

悪性リンパ腫治療における methylprednisolone の使用経緯・状況について

再発難治性悪性リンパ腫に対する salvage regimen として M. D. Anderson Cancer Center で開発された ESHAP 療法を構成する薬剤の中で methylprednisolone は 250-500 mg/day 点滴静注で、5日間投与されるよう規定されている。

本報告書は、悪性リンパ腫に対する多剤併用化学療法の構成薬品として methylprednisolone が使用されている経緯、状況を、公表論文から調査したものである。

1. Velasquez WS, McLaughlin P, Tucker S, Hagemester FB, Swan F, Rodriguez MA, Romaguera J, Rubenstein E, Cabanillas F. ESHAP—an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. *J Clin Oncol*. 1994 Jun;12(6):1169-76.
 - ESHAP 療法が、Velasquez WS らによって公表されたのは 1994 年である。
2. Coiffier B, Bryon PA, Berger F, et al. Intensive and sequential combination chemotherapy for aggressive malignant lymphomas (protocol LNH-80). *J Clin Oncol*. 1986 Feb;4(2):147-53.
 - 1986 年にフランスの臨床腫瘍研究グループである GELA は、aggressive 非ホジキンリンパ腫に対する初回治療として CHOP-Bleo (cyclophosphamide, doxorubicin, vindesine, methylprednisolone, and bleomycin) と CVAP-Bleo (cyclophosphamide, teniposide, cytarabine, methylprednisolone, and bleomycin) による臨床試験 (LNH-80) の結果を *J Clin Oncol* に発表した。このレジメンにおいて使用されたステロイド性剤は prednisolone ではなく methylprednisolone であった。
3. van Imhoff GW, Nieweg HO, Halie MR. High-dose methylprednisolone, vincristine, MTX, and ara-C (SOMA) as initial bulk reducing therapy in non-Hodgkin's lymphoma of unfavorable histology: preliminary results of an ongoing phase II study. *Semin Oncol*. 1987 Jun;14(2 Suppl 1):98-103.
 - 1987 年には van Imhoff GW らが、methylprednisolone、vincristine、MTX、ara-C からなる SOMA 療法の報告を *Sem Oncol* に報告している。

4. Selby PJ, Graham MA, et al. Pharmacokinetics of high dose methylprednisolone and use in hematological malignancies. *Hematol Oncol.* 1993 Mar-Apr;11(2):89-96.
 - 1993年にはPatel PMらが、経口および経静脈投与でのmethylprednisoloneの悪性リンパ腫を含む造血器腫瘍でのpharmacokineticsと有効性を検討した結果を報告し、methylprednisolone単剤での抗腫瘍効果、特に骨髄抑制のある症例での一時的な有効性を述べている。
5. ACES療法 (Niitsu N, Umeda M. Salvage chemotherapy for relapsed or refractory non-Hodgkin's lymphoma with a combination of ACES (high-dose Ara C, carboplatin, etoposide and steroids) therapy. *Eur J Haematol.* 1996 Oct;57(4):320-4.)
6. PEEC療法 (Cameron DA, White JM, Proctor SJ, et al. CHOP-based chemotherapy is as effective as alternating PEEC/CHOP chemotherapy in a randomised trial in high-grade non-Hodgkin's lymphoma. Scotland and Newcastle Lymphoma Group. *Eur J Cancer.* 1997, Jul;33(8):1195-201.
 - ESHAPの報告以後も、methylprednisoloneを組み込んだ、リンパ腫治療レジメンはいくつか報告されている。
7. Magnuson NS, McGuire TC, Banks KL, Perryman LE. In vitro and in vivo effects of corticosteroids on peripheral blood lymphocytes from ponies. *Am J Vet Res.* 1978 Mar;39(3):393-8.
8. Claman HN, Moorhead JW, Benner WH. Corticosteroids and lymphoid cells in vitro. I. Hydrocortisone lysis of human, guinea pig, and mouse thymus cells. *J Lab Clin Med.* 1971 Oct;78(4):499-507.
9. Galili U. Glucocorticoid induced cytolysis of human normal and malignant lymphocytes. *J Steroid Biochem.* 1983 Jul;19(1B):483-90.
 - ステロイド性剤は単独でin vitroで抗リンパ球作用、抗リンパ系腫瘍効果が確認され、抗腫瘍効果を期待するとともに、その制吐作用、抗炎症作用を目的として殆どのリンパ系腫瘍に対するレジメンの構成薬として採用されてきている。

Methylprednisoloneもこうした目的で、1980年代から悪性リンパ腫に対する多剤併用化学療法の構成薬品として広く使用されてきた状況である。

Methylprednisolone 悪性リンパ腫に対する抗がん剤との併用療法定文献

	Title	Author	Journal
1	話題 悪性リンパ腫のESHAP療法と末梢血幹細胞採取(総説)	田野崎隆二(慶應大学医学部輸血センター)	PAGE 31(6)494-500; 1995.12
2	小児悪性腫瘍の治療におけるGranisetronの制吐効果-第2報:Granisetron単独とGranisetron, Methylprednisolone併用療法の比較検討-	廣田貴久(愛知医科大学・小児科), 本庄孝江, 黒田理恵子, 佐伯公, 片野直之ほか	PAGE 20(15)2369-2373; 1993.12
3	Myeloablative radiochemotherapy followed by autologous peripheral blood stem cell transplantation as first-line therapy in peripheral T-cell lymphomas: first results of a prospective multicenter	Reimer Peter; Schertlin Tobias; Rudiger Thomas; Geissinger Eva; Roth Sabine; Kunzmann Volker; Weissinger Florian; Nerl Christoph; Schmitz Norbert; Muller-Hermelink Hans Konrad; Wilhelm Martin	hematology journal - the official journal of the European Haematology Association / EHA; 5 (4) p304-11
4	Three cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) or epirubicin, bleomycin, vinblastine, and methotrexate (EBVM) plus extended field radiation therapy in early and intermediate Hodgkin disease: 10-year results of a randomized	le Maignan Christine; Desablens Bernard; Delwail Vincent; Dib Mahmoud; Berthou Christian; Vigier Magda; Ghandour Christiane; Atmani Said; Casassus Philippe; Maisonneuve Herve; Le Mevel Annick; Traulle Catherine; Bernard Marc; Briere Josette; Colonna Pierre; Andrieu Jean-Marie	Blood; 103 (1) p58-66
5	High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962.	Poortmans Philip M P; Kluin-Nelemans Hanneke C; Haaxma-Reiche Hanny; Van't Veer Mars; Hansen Mads; Soubeyran Pierre; Taphoorn Martin; Thomas Jose; Van den Bent Martin; Fickers Martin; Van Imhoff Gustaaf; Rozewicz Cynthia; Teodorovic Ivana; van Glabbeke Martine	Journal of clinical oncology - official journal of the American Society of Clinical Oncology; 21 (24) p4483-8
6	Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma.	Vose J M; Crump M; Lazarus H; Emmanouilides C; Schenkein D; Moore J; Frankel S; Flinn I; Lovelace W; Hackett J; Liang B C	Journal of clinical oncology - official journal of the American Society of Clinical Oncology; 21 (3) p514-9

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	Title	Author	Journal
7	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.	Ozturk Mehmet Akif; Barista Ibrahim; Altundag M Kadri; Turker Alev; Yalcin Suayib; Celik Ismail; Gullu Ibrahim; Guler Nilufer; Ozisik Yavuz ; Kars Ayse; Kansu Emin; Baltali Esmen; Tekuzman Gulden	Chemotherapy; 48 (5) p252-8
8	Fludarabine, mitoxantrone, dexamethasone (FND) compared with an alternating triple therapy (ATT) regimen in patients with stage IV indolent lymphoma.	Tsimberidou Apostolia M; McLaughlin Peter; Younes Anas; Rodriguez Maria A; Hagemeister Fredrick B; Sarris Andreas; Romaguera Jorge; Hess Mark; Smith Terry L; Yang Ying; Ayala Ana; Preti Alejandro; Lee Ming-Sheng; Cabanillas Fernando	Blood; 100 (13) p4351-7
9	Response to induction chemotherapy is not essential to obtain survival benefit from high-dose melphalan and autotransplantation in myeloma.	Singhal S; Powles R; Sirohi B; Treleaven J; Kulkarni S; Mehta J	Bone marrow transplantation; 30 (10) p673-9
10	A prospective study of P-IMVP-16/CBDCA: a novel salvage chemotherapy for patients with aggressive non-Hodgkin's lymphoma who had previously received CHOP therapy as first-line chemotherapy.	Sawada Michio; Tsurumi Hisashi; Yamada Toshiki; Hara Takeshi; Fukuno Kenji; Goto Hideko; Shimizu Masahito; Kasahara Senji; Yoshikawa Takeshi ; Kanemura Nobuhiro; Oyama Masami; Takami Tsuyoshi; Moriwaki Hisataka	European journal of haematology; 68 (6) p354-61
11	A dose escalation study for salvage chemotherapy in patients with refractory lymphoma prior to high-dose myeloablative therapy with stem cell transplantation.	Lee C K; de Magalhaes-Silverman M; Hayashi M; Schlueter A; Strauss R G; Hohl R J; Girgrich R D	Bone marrow transplantation; 29 (8) p647-52
12	ASHAP--an effective salvage therapy for recurrent and refractory malignant lymphomas.	Hanel M; Kroger N; Hoffknecht M M; Peters S O; Metzner B; Fiedler F; Braumann D; Schubert J C; Illiger H J; Hanel A; Kruger W H; Zeller W; Weh H-J; Hossfeld D K; Zander A R	Annals of hematology; 79 (6) p304-11
13	ESHAP and G-CSF is a superior blood stem cell mobilizing regimen compared to cyclophosphamide 1.5 g m(-2) and G-CSF for pre-treated lymphoma patients: a ratched pairs analysis of 78 patients.	Watts M J; Ings S J; Leverett D; MacMillan A; Devereux S; Goldstone A H ; Linch D C CS-Department of Haematology, University College London, UK.	British journal of cancer; 82 (2) p278-82

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	Title	Author	Journal
14	Prevention of recurrence and prolonged survival in primary central nervous system lymphoma (PCNSL) patients treated with adjuvant high-dose methylprednisolone.	O'Neill B P; Habermann T M; Witzig T E; Rodriguez M	Medical oncology (Northwood, London, England); 16 (3) p211-5
15	Feasibility of ESHAP + G-CSF as peripheral blood hematopoietic progenitor cell mobilisation regimen in resistant and relapsed lymphoma: a single-center study of 22 patients.	Petit J; Boque C; Cancelas J A; Sarra J; Munoz J; Garcia J; Granena A	Leukemia & lymphoma; 34 (1-2) p119-27
16	ASHAP: a regimen for cytoreduction of refractory or recurrent Hodgkin's disease.]	Rodriguez J; Rodriguez M A; Fayad L; McLaughlin P; Swan F; Sarris A; Romaguera J; Andersson B; Cabanillas F; Hagemester F B	Blood; 93 (11) p3632-6
17	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.	Soussain C; Souleau B; Gabarre J; Zouabi H; Sutton L; Boccaccio C; Albin N; Charlotte F; Merle-Beral H; Delort J; Binet J L; Leblond V CS- Department of Hematology, Hopital Pitie-Salpetriere, Paris, France.]	Leukemia & lymphoma; 33 (5-6) p543-50
18	ESHAP as salvage therapy for refractory non-Hodgkin's lymphoma: Taiwan experience.	Wang W S; Chiou T J; Liu J H; Fan F S; Yen C C; Tung S L; Chen P M	Japanese journal of clinical oncology; 29 (1) p33-7
19	Ninety-six-hour paclitaxel infusion with mitoxantrone and ifosfamide/mesna and consolidation with ESHAP for refractory and relapsed non-Hodgkin's lymphoma.	Romaguera J E; Hagemester F B; McLaughlin P; Rodriguez M A; Bachier C; Preti H; Sarris A H; Weber D; Younes A; Cabanillas F	Leukemia & lymphoma; 32 (1-2) p97-106
20	A multivariate analysis of the survival of patients with aggressive lymphoma: variations in the predictive value of prognostic factors during the course of the disease. Groupe d'Etudes des Lymphomes de l'Adulte.]	Mounier N; Morel P; Haioun C; Coiffier B; Tilly H; Chatelain C; Lederlin P; Thyss A; Herbrecht R; Gisselbrecht C; Lepage E	Cancer; 82 (10) p1952-62]

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	Title	Author	Journal
21	A single-center study of 11 patients with intraocular lymphoma treated with conventional chemotherapy followed by high-dose chemotherapy and autologous bone marrow transplantation in 5 cases.	Soussain C; Merle-Beral H; Reux I; Sutton L; Fardeau C; Gerber S; Ben Othman T; Binet J L; Lehoang P; Leblond V	Leukemia & lymphoma; 23 (3-4) p339-45
22	A phase II study of high-dose methylprednisolone in refractory or relapsed multiple myeloma.	Gertz M A; Garton J P; Greipp P R; Witzig T E; Kyle R A	Leukemia - official journal of the Leukemia Society of America, Leukemia Research Fund, U.K; 9 (12) p2115-8
23	Role of granulocyte colony-stimulating factor in relapsed/resistant intermediate and high-grade non-Hodgkin's lymphoma patients treated with the E-SHAP regimen.	Mangiagalli M; Miccolis I; Maffe P; Pogliani E M; Corneo G	Tumori; 81 (2) p91-5