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Auto and allotransplant in cutaneous T-cell lymphomas

F. ONIDA

University of Milan, Italy

Cutaneous T-Cell lymphomas (CTCL), a very heterogeneous group of disease-entities, represent 2.2% of all lymphomas, with an incidence of about 0.30/100,000/year, which increases with age. They are more frequent in males than in females (ratio 2.2:1) and in black than in white populations. Among CTCL, mycosis fungoides (MF) represents the prototype and the most common form. The natural history of MF is usually indolent, even though, over time, a stepwise cutaneous evolution is usually observed. Hence, a clinical picture characterized by erythematous macular eruptions can be supplanted by sequential appearances of isolated or generalized patches, plaques and tumours, which correspond to different histopathological stages. In consequence, the prognosis of patients with MF is variable, mainly depending on their age and on the stage of the disease, being obviously poorer in advanced stage and elderly people. Overall, median survival for stage IV CTCL is around 12-15 months.

Sézary Syndrome (SS) is a rare variant of CTCL, representing less than 5% of all CTCL. SS is characterized by pruritus, erythroderma, lymphoadenopathy, blood involvement and a very poor prognosis. According to the TNM classification, patients with SS are all T4/B1, but staging varies from stage III if there is no lymph node involvement to IVB when bone marrow is involved. Therefore SS has a poor prognosis, with a median survival of 2 to 4 years.

Because of such dismal prognosis, also due to the lack of available effective therapies, treatment strategy including autologous and allogeneic hematopoietic stem cell transplantation (SCT) have been increasingly explored in patients with advanced MF and SS. In limited series of patients, autologous SCT has been shown to be effective in obtaining CR, but in all reported cases the duration of clinical response was usually very short. T-cell depletion and autologous SCT has also been investigated, demonstrating the feasibility and safety of this procedure. Results were encouraging, showing that CR was achievable in a significant proportion of patients. Despite a short relapse-free survival, most patients achieved good disease control at the time of relapse.

A role for allogeneic SCT is based on the evidence of anti-MF activity, which has been convincingly demonstrated. Indeed, allogeneic SCT following conventional myeloablative conditioning regimens have been shown to be very effective. However, because patients are often elderly and in poor clinical conditions, only a minority can actually considered for this approach, which is inevitably associated with an undesirable high transplant related mortality. Therefore, allogeneic reduced-intensity conditioning (RIC) HSCT represents an attractive and worth-investigating strategy of cure in this disease setting.

In our Institutions, from September 2000 to May 2006, fifteen patients with advanced mycosis fungoides or Sezary Sindrome underwent RIC allogeneic hematopoietic stem cell transplantation either from HLA-identical sibling, or from HLA-matched unrelated donor, or from unrelated cord blood. Conditioning regimens for patients with HLA-identical sibling included fludarabine/cyclophosphamide/TBI200 up to 2001, then pentostatin/TBI200. Patients who underwent unrelated transplants were treated with melphalan/CP1H/Fludarabine/TBI200 combination. All patients (10 males and 5 females) had a clinical diagnosis of MF (10 pts) or SS (5 pts) confirmed by histopathology, immunohistochemistry and molecular biology. Median age was 48 years (range 38-65). Median time

from diagnosis to transplant was 48 months (range 13 to 252). Disease stage for all patients was from IIIB to IVB. GVHD prophylaxis included oral Cy-A from day 0 to day +100 and oral MMF from day 0 to day +27, then tapered within 2 weeks. The source of donor stem cells was peripheral blood and bone marrow for siblings and MUD, respectively. A complete clinical remission was achieved in 10 patients, whereas 2 patients obtained a VGPR. Five patients died from various complications (3 with progressive disease, 1 in CR e 1 in PR) within a period ranging from 33 days to 8 months after transplant. A full donor chimerism was achieved within 6 months in 8 out of 10 evaluable patients, whereas no engraftment was observed in 2 patients (1 MUD and 1 UCB). 5 patients experienced acute GVHD of grade I-II, while limited chronic GVHD occurred in 7 patients. With a median follow-up of 38 months (range 2-70), ten patients were alive with an estimated overall survival greater than 60% at five years, whereas 7 patients were alive and disease-free at the last follow-up. Based on these highly encouraging results, we conclude that RIC allogeneic HSCT represents a feasible and effective treatment for advanced mycosis fungoides and Sezary Syndrome.