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Tandem transplant in oncohematology

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In this last decade, reduced-intensity conditioning (RIC) regimens have been evaluated as a valid alternative to myeloablative regimens. Storb showed in canine models that low doses of TBI provided sufficient immunosuppression to allow hematopoietic donor cell engraftment without the lethal effects of myeloablative preparative regimens.[1] These preliminary observations together with the antineoplastic effects following DLI, led to the diffuse utilization of RIC as a new strategy, mainly for older patients with or without comorbidities. A first review on RIC was published in 2000;[2] recently Giralt has discussed at the last ASH meeting what was learned over the last 10 years in this field.[3]

Tandem transplant in metastatic breast cancer

We aimed to use HDT and ASCT to achieve maximum tumour reduction in patients before proceeding to RICT. This tactic could provide the benefit of a conventional allograft but with reduction in the typical acute toxicities and associated mortality of myeloablative therapy. Between september 1997 and april 2004, we enrolled 17 patients with metastatic breast adenocarcinoma.[4] Median age was 41 years. To be enrolled the patients had to have evaluable disease but not brain metastases. At time of HDT/ASCT, the patients had received a median of 3 (range 2-5) previous chemotherapy lines; 14 patients had received hormone therapy, and seven patients had undergone radiotherapy on bone lesions. The primary endpoint of this study was to decrease the NRM from the current 20-35% noted after myeloablative allografting. Secondary endopoints included engraftment, donor chimerism, response, disease free survival, incidence of acute and chronic graft-versus-host disease (GVHD), overall survival. The patients received HDT/ASCT at a median of 53 months (range, 14-152) from the diagnosis of breast cancer. No patient died after HDT/ASCT. One patient who had been in complete remission (CR) and two who had been in partial remission before HDT/ASCT remained in complete or partial remission. Of the 14 patients with disease that was non-responsive to previous chemotherapy, three patients achieved partial remission. No NRM was noted in the first 100 days; 13 patients achieved full chimerism. Five patients (29%) developed grade II-III acute GVHD and six patients developed chronic GVHD (five patients with extensive disease) and needed intensive immuno-suppressive therapy. In the absence of acute GVHD, 11 patients received a median number of three DLI, with a total median dose of $3.9x10^7$ CD3/kg (range, $1x10^6$ to $13x10^7$). The median time from transplant to DLI was 55 days (range, 36-189). Three patients who were in partial remission after ASCT, achieved complete remission, and another patient, who had not responded to previous treatments including ASCT, achieved partial response – giving an overall response rate of 24%. The patients who reached CR were alive and well at 2040, 2250 and 2880 days. Two other patients maintained stable disease at 810 and 1200 days after transplant. One patient, who was in CR before tandem transplant, maintained complete remission after ASCT and RICT but died of extensive chronic GVHD and viral encephalitis 1440 days after RICT. At the time of death she was still in remission.

Attainment of remission was gradual. The first signs of clinical responsiveness in patients who reached complete remission began when they developed the first signs of GVHD (days 90, 80 and 110 after RICT) and the maximum response was on days 300, 240 and 390 after RICT.

All patients who responded to treatment achieved full chimerism and developed acute or chronic GVHD before regression of the disease.

In April 2006, five patients (29%) were alive (three with CR and two with stable disease) at a median of 2040 days (range, 810-2880) after RICT. All patients who reached CR responded after full chimerism

and GVHD developed. This finding confirms the existence of a graft-versus-tumour effect. Since the first clinical signs of response in these patients were noted between 80 and 110 days and the maximum response between 240 and 390 days after RICT (after DLI in one patient), these responses must be considered immunological responses and cannot be ascribed to conventional doses of fludarabine and cyclophosphamide. These results might be promising and could open new leads for chemoimmunotherapy of breast cancer.

Tandem transplant in multiple myeloma

Sixteen patients with multiple myeloma (MM) were treated with HDT/ASCT followed by RICT at Ospedale San Martino, Genova (Italy) and IRCCS *Casa Sollievo della Sofferenza*, San Giovanni Rotondo. The median age of the patients was 51 years (range, 36-63). All patients had stage III disease at diagnosis. Thirteen patients (81%) had β2-microglobulin greater than 2.5 mg/ml. Prior to HDT/ASCT, the patients had received a median of 4 cycles (range, 3-9) of vincristine, adriamycin and dexamethasone (VAD) or VAD-related regimens. Five patients (31%) had refractory disease from their first or subsequent line therapies and 11 patients (68%) had responsive disease, including one patient who achieved CR. High-dose melphalan (140 mg/m^2) was given at a median of 43 days (range, 31-95) after mobilization chemotherapy.

At a median of 79 days (range, 46-156) after ASCT, all patients underwent allografting procedure. The preparative regimens consisted of Fludarabine 30 mg/m^2 on days -4, -3, -2 and 2Gy TBI at 7cGy/min by linear accelerator on day –1. A median number of 2,4x10^6 CD34$^+$ cell/kg (range: 1,7–6,8) was infused on day 0. Acute GVHD prophylaxis consisted of mycophenolate mofetil (MMF) (15 mg/Kg orally twice a day until d +30) and cyclosphorine (CSP) (1 mg/kg i.v. throught d +15); subsequently, CSP was administered orally twice a day; on day +90, if GVHD was absent, the dose was tapered by 20% every week. All patients received antiviral, antibacterial, anti-*Pneumocistis carinii* and antifungal standard prophylaxis.

All patients were evaluated after HDT/ASCT and soon before RICT for response. Of 11 patients with responsive disease prior to ASCT, one patient maintained remission and one patient achieved CR from PR; all other nine patients in PR maintained this state; 1/5 no responsive patients achieved PR after ASCT.

The patients were allografted at a median of 79 days (range, 46-156) after HDT/ASCT. Full chimerism occurred in 14 patients (87%). Grade II-III aGVHD occurred in 7 patients (43%). No patient died of aGVHD. Six patients (37%) developed mild and 3 patients (18%) extensive cGVHD, which requiring intensive therapy with CSP, high-dose methylprednisolone (2 mg/kg) or MMF. One patient died of extensive cGVHD, progressive disease and interstitial pneumonitis.

Ten (1 patient after HDT/ASCT and 9 patients after RICT) (62%) of the 16 patients who were not in CR at our 2-step approach achieved CR and 1 (6%) achieved PR with an overall response rate of 68%. The patient who achieved CR after HDT/ASCT subsequently relapsed and died of MM 42 months after RICT. To date, nine patients are in CCR 11-36 months (median, 30), 3 of them are still under immunosuppressive therapy for extensive cGVHD. In all patients the achievement of CR was gradual and a continued regression of mononuclear bands was observed. Eight out of 9 patients who developed acute/chronic GVHD achieved CR. Six patients did not achieve CR and died of progressive disease (5 patients at 4,6,7,10 and 11 months) and progressive disease, infections and extensive cGVHD (one patient at 6 months). Eight patients received a median number of 2 (range, 1-3) DLI with the final dose infused being a median of 2,4x10^7 CD3/Kg (range, 1x10^6-6x10^7). The median time from transplant to DLI was 80 days (range, 42-170). The indication for DLI was disease progression in 3 patients and mixed chimerism in 5 patients. None of 3 patients in relapse/progressive disease attained response; one patient only converted from mixed to complete chimerism.

A very difficult question is how to separate the antimyeloma effects due to the HDT/ASCT and those due to the RICT ± DLI. A randomized trial evaluating HDT/ASCT vs RICT can be fundamental for this matter and it is now ongoing in USA. At this time we can only say that 68% of patients (11/16) treated with the tandem transplants showed tumor response with 10 patients (62%) achieving CR for the first time (1 after ASCT and 9 after RICT) and 1 patient (6%) achieving PR. These results are particularly important if we consider that 15/16 (93%) had never achieved CR before the tandem transplants and 5 patients (31%) had resistant disease after conventional chemotherapy. A good correlation between GVHD and remission was found. Eight of 9 patients (88%) who developed acute/chronic GVHD achieved CR. Differently from our experience, Maloney demonstrated that 5 patients achieved CR after 9 months from RICT without any GVHD suggesting subclinical GVHD or other antitumor effect of this approach may control multiple myeloma.[5] They treated 54 patients with a previously stage II-III (half of these patients resulted relapsed/refractory to previous therapies) with a median follow-up of 552 days after RICT; 78% of patients are surviving. Fifty-seven percent of patients achieved CR and 26% has achieved PR for an overall response of 83%. Despite many of these patients were older than 55 years, this

2-step approach has reduced the acute toxicities of conventional allograft while achieving potent anti-myeloma effects. Badros treated 31 patients with Melphalan 100 mg/m^2 following 1 or 2 prior autografts using identical sibling donors (25 patients) or unrelated donors grafts (6 patients) conditioned with fludarabine/TBI regimen.[6] More than half of patients developed acute GVHD and 61% achieved CR or good PR. Median overall survival was 15 months and it was better in patients who received the RICT as planned consolidation of a single autograft. 2-step approach was also employed by Kroger.[7] These authors treated 17 patients using unrelated or mismatched related donors. The conditioning regimen consisted of fludarabine, melphalan and ATG. Transplant-related mortality at d-100 was 11% and the estimated 2 years overall and disease free survival was 74% and 56%, respectively. The same author achieved similar results in 25 patients with HLA-identical sibling.[8]

In conclusion, all the published studies confirm that HDT/ASCT-RICT procedure is associated with lower TRM than myeloablative allograft alone also in older patients. We and others have confirmed the feasibility of the sequential combination HDT/ASCT-RICT; therefore this 2-step approach deserves further investigation, i.e. by comparing this approach with tandem autografting as recently proposed by Bone Marrow Transplant-Clinical Trials Network (BMT-CTN).

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