POST ALLOGENIC TRANSPLANT RELAPSE OF HODGKIN LYMPHOMA SAL-VAGED WITH CHEMOTHERAPY AND DONOR LEUCOCYTE INFUSION

VIGNESH KANDA KUMAR BALASUBRAMANIAM
Department of Medical Oncology,
CANCER INSTITUTE (W I A)

Abstract:
The use of non myeloablative and reduced intensity conditioning regimens have greatly reduced the treatment related mortality (TRM) associated with allografting for Hodgkin lymphoma (HL) and disease relapse is now the most common cause of treatment failure. The two major treatment strategies for relapsed HL after allogenic stem cell transplant (SCT) have been salvage chemotherapy and donor leucocyte infusion (DLI). Evidence supporting a potent allogenic graft versus Hodgkin lymphoma (GVHL) effect is increasingly compelling and DLIs have gained a prominent role in the management of HL patients who relapse following allogenic SCT. We report a case of relapsed HL after allogenic SCT salvaged by chemotherapy and adaptive immunotherapy.

Keyword: Recurrent Hodgkin lymphoma, Allogenic stem cell transplant, Donor leucocyte infusion, Immunotherapy

INTRODUCTION:
The prognosis of Hodgkin lymphoma patients who relapse after autologous stem cell transplantation (ASCT) remains dismal. Attempts have been made to salvage these patients with allogenic SCT. Myeloablative allogenic SCT (MAT) for patients with HL have been associated with high treatment related mortality (TRM). However this can be brought down using reduced intensity conditioning transplant (RIC). A central tenet of RICT has been that the initial transplantation procedure should act as a platform for subsequent allogenic graft versus malignancy reactions. Though this strategy has a relatively higher risk of relapse (44% to 81% at 2 to 3 years) the reduced TRM has increased the interest in this area. Management of patients who relapse even after allogenic SCT remains unanswered. The existence of durable responses after the infusion of donor leucocytes, and of somewhat lower relapse rate in patients who develop extensive graft versus host disease (GVHD) indicates a clinically significant graft versus HL
effect. Several factors could contribute to rates and of response following DLI, including disease bulk at the time of DLI and whether relapse occurs in the setting of failed alloreactivity.

CASE REPORT:
In 2006, a 34 year old lady who presented with non bulky bilateral cervical and mediastinal adenopathy was diagnosed to have HL (nodular sclerosis) stage IIA (Computed Tomography scan staged). She was treated with Adriamycin/Bleomycin/Vinblastine/Dacarbazine (ABVD) chemotherapy and attained complete remission (CR) after 4 cycles. She received 6 cycles of ABVD chemotherapy and was kept under follow up. She relapsed after 2 months, was salvaged with 3cycles of Ifosphamide/Carboplatin/Etoposide (ICE) chemotherapy, achieved partial remission (PR) and underwent ASCT after conditioning with Cyclophosphamide/Carmustine/Etoposide (CBV) chemotherapy. She was in PR at end of ASCT, received radiotherapy to neck and mediastinum and kept under follow up from April 2007. In October 2008, she presented with dry cough and positron emission tomography – computed tomography (PET-CT) scan revealed active nodular lesion in left lower basal segment of lung and mediastinal nodes. Multiple bronchoscopic biopsies were inconclusive. She was offered salvage and allogenic SCT, however she opted for oral palliative chemotherapy and received metronomic oral etoposide for 8 months. A repeat PET –CT scan showed stable disease (figure1).

PRE ALLOGENIC SCT-PET CT SCAN (FIG-1)
CT guided FNAC of left lung basal lesion was done which confirmed residual HL. She opted to continue oral chemotherapy and received 3 cycles of oral Cyclophosphamid/Prednisone/Etoposide. In June 2010 she desired to have allogenic SCT, evaluation revealed that she had seroconverted to Hepatitis B (however with normal liver function tests and negative HbeAg status and <20copies/ml of HBV DNA). Growth factor primed non T- cell depleted peripheral blood stem cells (mononuclear cells 4x10^6/kg and CD34 cells 3x10^6/kg) were used from a 6/6 matched sibling donor after conditioning with Fludarabine and Cyclophosphamide. Her disease was active as per PET CT scan at the time of allogenic SCT. She engrafted by day+18, had 95% donor chimerism by day+84, 93% donor chimerism by day+116 and grade I graft versus host disease (GVHD). PET-CT scan on day+116 revealed metabolic CR even though residual left lung basal segment nodular lesion persisted. She had disease free survival of 10 months and presented with relapse (B symptoms and increasing cough) in April 2011. Her PET-CT (figure2) showed active disease in the mediastinum, lung node and also below the diaphragm. Her donor chimerism had dropped to 82% at this point. She was started on gemcitabine and vinorelbine based chemotherapy and received DLI one dose while she was in PR. Repeat PET -CT scan 3 months after DLI revealed both anatomic and metabolic CR including resolution of the left lung basal segment nodular lesion (figure3). Post DLI, donor chimerism increased to 89%.
PRE DLI-PET CT SCAN (FIG-2) POST DLI-PET CT SCAN (FIG-3)

DISCUSSION:

Our patient had proven lung parenchymal involvement by HL which attained both anatomic and metabolic complete remission to salvage chemotherapy and DLI. She also had mixed donor chimerism prior to DLI and is the likely reason for good response to DLI. Peggs et al reported 76 consecutive patients with multiple relapse or refractory HL who underwent RICT. The 4-year cumulative incidence of relapse was significantly lower in group that developed grade 2 to 4 acute/chronic GVHD (22% for group with GVHD vs 53% for group without GVHD). Forty five DLIs (22 for mixed chimerism and 23 for relapse) were administered with overall response rate of 79%. The 4-year relapse incidence in mixed chimeras was only 5%, considerably better than the 43% incidence of relapse in patients who remained relapse-free but were already full-donor chimeras at 9 months post RICT. It is possible that in allogenic setting, there is a possible balance between the GVHL effect of donor T cells and the ability of residual HL cells to dampen donor T-cell responses. This balance could be altered by DLI following allogenic SCT. The reason why DLI works better in mixed chimera group is not clear but might well be related to a resetting of the immune environment in which the donor cells are able to maintain a GVL effect. Functional imaging (PET), particularly in combined modality with computed tomography (PET-CT) analysis may both limit inappropriate therapy for equivocal residual post transplant masses and allow earlier intervention prior to the development of significantly increased volume on CT scans. Again, it remains unclear whether this will improve overall outcome, but it is an area that warrants further study.

In conclusion, DLI is an important option in management of HL patients who relapse after allogenic SCT. DLI may be preceded by salvage chemotherapy to optimize disease control.

REFERENCES:


