Salvage Therapy for Hodgkin's Lymphoma

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Abstract: Hodgkin's lymphoma (HL) is a clonal lymphoid malignancy that affects over 7000 patients in the United States annually. The disease remains one of the great success stories in the recent history of cancer treatment. More than 80% of HL patients will be expected to be long-term survivors because of recent advances in radiation therapy and combined chemotherapy. However, for the subset of patients who relapse after initial therapy, HL remains a challenging disease. Indeed, for patients who relapse after salvage high-dose chemotherapy and autologous stem cell transplant, effective therapeutic options remain limited, and further new therapies are warranted. This article provides a review of the current literature regarding salvage therapy for HL.

Key Words: Hodgkin's lymphoma, salvage therapy, autologous stem cell transplant

(*Cancer J* 2009;15: 161–163)

Hodgkin's lymphoma (HL) is a clonal lymphoid malignancy mainly confined to the lymph nodes and the lymphoid organs. HL (previously Hodgkin's disease) affects approximately 7500 new patients annually in the United States.[1] The disease incidence varies considerably and seems to have a bimodal pattern with first peak in the late 20's, and a second peak in patients 55 years and older.[2] The disease is composed of 2 distinct entities: the more common, classic HL, and the rarer nodular lymphocyte predominant HL. Classic HL includes the subgroups, nodular sclerosis, which is the most common type in United States, mixed cellularity, lymphocyte depleted, and lymphocyte rich.

From the period 1960 to 1963, the 5-year survival from HL was 40%. However, with advances in radiation therapy and in combination chemotherapy, from the period 1989 to 1993, the 5-year survival has considerably increased to more than 80%.

FAILURE TO INITIAL THERAPY

Depending on the initial stage as well as the various prognostic factors, up to 30% of HL patients can be expected to relapse after initial induction of remission.[3] However, the biologic features of HL that contribute to its sensitivity to chemotherapy and radiation therapy during initial treatment can be retained at the time of relapse, thus allowing for durable responses and remissions with second-line (and even third-line) therapeutic measures.

For the purpose of this article, it might be useful to review some of the basic terminologies associated with salvage therapy for HL. "Relapse" itself may be defined as reappearance of disease in sites of prior disease and/or in new sites after an initial complete response to therapy. "Progression" refers to increasing evidence of disease after achieving a partial response, and "refractory disease" refers to a failure to achieve even a partial response.

Despite the high cure rate with initial therapy, in approximately 5% to 10% of patients with HL, the disease is refractory to initial treatment, and 10% to 30% of patients will experience disease relapse after an initial complete response.[4,5] Of note, the majority of the relapses after initial complete response are detected during physical examination or during evaluation of various symptoms rather than routine blood work or imaging.

It is essential to document disease recurrence histologically via a biopsy. Positron emission tomography in combination with computed tomography remains the test of choice for detecting disease activity or relapse post treatment.[6–9] Compared with computed tomography alone, positron emission tomography in combination with computed tomography is better able to distinguish between active tumor and necrosis or fibrosis in residual masses. However, the positive predictive value of positron emission tomography in detecting disease response is only about 65%. As per literature, as much as 40% of so-called positive positron emission tomography scans at the end of therapy do not recur in the next 5 years of follow-up.[10] Causes of a falsely positive positron emission tomography scan include inflammatory changes postchemotherapy, radiation therapy, rebound thymic hyperplasia, brown fat, inflammation, and infection.[11] In contrast, the negative predictive value of a positron emission tomography is as high as 90%,[7] with the 10% to 20% false negatives likely secondary to possible microscopic disease.

PROGNOSTIC FACTORS

As the initial treatment strategies for HL become more effective, the various prognostic factors for relapse will possibly change as well. For now, the duration of remission after initial chemotherapy remains the single most important prognostic factor for relapsed HL patients with respect to how well the patients will respond to subsequent salvage therapy. The National Cancer Institute in 1992 updated its experience with long-term follow up of HL patients who had relapsed after initial conventional dose combination chemotherapy.[12] No patient with primary progressive disease survived more than 8 years. In contrast, the 20-year survival rate for patients with early (less than 12 months) and late relapse (more than 12 months) was 11% and 22%, respectively.[12]

The German Hodgkin's Lymphoma Study Group reported on 422 patients with relapsed HL after initial therapy, which included radiation therapy, conventional chemotherapy, and a combination of the 2.[13] The 3 most important prognostic factors for a possible third relapse for these patients included in order of importance: duration of initial remission, stage of disease at relapse, and anemia. It is to be noted that one-third of the included patients underwent hematopoietic stem cell transplantation as salvage therapy.

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ISSN: 1528-9117/09/1502-0161

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TREATMENT

Radiotherapy

Radiation therapy alone in the setting of disease relapse is now rarely used. Only limited studies have been reported with this particular approach, and the data are supportive of combined modality being superior to radiation alone.[14]

Occasionally, radiation therapy alone can be used with some success in highly selected patient with prolonged period of initial remission, and localized recurrence with no extranodal disease, absence of B symptoms, and the ability of encompassing the entire disease recurrence site within the radiation field.[15–17]

Nodal or involved field radiotherapy is often used in combined-modality salvage of relapse after chemotherapy. Radiation therapy is also frequently added to patients with relapsed disease undergoing high-dose chemotherapy and autolgous stem cell transplant, especially to sites of bulky disease. Prospective data showing a benefit of this approach are currently lacking, with concern for added toxicity.

Conventional Chemotherapy

Until recently, it was standard practice to treat HL patients who relapse after more than 1 year with the same chemotherapy regimen as the one used for initial remission induction. Most commonly used chemotherapy regimens for first-line therapy include doxorubicin, bleomycin, vinblastine, dacarbazine, nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP), or the newer regimens such as Stanford V (nitrogen mustard, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. As such, these patients were able to achieve a second complete remission approximately 80% of the times with a mean survival of about 4 years.[14] Patients who relapsed within a year of disease remission were offered a different chemotherapy regimen avoiding drugs that were used in the first regimen.[18–20] No randomized clinical trial has shown any benefit of one standard salvage chemotherapy regimen over the other to date. However, despite responses, these patients even after achieving a second remission go on to relapse and die of the disease or its complications. Thus, there is currently a shift in practice where almost all eligible patients with relapsed disease are offered high-dose chemotherapy and autologous stem cell transplantation.

Patients ineligible for high-dose chemotherapy and autologous stem cell transplantation can be considered for conventional chemotherapy regimens in combination with radiation therapy if possible. Most such patients can be treated with a first-line conventional chemotherapy regimen that was not used initially.[21–23]

High-Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplant

High-dose chemotherapy with autologous hematopoietic stem cell transplantation is the cornerstone of salvage therapy for most relapsed HL patients. It is also considered the standard of care for those who experience progression during remission induction.

The likelihood of attaining a successful second remission is related greatly to the duration of the initial remission.[14] Patients whose initial remission lasted more than 12 months have an impressive 75% to 80% chance of achieving a durable second remission. In contrast, patients whose initial remission lasted less than 12 months have a 40% to 50% chance of a second durable remission. Figures are even more dismal for patients who had progressive disease during induction chemotherapy, with likelihood of attaining a durable remission at only 20%.

In general, the salvage therapy is administered in 2 phases. Initially, a conventional chemotherapy regimen is administered with the hope to reduce the tumor bulk as much as possible. This usually is followed by stem cell mobilization, and subsequent high-dose chemotherapy along with stem cell rescue.

The choice of the conventional chemotherapy regimen used for salvage usually depends on the original chemotherapy regimen used during first remission induction as well as the duration of the initial remission. Patients who have progressed on a certain first-line chemotherapy regimen (ie, doxorubicin, bleomycin, vinblastine, and dacarbazine) may respond better to another chemotherapy regimen, which avoids agents used in the first regimen (ie, MOPP or MOPP-like regimen). A new regimen with novel agents, such as etoposide, methylprednisolone, high-dose cytarabine, and cisplatin, may be more effective.[24] Newer agents such as gemcitabine may also be effective in achieving an adequate reduction in this initial tumor bulk. Ultimately, the goal is to reduce the tumor burden as much as possible, before embarking on the high-dose chemotherapy and autologous stem cell transplant. Patients with the lowest tumor burden before high-dose chemotherapy and autologous stem cell transplant are most likely to attain a durable second remission.

Sequential High-Dose Chemotherapy

Keeping in mind the Norton-Simon hypothesis, sequential high-dose chemotherapy regimen offers the highest possible dosing of chemotherapeutic agents in the shortest duration possible.

This dose- and time-intensification approach was initially studied in a phase II multicenter trial by the German Hodgkin's Lymphoma Study Group.[25] Patients included in the study had histologically proven primary progressive or relapsed HL. Treatment consisted of 2 cycles dexamethasone, high-dose cytarabine, and cisplatin; patients with chemosensitive disease received cyclophosphamide followed by peripheral blood stem cell harvest; methotrexate plus vincristine, etoposide and carmustine, etoposide, cytarabine, malphalan plus peripheral blood stem cell transplantation. A total of 102 patients (median age 34 years, range 18–64) were enrolled. The response rate was 80% (72% complete response, 8% partial response). With a median follow-up of 30 months (range 3–61 months), freedom from second failure and overall survival were 59% and 78% for all patients, respectively. Freedom from second failure and overall survival for patients with early relapse were 62% and 81%, for late relapse 65% and 81%; for progressive disease 41% and 48%, and for multiple relapse 39% and 48%, respectively.

Based on the promising results of this study, a prospective randomized European intergroup study was started comparing this intensified regimen with 2 courses of dexamethasone, high-dose cytarabine, and cisplatin followed by carmustine, etoposide, cytarabine, and malphalan. The results of this study (HD-R2 protocol) remain pending at this point.

Allotransplant

Allogeneic transplant is not routinely considered for HL patients secondary to donor availability as well as the advanced age of many of these patients. In addition, a reduced relapse rate after an allogeneic transplant due to its graft-versus-tumor effect comes at the expense of potentially lethal graft-versus-host toxicity. For patients with HL treated with low-intensity allogeneic transplant, the treatment related mortality at 1 year was approximately 20%, and the 2-year overall survival was approximately 50%.[26] The treatment related mortality was considerably worse for the older age group. Nevertheless, this approach, in particular the nonmyeloablative conditioning regimens, warrants further investigation especially for patients with refractory disease who have failed other therapies.

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New Directions

HL patients who progress after high-dose chemotherapy and autologous stem cell transplantation have few good therapeutic options left, and generally have a poor outcome. In one study, HL patients who failed high-dose chemotherapy and autologous stem cell transplantation, the median time to progression after the next therapy was only 3.8 months, with the median survival after high-dose chemotherapy and autologous stem cell transplantation failure being 26 months.[27]

Of the various novel therapies available, the 2 cytotoxic agents, gemcitabine[28] and vinorelbine[29] seem the most promising. Both agents have shown activity in heavily pretreated HL patients, even though the duration of responses was short. Vinorelbine, a vinca alkaloid, demonstrated activity in patients who were treated in the past with vincristine and vinblastine.[29] Further role of these agents in first and second-line therapies is currently under investigation.

Recent studies also included exploitation of the expression of CD30 on the Reed-Sternberg cells. Antibodies targeting the molecule had shown promise in vitro. Recent trials of SGN-30 (humanized mouse monoclonal antiCD30) and MDX-060 (fully humanized antibody) showed few side effects, however, only limited clinical response was seen.[30,31] Other areas of interest include immunotoxins directed against CD25, as well as immunotherapy with cytotoxic T-cells targeting Ebstein-Barr Virus antigens as well as the Reed-Sternberg cells.

CONCLUSIONS

Considerable progress has been made in recent years with respect to HL therapy, and its cure rate has significantly increased. Currently, more than 80% of newly diagnosed HL patients are expected to be long-term survivors. Nevertheless, for the subset of patients who relapse or progress after initial therapy, HL remains a challenging disease. Indeed for patients who progress after high-dose chemotherapy and autologous stem cell transplantation (or are ineligible), therapeutic options remain limited, and further new therapies are warranted.

REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin.* 2005;55:10–30; erratum in *CA Cancer J Clin.* 2005;55:259.
2. Glaser SL, Jarrett RF. The epidemiology of Hodgkin's disease. *Baillieres Clin Haematol.* 1996;9:401–416.
3. Oza AM, Ganesan TS, Leahy M, et al. Pattern of survival in patients with Hodgkin's disease: long follow up in a single center. *Ann Oncol.* 1993;4: 385–392.
4. Horning SJ. Hodgkin's disease. In: Cavalli F, Hansen HH, Kaye SB, eds. *Textbook of Medical Oncology.* 2nd ed. London, England: Martin Dunitz; 2000:461–474.
5. Diehl V, Mauch PM, Harris NL. Hodgkin's disease. In: Devita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* vol 2. 6th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2001: 2339–2387.
6. Juweid ME. Utility of positron emission tomography (PET) scanning in managing patients with Hodgkin's lymphoma. *Hematology Am Soc Hematol Educ Program.* 2006;259–265.
7. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25:579–586.
8. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood.* 1999;94:429–433.
9. Hoh CK, Glaspy J, Rosen P, et al. Whole-body FDG-PET imaging for staging of Hodgkin's disease and lymphoma. *J Nucl Med.* 1997;38:343–348.
10. Hutchings A, Loft A, Hansen M, et al. FDG-PET after 2 cycles of chemotherapy predicts treatment failure and progression free survival in Hodgkin's lymphoma. *Blood.* 2005;108:52.
11. Fallanca F, Giovacchini G, Ponzoni M, et al. Cervical thymic hyperplasia after chemotherapy in an adult patient with Hodgkin's lymphoma: a potential cause of false-positivity on [18F]FDG PET/CT scanning. *Br J Haematol.* 2008;140:477.
12. Longo DL, Puffey PL, Young RC, et al. Conventional dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. *J Clin Oncol.* 1992;10:210–218.
13. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. *J Clin Oncol.* 2002;20:221–230.
14. Uematsu M, Tarbell N, Silver B, et al. Wide field radiation therapy with or without chemotherapy for patients with Hodgkin's disease in relapse after initial combination chemotherapy. *Cancer.* 1993;72:207–212.
15. Brada M, Eeles R, Ashley S, et al. Salvage radiotherapy in recurrent Hodgkin's disease. *Ann Oncol.* 1992;3:131–135.
16. Wirth A, Corry J, Laidlaw C, et al. Salvage radiotherapy for Hodgkin's disease following chemotherapy failure. *Int J Radiat Oncol Biol Phys.* 1997;39:599–607.
17. Pezner RD, Lipsett JA, Vora N, et al. Radical radiotherapy as salvage treatment for relapse of Hodgkin's disease initially treated by chemotherapy alone: prognostic significance of the disease-free interval. *Int J Radiat Oncol Biol Phys.* 1994;30:965–970.
18. Pfreundschuh MG, Rueffer U, Lathan B, et al. Dexa-BEAM in patients with Hodgkin's disease refractory to multidrug chemotherapy regimens: a trial of the German Hodgkin's Disease Study Group. *J Clin Oncol.* 1994;12:580–586.
19. Ferme C, Bastion Y, Lepage E, et al. The MINE regimen as intensive salvage chemotherapy for relapsed and refractory Hodgkin's disease. *Ann Oncol.* 1995;6:543–549.
20. Rodriguez J, Rodriquez MA, Fayad L, et al. ASHAP: a regimen for cytoreduction of refractory or recurrent Hodgkin's disease. *Blood.* 1999;93:3632–3636.
21. Bonfante V, Santoro A, Viviani S, et al. Outcome of patients with Hodgkin's disease failing after primary MOPP-ABVD. *J Clin Oncol.* 1997;15:528–534.
22. Bonadonna G, Santoro A, Gianni AM, et al. Primary and salvage chemotherapy in advanced Hodgkin's disease: the Milan Cancer Institute experience. *Ann Oncol* 1991;2(Suppl 1):9–16.
23. Harker WG, Kushlan P, Rosenberg SA. Combination chemotherapy for advanced Hodgkin's disease after failure of MOPP: ABVD and B-CAVe. *Ann Intern Med.* 1984;101:440–446.
24. Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. *Ann Oncol.* 1999;10:593–595.
25. Robinson SP, Goldstone AH, Mackinnon S, et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced intensity allogeneic progenitor cell transplantation: an analysis from the lymphoma working party of the European Group for Blood and Bone Marrow Transplantation. *Blood.* 2002;100:4310–4316.
26. Kewalramani T, Nimer SD, Zelenetz AD, et al. Progressive disease following autologous transplant in patients with chemosensitive relapsed or primary refractory Hodgkin's disease or aggressive non-Hodgkin's lymphoma. *Bone Marrow Transplant.* 2003;32:673–679.
27. Santoro A, Bredenfeld H, Devizzi L, et al. Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II sudy. *J Clin Oncol.* 2000;18:2615–2619.
28. Devizzi L, Santoro A, Bonfante V, et al. Vinorelbine: a new promising drug in Hodgkin's disease. *Leuk Lymphoma.* 1996;22:409–414.
29. Josting A, Rudolph C, Mapara M, et al. Cologne high-dose sequential chemotherapy in relapsed and refractory Hodgkin's lymphoma: results of a large multicenter study of the German Hodgkin's Lymphoma Study Group (GHSG). *Ann Oncol*. 2005;16:116–123.
30. Ansell S, Byrd J, Horwitz S, et al. Phase I/II study of a fully human anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's disease and anaplastic large cell lymphoma. *Blood.* 2003;102 (11, pt 1):181a (abstract 632).
31. Barlett NL, Berstein SH, Leonard JP, et al. Safety, anti-tumor activity and pharmacokinetics of six weekly doses of SGN-30 (anti-CD30 monoclonal antibody) in patients with refractory or recurrent $CD30^+$ hematologic malignancies. *Blood.* 2003;102 (11, pt 1):647a (abstract 2390).

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