Treatment of refractory and relapsed Hodgkin's lymphoma: facts and perspectives

Ercole Brusamolino, Angelo Michele Carella

Clinica Ematologica, Fondazione Policlinico San Matteo IRCCS, Università di Pavia, Italy (EB); Divisione di Ematologia, Centro Trapianto di Cellule Staminali, Azienda Ospedaliera Universitaria San Martino, Genova, Italy (AMC).

E-mail: ebrusa@smatteo.pv.it

The most effective salvage strategy for patients with Hodgkin's lymphoma relapsed or refractory to front-line therapy has yet to be conclusively defined. This problem has evolved in the last years and it is time to reconsider its dimension and to comment on mature data, new facts and perspectives. One of the most important new facts is the introduction of fluorodeoxyglucose positron emission tomography (FDG-PET) evaluation of response during the induction treatment. In patients with advanced-stage or extranodal disease, a positive FDG-PET scan after the first cycles of chemotherapy is highly predictive of progression[1] and can accordingly represent a warning that early alternative or salvage therapy is needed. Early salvage therapy would in turn spare the toxicity of an ultimately ineffective therapy, in view of further more intensive treatments. Another fact that could modify management decisions is the wider use of dose-intensive combinations, such as Stanford V[2] or dose-escalated BEACOPP,[3] as front-line chemotherapy in advanced stages. We do not yet know whether salvage regimens are as feasible or as effective after dose-intensive regimens as they are after less intensive regimens such as the standard ABVD combination. As far as early stage disease is concerned, there is a tendency to reduce or abolish the use of radiotherapy and to adopt a chemotherapy only approach; this raises the problem of local failures in areas not previously irradiated and may re-open the issue of a role for salvage radiotherapy with a curative intent in this category of patients.

The dimension of the problem and the different options

Virtually no cases of early stage disease[4] are resistant to combined modality therapy, and the rate of long-term, progression-free survival is higher than 90%. In advanced stage disease, treatment failures are not evenly distributed across all prognostic subgroups: a study from the International Prognostic Factors Project[5] showed that the risk of resistant or relapsing disease is less than 20% among patients with a prognostic score of 0-1 (30% of total), but that it exceeds 40% among those with four or more adverse prognostic factors (19% of total). About 20-25% of patients with advanced Hodgkin's disease do not achieve a complete remission (primary resistant disease) with the standard front-line ABVD chemotherapy or the alternating ABVD and MOPP regimens, and a proportion of remitters will relapse at different time intervals (relapsed disease). Indeed, the long-term analysis of the CALGB study[6] indicates a 15-year failure-free survival of about 50% for both the ABVD and the alternating ABVD and MOPP treatment cohorts, and a significantly lower probability in the group treated with MOPP alone. Besides, the very long-term analysis (25 years) of the Milan experience[7] indicates an actuarial freedom from progression of 58% for patients treated with the alternating MOPP/ABVD regimen and 31% for those treated with MOPP alone. With more intensive regimens such as Stanford V,[2] MOPPEBVCAD[8] or BEACOPP, either standard or escalated,[3] the percentage of patients with primary refractory disease is lower (about 10%), and the 5-year progression-free survival varies from 80 to 90%. The choice of the best salvage approach should rely on the evaluation of prognostic factors and clinical characteristics of patients; the therapeutic options include conventional-dose salvage chemotherapy, high-dose chemotherapy followed by autologous stem cell transplant (ASCT), and allogeneic stem cell transplant.[9]

The role of standard dose chemotherapy

In a retrospective analysis of the German Hodgkin's Lymphoma Study Group on 513 patients, no patient with primary progressive disease treated with conventional-dose chemotherapy survived more than 8 years, while the projected 20-year survival for patients with early or late relapse was 11% and 22%, respectively.[10] Thus, conventional-dose chemotherapy has virtually no curative potential in resistant or early relapsing Hodgkin's lymphoma, as previously indicated.[11,12] The role of conventional-dose therapy is two-fold: to achieve maximum tumor reduction prior to high-dose chemotherapy (pretransplant debulking), and to efficiently mobilize hematopoietic progenitors cells into the peripheral blood for subsequent autologous rescue. Moreover, conventional-dose chemotherapy should be used in patients who are not candidates for ASCT, because of age and poor performance status. The combination of anti-tumor activity and efficient stem cell mobilizing capacity is a prerequisite for all candidate regimens.[13] Several pretranplant regimens of different intensity and toxicity have been developed; examples of intensive pretransplant salvage chemotherapy are dexa-BEAM[14] and miniBEAM (carmustine, etoposide, cytarabine and melphalan).[15] These regimens produce a fairly good overall response rate (over 50%); however, their activity is associated with substantial toxicity and risk of treatment-related death; besides, they contain melphalan

and carmustine which impair hematopoietic stem cell mobilization and for this reason are not ideal candidate regimens. Non-cross-resistant platinum-based combinations have been devised. The ASHAP[16] (doxorubicin, high-dose cytarabine, cisplatin, methylprednisolone), ICE[17] (ifosfamide, carboplatin, etoposide) and DHAP[18] (cisplatin, high-dose cytarabine and dexamethasone) regimens proved to have both efficacy and capacity to mobilize peripheral blood progenitor cells (PBPC). In particular, the ICE regimen, administered on a bi-weekly dose-dense schedule produced an overall response rate of 88%, with efficient PBPC mobilization. Gemcitabine, a new pyrimidine antimetabolite, was found to be active as a single agent in Hodgkin's lymphoma, with an overall 40% response rate and a favorable toxicity profile in comparison to other cytotoxic agents;[19,20] this antimetabolite was, therefore, incorporated with ifosfamide and vinorelbine into the IGEV regimen.

A contribution to the subject of pretransplant standard dose chemotherapy is provided in this issue of the journal by Santoro *et al*.[21] These authors report on results obtained with four cycles of IGEV in a cohort of 91 patients with refractory (40% of total) or relapsed Hodgkin's lymphoma. The reported complete remission rate (54%) is higher than that obtained with other standard regimens, with a low toxicity profile. Of note is the good complete remission rate in primary resistant disease (33%) and the optimal mobilizing potential of this regimen; these characteristics make IGEV a valid candidate regimen for pretransplant standard-dose chemotherapy.

Because disease status before ASCT is the most important factor predicting the final outcome, the ultimate goal of any pretransplant standard dose chemotherapy should be to achieve a status of minimal or no detectable disease, without prohibitive toxicity and with efficient PBPC harvesting. Again, FDG-PET scan may help to assess the pre-transplant status of disease reliably. Hence, in Pavia, we now use the IGEV combination as a mobilizing and debulking regimen and re-evaluate the disease status with FDG-PET after the fourth cycle; patients who are still PET-positive after IGEV are given further chemotherapy with two cycles of BEACOPP, intensified or standard, to possibly obtain a status of minimal disease or of PET-negativity before ASCT (*unpublished data*).

The superiority of ASCT over standard-dose chemotherapy

The most compelling evidence for a higher failure-free survival after high-dose therapy with ASCT than after conventional-dose therapy in chemosensitive relapses and refractory disease has derived from the BNLI and the European Blood and Marrow Transplantation (EBMT) studies.[22,23] In the first trial, patients were treated with conventional-dose mini-BEAM or high-dose BEAM with ASCT; the actuarial 3-year event-free survival was significantly better in patients who received high-dose therapy (53% versus 10%). In the EBMT trial, patients who relapsed after chemotherapy were randomly assigned to four cycles of mini-BEAM+dexamethasone (dexa-mini-BEAM) or two cycles of dexa-mini-BEAM followed by BEAM and ASCT; the final analysis showed a significantly higher rate of freedom from progression in the BEAM+ASCT group (55% versus 34%). Other non-randomized studies comparing autografting and conventional salvage therapy include the Stanford experience,[24] with a 4-year progression-free survival of 52% and 19% for transplant and standard-dose chemotherapy, respectively, and the French Transplant Registry case-control study,[25] with a 6-year progression-free survival of 25% for transplanted patients and 0% for those treated with conventional chemotherapy. The reduction of transplant-related mortality (TRM) from 10-15% in early experiences to less than 4% in recent studies has led to a widespread acceptance of high-dose chemotherapy followed by ASCT as the standard of care for patients with relapsed or primary resistant Hodgkin's lymphoma. In all experiences, the outcome of patients receiving ASCT for relapsed disease is significantly better than that of patients with primary refractory disease.

The role of ASCT

It has long been observed that the duration of remission after first-line therapy has a significant effect on the success of subsequent salvage treatment. In a multivariate analysis from the German Hodgkin's Lymphoma Study Group,[10] significant risk factors for a worse outcome of relapsed patients were a time to relapse shorter than 12 months, an advanced stage of disease at relapse, and anemia. Large series of ASCT in Hodgkin's lymphoma[26–28] included patients at first relapse and after multiple relapses and clearly demonstrated that two or more lines of therapy before transplantation are adverse prognostic factors for the outcome; therefore, in suitable patients, the ASCT should be performed at first relapse, irrespective of the duration or first remission. The eligibility criteria include age less than 65 years and the absence of concomitant diseases that can be precipitated by the high-dose procedure, such as pulmonary, cardiac or renal insufficiency. The mature results of ASCT carried out at first relapse indicate a progression-free survival rate ranging from 45% to 77%, with an overall survival rate from 50 to 80%;[27,28] the results are significantly better when a second remission or a status of minimal disease is achieved before ASCT, and clearly demonstrate that ASCT is able to cure more than half of patients in first chemosensitive relapse.

Some of the patients failing to achieve a complete remission with first-line therapy can be salvaged by high-dose therapy followed by ASCT; this is particularly true for patients without residual bulky disease and no progression before transplant. A case-control study compar-

ing high-dose therapy and ASCT with conventional therapy for induction failures indicated that ASCT is the best therapeutic option currently available for these patients and that it is associated with acceptable toxicity.[25] Response to second-line treatment before high-dose chemotherapy is the only prognostic factor that can be correlated with survival. Therefore, a number of aggressive pretransplant approaches have been used to achieve a complete remission or at least a status of minimal disease before transplantation. Such approaches include different attempts at intensive debulking before transplantation such as the MSKCC two-step protocol with dose-dense and dose-intense second-line chemotherapy,[17] or a high-dose sequential chemotherapy. In the MSKCC experience, patients resistant to second-line therapy had a 10-year event-free survival of 17% versus the 60% of patients responding to second-line therapy (with at least a 25% decrease of measurable lesions). In the high-dose sequential chemotherapy experience,[29] the complete response rate of primary refractory patients was 42%, with a 5-year event-free survival rate of 33%, which is one of the best results reported to date. Altogether, the mature data of the largest series of ASCT in patients with resistant disease indicate that these patients have a significantly worse outcome than those with relapsed disease, with a progression-free survival rate from 25% to 40% and an overall survival rate from 30% to 40%.[25,28-32]

A mature assessment of late events after ASCT

It is generally accepted that ASCT survivors have an increased risk of secondary malignancies, particularly secondary myelodysplasia/leukemia (MDS/AML);[28,32,33] few studies, however, have a long enough follow-up to address this problem conclusively. Data from the French registry[34] indicate a higher risk (about 9% at 5 years) of developing any second cancer after ASCT than after conventional therapy; however, the risk of MDS/AML is similar in the two cohorts suggesting that this late event is not related to the transplant procedure *per se*, but that the major factor contributing to the development of MDS/AML is the extent of therapy with potentially leukemogenic agents before autografting. A recent long-term analysis from the Vancouver group[32] indicates a cumulative risk of a second malignancy of 9% at 15 years after ASCT. A systematic, prospective evaluation of major organ function is necessary for a correct assessment of the long-term complications of ASCT. Long-term cardiac, pulmonary, and endocrine dysfunction are major concerns; however, their incidence does not seem to differ significantly from that reported in patients with Hodgkin's lymphoma treated with a combined modality approach. Data on the gonadal damage and infertility after ASCT are scanty and, in this perspective, the clinical application of techniques to preserve fertility is warranted.

The role of allogeneic stem cell transplant

Relapse is the most important cause of failure after ASCT; most relapses occur in the first year following autografting, even though recurrences up to 8 years after ASCT have been reported.[35] The median survival for patients relapsing after ASCT is less than 2 years and the most important predictor of outcome is the response to further salvage therapy. This prompted researchers to explore the potential of allogeneic stem cell transplantation which couples the anti-tumor effect of chemotherapy with the adoptive immunologic effect of the graft-versus-lymphoma reaction. The number of allografts performed in Hodgkin's lymphoma is still rather small and results have generally been disappointing, with a TRM varying from 22% to 61% and a very low probability of failure-free survival.[36-38] The reasons for the high TRM may include selection of very high risk patients, previous thoracic radiotherapy and immunologic mechanisms peculiar to Hodgkin's lymphoma. A new enthusiasm for allografting has arisen from the use of allogeneic transplantation with non-myeloablative reduced intensity conditioning which provides sufficient immunosuppression for engraftment and allows a graft-versus-lymphoma effect to develop, with lesser morbidity than after myeloablative allogeneic transplant.[39] Several papers dealing with allogeneic transplantation following reduced intensity conditioning in Hodgkin's lymphoma argue for a graft-versus-lymphoma reaction as the most important therapeutic effect of this approach.[40-43] The EBMT results after reduced intensity conditioning indicate a TRM of 18%, with progression-free and overall survival rates of 35% and 45%, respectively. Half of the patients in this series had relapsed after a prior ASCT and, again, the only significant prognostic indicator was the chemosensitivity of relapse. In a British experience,[42] patients with less than a complete response or progression at 3 months after reduced intensity conditioning received donor lymphocyte infusions, and achieved a 4-year overall survival after transplant of 56%. A strategy of autografting followed by non-myeloablative allografting (tandem transplant) has been designed in Genoa to take advantage of both the anti-tumor and graft-versus-lymphoma effects. In the original study,[40] 17 patients with advanced Hodgkin's lymphoma who had HLA-identical donors received, after ASCT, a reduced intensity conditioning regimen for allografting consisting of fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) for 3 days, followed by the infusion of fresh, not T-depleted allogeneic PBPC mobilized in HLA-identical siblings. Thirteen patients achieved complete donor engraftment (four after donor lymphocyte infusion), three had mixed chimerism and one patient had autologous hematopoietic recovery; 11 patients obtained a major response. The Genoa experience with tandem transplant has thus far been extended to more than 90 patients.

In conclusion, a fraction of patients in whom autotransplantation fails can be rescued with allotransplantation, even though conventional myeloablative procedures are still associated with high morbidity and mortality and have a low curative potential. New perspectives of reducing toxicity and TRM are now being explored with reduced intensity conditioning regimens. The position of allogeneic stem cell transplantation in the salvage therapy algorithm remains a point of debate. To date, the large majority of patients undergoing allogeneic transplants in Hodgkin's lymphoma (either with standard or reduced intensity conditioning) had relapsed after a prior autotransplant. However, in selected cases, such as young, very poor risk patients with HLA-matched sibling donors, the prioritization of allogeneic over autologous transplant might be advantageous. Indeed, the Johns Hopkins's experience[44] with conventional allogeneic transplant in patients who had not had prior autografting has demonstrated a lower relapse rate than in those treated with ASCT, with no relapses or cases of MDS/AML beyond the third year after allotransplant.

New approaches

Among the different experimental strategies being used in the treatment of Hodgkin's lymphoma, antibody-based constructs have given the most promising results in experimental Hodgkin's lymphoma models. Hodgkin's lymphoma is a suitable candidate for monoclonal antibody-based therapy because Reed-Sternberg and Hodgkin's cells of the classical Hodgkin's lymphoma express specific surface antigens such as CD15, CD25 and CD30. Among the different target antigens on Reed-Sternberg cells, CD30 seems to be the most promising, since it is expressed at very high levels. So far, two anti-CD30 monoclonal antibodies have been developed: the humanized SGN-30 and the fully human MDX-60. These anti-CD30 monoclonal antibodies are now being tested in clinical phase I/II studies and have demonstrated a moderate antitumor activity, with no limiting toxicity. Besides, monoclonal antobodies can be utilized in conjunction with chemotherapy and that can prospectively improve their clinical applicability and efficacy. The monoclonal anti-CD20 antibody (rituximab) has demonstrated clinical efficacy in the nodular lymphocyte-predominant variant of Hodgkin's lymphoma, whose cells express this B-cell associated antigen. In relapsed nodular lymphocyte-predominant Hodgkin's lymphoma, a phase II trial with rituximab at the standard dose of 375 mg/m^2 weekly, for 4 weeks, indicated an 86% overall response rate.[45] As far as new drugs are concerned, the proteasome inhibitor bortezomib is now being tested in relapsed or resistant Hodgkin' lymphoma. In heavily pretreated patients,[46] bortezomib, as single agent, has demonstrated only minimal activity; further evaluation in conjunction with chemotherapy in less unfavorable categories of patients is therefore required.

Conclusions

High-dose chemotherapy followed by autologous stem cell transplantation has a definite role in relapsed Hodgkin's lymphoma, with rescue (and possibly cure) in more than 50% of patients. Best results are achieved in chemosensitive relapses, with minimal or no evidence of disease at transplantation. Unfortunately, for the minority of patients refractory to first-line chemotherapy, there are no new drugs to overcome resistance and high-dose procedures with autologous and/or reduced intensity allogeneic transplantation rescue only about 25-30% of patients. New salvage strategies should be explored for this latter category.

References

1. Hutchings M, Loft A, Hansen M, Pedersen Möller L, Buhl T, Jurlande J, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006;107:52-9.
2. Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown W, Rosenberg SA. StanfordV and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol 2002;20:630-7.
3. Diehl V, Franklin J, Pfreundschuh M, Lathan B, Paulus U, Hasenclever D, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med 2003;348:2386-95.
4. Brusamolino E, Baio A, Orlandi E, Arcaini L, Passamonti F, Griva V, et al. Long-term events in adult patients with clinical stage IA-IIA nonbulky Hodgkin's lymphoma treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine and adjuvant radiotherapy: a single-institution 15-year follow-up. Clin Cancer Res 2006;12: 6487-93.
5. Hasenclever D, Diehl V, Armitage JO, Assouline D, Björkholm M, Brusamolino E, et al. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. N Engl J Med 1998; 339:1506-14.
6. Canellos GP, Niedzwiecki D. Long-term follow-up of Hodgkin's disease trial. N Engl J Med 2002;346:1417-8.
7. Bonadonna G, Viviani S, Bonfante V, Gianni AM, Valagussa P. Survival in Hodgkin's disease patients – Report of 25 years of experience at the Milan Cancer Institute. Eur J Cancer 2005;41:998-1006.
8. Gobbi PG, Levis A, Chisesi T, Broglia C, Vitolo U, Stelitano C, et al. ABVD versus modified StanfordV versus MOPPEB-VCAD with optional and limited radiotherapy in intermediate- and advanced-stage Hodgkin's lymphoma: final results of a multicenter randomized trial by the Intergruppo Italiano Linfomi. J Clin Oncol 2005;23:9198-207.
9. Bartlett N. Therapies for relapsed Hodgkin lymphoma: transplant and non-transplant approaches including immunotherapy. Hematology 2005. American Society of Hematology Education Program Book, 2005. p. 245-51.
10. Josting A, Franklin J, May M, Koch P, Beykirch MK, Heinz J, 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;20:221-30.
11. Longo L, Duffey PL, Young RC, Hubbard SM, Ihde DC, Glatstein E, 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;10:210-8.
12. Brusamolino E, Orlandi E, Canevari A, Morra E, Castelli G, Alessandrino EP, et al. Results of CAV regimen (CCNU, melphalan, and VP-16) as third-line salvage therapy for Hodgkin's disease. Ann Oncol 1994;5:427-32.
13. Carella AM, Congiu A, Nati S, Brusamolino E. Treatment of relapsed or refractory Hodgkin's lymphoma and new frontiers in Hodgkin's lymphoma therapy. In: Clinical Malignant Hematology. Sekeres MA (Editor)-McGraw-Hill (in press).

14. Pfreundschuh MG, Rueffer U, Lathan B, Schmitz N, Brosteanu O, Hasenclever D, 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;12:580-6.
15. Colwill R, Crump M, Couture F, Danish R, Stewart AK, Sutton DM, et al. Mini-BEAM as salvage therapy for relapsed or refractory Hodgkin's disease before intensive therapy and autologous bone marrow transplantation. J Clin Oncol 1995; 13:396-402.
16. Rodriguez J, Rodriguez MA, Fayad L, McLaughlin P, Swan F, Sarris A, et al. ASHAP: a regimen for cytoreduction of refractory or recurrent Hodgkin's disease. Blood 1999;93: 3632-6.
17. Moskowitz CH, Nimer SD, Zelenetz AD, Trippet T, Hedrick EE, Filippa DA, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97:616-23.
18. Josting A, Rudolph C, Reiser M, Mapara M, Sieber M, Kirchner HH, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol 2002;13:1628-35.
19. Santoro A, Bredenfeld H, Devizzi L, Tesch H, Bonfante V, Viviani S, et al. Gemcitabine in the treatment of refractory Hodgkin's disease: results of a multicenter phase II study. J Clin Oncol 2000;18:2615-9.
20. Zinzani PL, Bendandi M, Stefoni V, Albertini P, Gherlinzoni F, Tani M, et al. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. Haematologica 2000; 85:926-9.
21. Santoro A, Magagnoli M, Spina M, Pinotti G, Siracusano L, Michiel M, et al. Ifosfamide, gemcitabine, and vinorelbine (IGEV): a new induction regimen for refractory and relapsed Hodgkin's lymphoma. Haematologica 2007;92:35-41.
22. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's disease. Results of a BNLI randomized trial. Lancet 1993; 341:1051-4.
23. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous hemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet 2002;359:2065-71.
24. Yuen AR, Rosenberg SA, Hoppe RT, Halpern JD, Horning JS. Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent or refractory Hodgkin's disease. Blood 1997;89:814-22.
25. André M, Henry-Amar M, Pico JL, Brice P, Didier B, Kuentz M, et al. Comparison of high-dose therapy and autologous stem cell transplantation with conventional therapy for Hodgkin's disease induction failure: A case-control study. J Clin Oncol 1999;17:222-9.
26. Carella AM, Congiu AM, Gaozza E, Mazza P, Ricci P, Visani G, et al. High dose chemotherapy with autologous bone marrow transplantation in 50 advanced resistant Hodgkin's disease patients: An italian study group report. J Clin Oncol 1988;6:1411-6.
27. Reece DE, Connors JM, Spinelli JJ, Barnett MJ, Fairey RN, Klingemann HG, et al. Intensive therapy with cyclophosphamide, carmustine, etoposide±cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy. Blood 1994; 83: 1193-9.
28. Sureda A, Arranz R, Iriondo A, Carreras E, Lahuerta JJ, Garcia-Conde J, et al. Autologous stem-cell transplantation for Hodgkin's disease: Results and prognostic factors in 494 patients from the Grupo Español de Linfomas/Transplante Autologo de Medula Osea Spanish Cooperative Group. J Clin Oncol 2001;19:1395-404.
29. Tarella C, Cuttica A, Vitolo U, Liberati M, Di Nicola M, Cortelazzo S, et al. High-dose sequential chemotherapy and peripheral blood progenitor cell autografting in patients with refractory and/or recurrent Hodgkin lymphoma. Cancer 2003;97:2748-59.
30. Lazarus HM, Rowlings PA, Zhang MJ, Vose JM, Armitage JO, Bierman PJ, et al. Autotransplants for Hodgkin's disease in patients never achieving remission: A report from the Autologous Blood and Marrow Transplant Registry. J Clin Oncol 1999;17:534-45.
31. Sweetenham JW, Carella AM, Taghipour G, Cunningham D, Marcus R, Della Volpe A, et al. High-dose therapy and autologous stem-cell transplantation for adult patients with Hodgkin's disease who do not enter remission after induction chemotherapy: Results in 175 patients reported to the European Group for Blood and Marrow Transplantation. J Clin Oncol 1999;17:3101-9.
32. Lavoie JC, Connors JM, Phillips GL, Reece DE, Barnett MJ, Forrest DL, et al. High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: Long-term outcome in the first 100 patients treated in Vancouver. Blood 2005;106:1473-8.
33. Metayer C, Curtis RE, Vose J, Sobocinski KA, Horowitz MM, Bhatia S, et al. Myelodysplastic syndrome and acute myeloid leukaemia after autotransplantation for lymphoma: A multicenter case-control study. Blood 2003;101: 2015-23
34. André M, Henry-Amar M, Blaise D, Colombat P, Fleury J, Milpied N, et al. Treatment-related deaths and second cancer risk after autologous stem cell transplantation for Hodgkin's disease. Blood 1998;92:1933-40.
35. Armitage JO, Goldstone AH, Carella AM, Schmitz N, Philips G, Bierman PG. Role of bone marrow transplantation in Hodgkin's Disease. In: Hodgkin's Disease. Mauch PM, Armitage JO, Diehl V, Hoppe RT, Weiss LM, eds. Lippincott-Williams and Wilkins 1999. p. 521-30.
36. Anderson JE, Litzow MR, Appelbaum FR, Schoch G, Fisher LD, Buckner CD, et al. Allogeneic, syngeneic, and autologous marrow transplantation for Hodgkin's disease: The 21-year Seattle experience. J Clin Oncol 1993;11:2342-50.
37. Milpied N, Fielding AK, Pearce RM, Ernst P, Goldstone AH. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. European Group for Blood and Bone Marrow Transplantation. J Clin Oncol 1996;14:1291-6.
38. Gajewski JL, Phillips GL, Sobocinski KA, Armitage JO, Gale RP, Champlin RE, et al. Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. J Clin Oncol 1996;14:572-8.
39. Carella AM, Champlin R, Slavin S, McSweeney P, Storb R. Mini-allografts: Ongoing trials in humans. Bone Marrow Transplant. 2000;25:345-50.
40. Carella AM, Cavaliere M, Lerma E, Ferrara R, Tedeschi L, Romanelli A, et al. Autografting followed by nonmyeloablative immunosuppressive chemotherapy and allogeneic peripheral blood hematopoietic stem cell transplantation as treatment of resistant Hodgkin's disease and non-Hodgkin's lymphoma. J Clin Oncol 2000;18:3918-24.
41. Porter DL, Stadtmauer EA, Lazarus HM. GvHD: Graft-versus-host disease or graft-versus-Hodgkin's disease? An old acronym with new meaning. Bone Marrow Transplant 2003; 31:739-46.
42. Peggs KS, Hunter A, Chopra R, Parker A, Mahendra P, Milligan D, et al. Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. Lancet 2005;365:1934-41.
43. Anderlini P, Saliba R, Acholonu S, Okoroji GJ, Donato M, Giralt S, et al. Reduced-intensity allogeneic stem cell transplantation in relapsed and refractory Hodgkin's disease: Low transplant-related mortality and impact of intensity of conditioning regimen. Bone Marrow Transplant 2005; 35:943-51.
44. Akpek G, Ambinder RF, Piantadosi S, Abrams RA, Brodsky RA, Vogelsang GB, et al. Long-term results of blood and marrow transplantation for Hodgkin's lymphoma. J Clin Oncol 2001;19:4314-21.
45. Rehwald U, Schulz H, Reiser M, Sieber M, Staak JO, Morschhauser F, et al. Treatment of relapsed CD20+ Hodgkin lymphoma with the monoclonal antibody rituximab is effective and well tolerated: Results of a phase 2 trial of the German Hodgkin Lymphoma Study Group. Blood 2003; 101: 420-4.
46. Younes A, Pro B, Fayad L. Experience with bortezomib for the treatment of patients with relapsed classical Hodgkin lymphoma. Blood 2006;107:1731-2.