusion criteria; 5) small sample size; and 6) possible selection bias since the patients were not recruited in a random or consecutive manner. A major strength of the study was that the effect of potential confounding factors on outcomes was statistically examined and controlled. Other strengths were 1) defined response; and 2) complete and partial responses were confirmed at 4 weeks.</p> | <p>3</p> |
| <p>Wang WS, et al. ESHAP as salvage therapy for refractory non-Hodgkin's lymphoma: Taiwan experience. Jpn J Clin Oncol Jan 1999; Vol 29, Issue 1; pp. 33-37.</p> | <p><u>Study methodology comments:</u> This was an open-label, time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of potential confounding factors on outcomes. Additional weaknesses included 1) open-label design without the use of independent reviewers; 2) absence of a power analysis; 3) no exclusion criteria; 4) did not examine the effect of potential confounding factors on outcomes; and 5) possible selection bias since the patients were not recruited in a random or consecutive manner. Strengths of the study included 1) defined response; 2) had inclusion criteria; 3) a complete response was confirmed at 4 weeks; 4) analyzed the intent-to-treat population; 5) presented 95% confidence intervals; and 6) the use of a within-subject design to control for confounding effects of patient characteristics.</p> | <p>3</p> |
| <p>Press OW, et al. Treatment of relapsed non-Hodgkin's lymphomas with dexamethasone, highdose cytarabine, and cisplatin before marrow transplantation. J Clin Oncol. 1991 Mar;9(3):423-31.</p> | <p><u>Study methodology comments:</u> This was an open-label, time-series trial that should be interpreted with caution. A major weakness of the study was the absence of a control group which would have controlled for the effect of potential confounding factors. Additional weaknesses included 1) open-label design without the use of independent reviewers; 2) absence of a power analysis; 3) did not present 95% confidence intervals; and 4) possible selection bias since subjects were not recruited in a random or consecutive manner. Strengths of the study included 1) had inclusion and exclusion criteria; 2) defined response; 3) responses had to be sustained for 4 weeks; 4) analyzed the intent-to-treat population; 5) examined the effect of potential confounding factors on outcomes; and 6) the use of a within-subject design to control for confounding effects of patient characteristics.</p> | <p>3</p> |

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| <p>Park SH, et al. ESHAP salvage therapy for refractory and relapsed non-Hodgkin's lymphoma: a single center experience. Korean J Intern Med. 2006 Sep;21(3):159-64.</p> | | <p>3</p> |
| <p>Harting, Rekha, et al: Efficacy and safety of rituximab combined with ESHAP chemotherapy for the treatment of relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. Clinical Lymphoma & Myeloma May 2007; Vol 7, Issue 6; pp. 406-412.</p> | | <p>3</p> |
| <p>Abali H, ET AL. Comparison of ICE (ifosfamidecarboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest 2008 May;26(4):401-6.</p> | | <p>3</p> |
| <p>Johnson PW, et al. E-SHAP: inadequate treatment for poor-prognosis recurrent lymphoma. Ann Oncol Jan 1993; Vol 4, Issue 1; pp. 63-67.</p> | | <p>3</p> |
| <p>Seymour JF, et al. Cisplatin, fludarabine, and cytarabine: a novel, pharmacologically designed salvage therapy for patients with refractory, histologically aggressive or mantle cell non-Hodgkin's lymphoma. Cancer Feb 01, 2002; Vol 94, Issue no.3; pp. 585-593.</p> | | <p>1</p> |
| <p>Akhtar, S., et al: ESHAP + fixed dose G-CSF as autologous peripheral blood stem cell mobilization regimen in patients with relapsed or refractory diffuse large cell and Hodgkin's lymphoma: a single institution result of 127 patients. Bone Marrow Transplantation Feb 2006; Vol 37, Issue 3; pp. 277-282.</p> | | <p>1</p> |

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| Romaguera JE, et al. Ninety-six-hour paclitaxel infusion with mitoxantrone and ifosfamide/mesna and consolidation with ESHAP for refractory and relapsed non-Hodgkin's lymphoma. Leuk Lymphoma Dec 1998; Vol 32, Issue 1-2; pp. 97-106. | | 1 |
| Rodriguez MA, et al. Results of a salvage treatment program for relapsing lymphoma: MINE consolidated with ESHAP. J Clin Oncol. 1995 Jul;13(7):1734-41. | | 1 |
| Hänel M, et al. Salvage chemotherapy with mitoxantrone, fludarabine, cytarabine, and cisplatin (MIFAP) in relapsing and refractory lymphoma. J Cancer Res Clin Oncol. 2001;127(6):387-95. | | 1 |
| Hänel M, ASHAP--an effective salvage therapy for recurrent and refractory malignant lymphomas. Ann Hematol Jun 2000; Vol 79, Issue 6; pp. 304-311. | | 1 |
| Buzzoni R, et al. Results of a salvage regimen in refractory or relapsed non-Hodgkin's lymphoma. Leuk Lymphoma. 1994 Jun;14(1-2):121-8. | | 1 |
| Kim KH, et al. Gemcitabine, etoposide, cisplatin, and dexamethasone in patients with refractory or relapsed non-Hodgkin's lymphoma. Korean J Intern Med. 2009 Mar;24(1):37-42. | | 1 |
| Biagi JJ, et al. A phase II study of dexamethasone, ifosfamide, cisplatin and etoposide (DICE) as salvage chemotherapy for patients with relapsed and refractory lymphoma. Leuk Lymphoma. 2005 Feb;46(2):197-206. | | 1 |

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| Goss P, et al. DICE (dexamethasone, ifosfamide, cisplatin, etoposide) as salvage therapy in non-Hodgkin's lymphomas. <i>Leuk Lymphoma</i> 1995 Jun;18(1-2):123-9. | | 1 |
| Goss PE, et al. Dexamethasone/ifosfamide/cisplatin/etoposide (DICE) as therapy for patients with advanced refractory non-Hodgkin's lymphoma: preliminary report of a phase II study. <i>Ann Oncol.</i> 1991 Jan;2 Suppl 1:43-6. | | 1 |
| Coleman M, et al. DICE (dexamethasone, ifosfamide, cisplatin, etoposide) infusional chemotherapy for refractory or relapsed non-Hodgkin's lymphoma (NHL). <i>European Journal of Haematology Supplementum</i> Jul 2001; Vol 64 p41-5, pp. 41-555. | | 1 |
| Hickish T, et al. EPIC: an effective low toxicity regimen for relapsing lymphoma. <i>Br J Cancer.</i> 1993 Sep;68(3):599-604. | | 1 |
| Kang HJ, et al. Irinotecan plus cisplatin and dexamethasone (ICD) combination chemotherapy for patients with diffuse large B-cell lymphoma previously treated with Rituximab plus CHOP. <i>Cancer Chemotherapy and Pharmacology</i> Jul 2008; Vol 62, Issue 2; pp. 299-304 | | 1 |
| Dantas AA, et al. Topotecan, Ara-C, cisplatin and prednisolone (Toposhap) for patients with refractory and relapsing lymphomas: Results of a phase II trial. <i>Acta Haematol.</i> 2006;116(4):275-8. | | 1 |
| Girinsky T, et al. Phase II study of concomitant chemoradiotherapy in bulky refractory or chemoresistant relapsed lymphomas. <i>Int J Radiat Oncol Biol Phys.</i> 2005 Feb 1;61(2):476-9. | | 1 |

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| Neidhart JA, et al. Multiple cycles of dose-intensive cyclophosphamide, etoposide, and cisplatin (DICEP) produce durable responses in refractory non-Hodgkin's lymphoma. Cancer Invest 1994; Vol 12, Issue 1; pp. 1-11. | | 1 |
| Abate G, et al. CEOP/PEB alternating chemotherapy in advanced intermediate and high-grade non-Hodgkin's lymphomas. Haematologica Jul 1992; Vol 77, Issue 4; pp. 322-325. | | 1 |
| Spiers AS, et al. Treatment of advanced refractory lymphomas with a combination of carmustine, bleomycin, teniposide, dexamethasone, and cisplatin (the BBVDD regimen). An ECOG pilot study. Am J Clin Oncol Dec 1991; Vol 14, Issue 6; pp. 519-525. | | 1 |
| Vitolo U, et al. Mitoxantrone, etoposide, cisplatin and dexamethasone (MEPD) as salvage chemotherapy in resistant non-Hodgkin's lymphoma. Haematologica Jan-Feb 1991; Vol 76, Issue 1; pp. 43-46 | | 1 |
| Bieker, Ralf, et al: Rituximab in combination with platinum-containing chemotherapy in patients with relapsed or primary refractory diffuse large B-cell lymphoma. Oncol Rep Nov 2003; Vol 10, Issue 6; pp. 1915-1917 | | 1 |
| Dabich, L.: Cisplatin vp-16-213 and mgbg methylglyoxal bisguanylhydrazone combination chemotherapy in refractory lymphoma a phase II study. Investigational New Drugs 1988; Vol 6, Issue 3; pp. 231-238. | | 1 |

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| Crump M., et al: 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 Oct 15, 2004; Vol 101, Issue 8; pp. 1835-1842. | | 1 |
| Martelli M, et al. High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: a prospective randomized Italian multicenter study. J Clin Oncol. 1996 Feb;14(2):534-42. | | 1 |
| Seshadri T., et al: Utility of subsequent conventional dose chemotherapy in relapsed/refractory transplanteligible patients with diffuse large B-cell lymphoma failing platinum-based salvage chemotherapy. Hematology (Amsterdam, Netherlands) Oct 2008; Vol 13, Issue 5; pp. 261-266. | | 1 |
| Martin A., et al: R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large Bcell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica Dec 2008; Vol 93, Issue 12; pp. 1829-1836. | | 1 |
| Aviles,Agustin, et al: Gemcitabine and cisplatin in refractory malignant lymphoma. Oncology 2004; Vol 66, Issue 3; pp. 197-200. | | 1 |

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| <p>Tarella C., et al: Prolonged survival in poor-risk diffuse large B-cell lymphoma following front-line treatment with rituximab-supplemented, earlyintensified chemotherapy with multiple autologous hematopoietic stem cell support: a multicenter study by GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). Leukemia - Official Journal of the Leukemia Society of America, Leukemia Research Fund, U K Aug 2007; Vol 21, Issue 8; pp. 1802-1811.</p> | | <p>1</p> |
| <p>Mey Ulrich,J.M., et al: DHAP in combination with rituximab vs DHAP alone as salvage treatment for patients with relapsed or refractory diffuse large Bcell lymphoma: a matched-pair analysis. Leukemia & Lymphoma Dec 2006; Vol 47, Issue 12; pp. 2558- 2566.</p> | | <p>1</p> |
| <p>O'Donnell,M.R., et al: Cytarabine, cisplatin, and etoposide chemotherapy for refractory non-Hodgkin's lymphoma. Cancer Treat Rep Feb 1987; Vol 71, Issue 2; pp. 187-189.</p> | | <p>1</p> |
| <p>Sirohi,Bhawna, et al: Gemcitabine, cisplatin and methylprednisolone (GEM-P) with or without Rituximab in relapsed and refractory patients with diffuse large B cell lymphoma (DLBCL). Hematology (Amsterdam, Netherlands) Apr 2007; Vol 12, Issue 2; pp. 149-153.</p> | | <p>1</p> |
| <p>Crump,M.: A randomized phase III study of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin as salvage chemotherapy followed by posttransplantation rituximab maintenance therapy versus observation for treatment of aggressive B-cell and T-cell non- Hodgkin's lymphoma. Clinical Lymphoma Jun 01, 2005; Vol 6, Issue 1; pp. 56-60.</p> | | <p>4</p> |

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| <p>Illidge,T.: Current treatment approaches for diffuse large B-cell lymphoma. Leukemia and Lymphoma Apr 01, 2008; Vol 49, Issue 4; pp. 663-676.</p> | | 4 |
| <p>Crump,M: What is the role of rituximab in salvage treatment for patients with diffuse large B-cell lymphoma?. Leukemia & Lymphoma Dec 2006; Vol 47, Issue 12; pp. 2437-2439.</p> | | 4 |
| <p>Martin,Alejandro and Caballero,Maria: R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: influence of prior autologous stem-cell transplantation on outcome. Haematologica May 2009; Vol 94, Issue 5; p. 744.</p> | | 4 |
| <p>Piliotis Eugenia, et al: A phase II trial of Rituximab plus ESHAP as salvage chemotherapy in relapsed/refractory aggressive histology Non-Hodgkin's Lymphoma. Blood Nov 16, 2003; Vol 102, Issue 11; p. 288b.</p> | | 3 |
| <p>Gill,Karamjit K., et al: BP-VACOP and extensive lymph node irradiation (RT) in the treatment of advanced stage low grade non-Hodgkin's lymphoma (NHL) at diagnosis. Blood Nov 16, 2000; Vol 96, Issue 11 Part 1; p. 134a.</p> | | 3 |
| <p>Venugopal,Parameswaran, et al: ESHAP combined with Rituximab and GMCSF is highly active in relapsed/refractory aggressive lymphoma. Blood Nov 16, 2003; Vol 102, Issue 11; p. 307b.</p> | | 3 |

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| <p>Martin,Alejandro, et al: R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: A Spanish GEL-TAMO multicenter study. Blood Nov 16, 2007; Vol 110, Issue 11, Part 1; pp. 1007A-1008A.</p> | | <p>3</p> |
| <p>Akhtar,S., et al: ESHAP as salvage followed by BEAM as high-dose chemotherapy and autologous stem cell transplant for relapsed or refractory diffuse large cell non-Hodgkin lymphoma. A single-centre experience of 63 patients. Bone Marrow Transplantation Apr 2007; Vol 39, Issue Suppl. 1; p. S150.</p> | | <p>3</p> |
| <p>Venugopal,Parameswaran, et al: Rituximab (Rituxan) combined with ESHAP chemotherapy is highly active in relapsed/refractory aggressive non-Hodgkin's lymphoma. Blood Nov 16, 2004; Vol 104, Issue 11, Part 2; p. 243B.</p> | | <p>3</p> |
| <p>Threja,Rekha R., et al: ESHAP with rituximab is highly efficacious with durable responses in patients with relapsed/refractory aggressive non-Hodgkin's lymphoma. Blood Nov 16, 2005; Vol 106, Issue 11, Part 2; p. 277B.</p> | | <p>3</p> |
| <p>Goldberg,Stuart L., et al: Risk adapted dose intensive DICEP salvage chemotherapy prior to autologous stem cell transplantation yields successful outcomes in chemotherapy refractory lymphoma. Blood Nov 16, 2004; Vol 104, Issue 11, Part 1; p. 256A.</p> | | <p>3</p> |
| <p>Shrestha,Sagun, et al: ESHAP +/- rituximab as salvage therapy for relapsed lymphoma prior to stem cell-transplant: Single institution experience. Blood Nov 16, 2004; Vol 104, Issue 11, Part 2; p. 234B.</p> | | <p>3</p> |

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| <p>Martelli,M., et al: Cisplatinum, idarubicin, prednisone (CIP) after P-VABEC chemotherapy improves survival in elderly patients with diffuse large cell lymphoma: Long term follow-up. Annals of Oncology Jun 2005; Vol 16, Issue 5; pp. 104-104.</p> | | <p>3</p> |
| <p>Chubar,Yevgene, et al: Dexamethasone, etoposide, ifosfarnide and cisplatin (DVIP) as salvage therapy in non-Hodgkin's lymphoma and Hodgkin's disease. Blood Nov 16, 2006; Vol 108, Issue 11, Part 2; p. 246B.</p> | | <p>3</p> |
| <p>Hagberg,H. and Gisselbrecht,C.: Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. Annals of Oncology May 2006; Vol 17 Suppl 4 iv31-2</p> | | <p>3</p> |
| <p>Sobrevilla-Calvo,P., et al: Dexamethasone, etoposide and cisplatin (DEP) as second line chemotherapy in patients with diffuse large B cell lymphoma (DLBCL). Journal of Clinical Oncology Jun 01, 2005; Vol 23, Issue N16,1,S; pp. 614S-614S.</p> | | <p>3</p> |
| <p>Khouri,Issa F., et al: Long term remission and low mortality achieved with cisplatin, fludarabine, cytarabine nonablative preparative regimen and allogeneic stem transplantation (AST) for histologically aggressive non-Hodgkins lymphoma (NHL). Blood Nov 16, 2001; Vol 98, Issue 11 Part 1; p. 190a.</p> | | <p>3</p> |

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| Borghaei,H., et al: Long term follow-up of high dose cyclophosphamide, etoposide and cisplatin (CEP) and autologous hematopoietic stem cell transplant for refractory/relapsed large cell non-Hodgkin's lymphoma. Blood Nov 16, 2002; Vol 100, Issue N11,2; pp. 478B-478B. | | 3 |
| Tarella,Corrado, et al: Rituximab-Supplemented High-Dose Chemotherapy with Autografting in High- Risk B-Diffuse Large Cell Lymphoma: A Multicenter, Prospective Study of GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). Blood Nov 16, 2002; Vol 100, Issue 11 | | 3 |
| Telio D, et al. Outcomes of Second-Line Chemotherapy and Autologous Stem Cell Transplantation for Primary Refractory Diffuse Large B Cell Lymphoma. Blood (ASH Annual Meeting Abstracts), Nov 2008; 112: 4445. | | 3 |
| Sirohi B, et al. Use of Gemcitabine, Cisplatin and Methylprednisolone (GEM-P) with or without Rituximab in Relapsed and Refractory Patients with Diffuse Large B Cell Lymphoma (DLBCL). Blood (ASH Annual Meeting Abstracts), Nov 2005; 106: 939. | | 3 |
| Mey UJM, et al. A Phase II Trial of Dexamethasone, High-Dose Cytarabine, and Cisplatin (DHAP) in Combination with Rituximab as Salvage Treatment for Patients with Refractory or Relapsed Aggressive Non-Hodgkin's Lymphoma. Blood (ASH Annual Meeting Abstracts), Nov 2004; 104: 4618. | | 3 |

Literature evaluation codes: S = Literature selected; 1 = Literature rejected = Topic not suitable for scope of content; 2 = Literature rejected = Does not add clinically significant new information; 3 = Literature rejected = Methodology flawed/Methodology limited and unacceptable; 4 = Other (review article, letter, commentary, or editorial)

CONTRIBUTORS:

*to meet requirement 3

| PACKET PREPARATION | DISCLOSURES | EXPERT REVIEW | DISCLOSURES |
|------------------------|-------------|------------------------|-------------|
| Amy Hemstreet, PharmD | None | Edward P. Balaban, DO | None |
| Stacy LaClaire, PharmD | None | Keith A. Thompson, MD | None |
| Felicia Gelsey, MS | None | James E. Liebmann, MD | None |
| | | Susan Goodin, PharmD | None |
| | | John M. Valgus, PharmD | None |

ASSIGNMENT OF RATINGS:

*to meet requirement 4

| | EFFICACY | STRENGTH OF RECOMMENDATION | COMMENTS | STRENGTH OF EVIDENCE |
|-----------------------|--------------------------|---------------------------------------|---|----------------------|
| MICROMEDEX | --- | --- | | B |
| Edward P. Balaban, DO | Evidence Favors Efficacy | Class IIa Recommended, In Most Cases | I believe the long term data has held up sufficiently – this is efficacious therapy | N/A |
| Keith A. Thompson, MD | Evidence Favors Efficacy | Class IIb, Recommended, In Some Cases | None | N/A |
| James E. Liebmann, MD | Effective | Class I Recommended | DHAP and ESHAP are well accepted salvage regimens, and have been used for over two decades. The data reported in these papers are reproducible and believable. The only change to DHAP/ESHAP in treatment of relapsed lymphomas is the addition of Rituximab in CD-20 (+) disease | N/A |
| Susan Goodin, PharmD | Effective | Class IIa Recommended, In Most Cases | Few alternatives for relapsed or refractory disease. Data from trials of both DHAP and ESHAP are mature (with long term follow-up) revealing improvements in survival, particularly with ESHAP. | N/A |

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|------------------------|--------------------------|--------------------------------------|---|-----|
| John M. Valgus, PharmD | Evidence Favors Efficacy | Class IIa Recommended, In Most Cases | Considered a standard regimen for relapsed disease with strong long term follow up. Only a randomized trial with or without Cisplatin would improve strength of recommendation. | N/A |
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