Research program

Current situation

Even today, despite the constant improvement of multiple myeloma therapies with new, more effective molecules, multiple myeloma remains incurable for the vast majority of patients with this terrible disease. For the majority of patients, the conceivable survival is on average at least 5 years. In contrast, there is a group of patients (approximately 25-30%) who have a poorer-risk disease, with survival of about 2 to 3 years only. Although this is a heterogeneous disease, certain factors are associated with a poor prognosis. Several recurrent genetic abnormalities such as the del17p13, the t(4;14)(p16;q32), t(14;16)(q32;q23) and t(14;20)(q32;q12), and chromosome 1 abnormalities (del1p and amplification of 1q) are associated with a poorer outcome. Some biological anomalies (increased β2-microglobulin and decreased albumin concentration) included in the International Staging System (ISS) are also associated with a poorer prognosis. For example, diagnosis, patients at Stage III according to the ISS have a median survival of only 29 months, compared to 62 months for patients at Stage I according to the ISS. The same is true for patients with plasma cell leukemia; their prognosis is bleak. For these patients, new therapeutic strategies are necessary, in addition to the current therapeutic arsenal.

Of all the treatments of multiple myeloma, the only curative-intent therapy is allogeneic transplantation of hematopoietic stem cells. However, because of the initial disappointing experiences and significant toxicity, allogeneic transplantation was not considered a standard treatment modality. Since then, allogeneic transplantation has improved with better donor selection, better supporting treatments with more effective

antibiotics, and the results of the allogeneic transplantation have improved in parallel.

Experience of Hôpital Maisonneuve-Rosemont in allogeneic hematopoietic stem cell transplantation in the treatment of multiple myeloma

Over the past 20 years, the department of hematology and oncology at Hôpital Maisonneuve-Rosemont has developed significant expertise in allogeneic hematopoietic stem cell transplantation in the treatment of hematological cancers. More specifically in multiple myeloma, experience was first built with myeloablative preparation regimes that have been associated with higher toxicity [Le Blanc, Bone Marrow Transplant 2001]. In the past 15 years, nonmyeloablative preparation regimes have allowed for significantly reducing certain associated toxicities. Between 2001 and 2010, we conducted a phase II study in 93 *newly* diagnosed multiple myeloma patients who were eligible for transplant [(Ahmad, ASH 2013 #3353; article in preparation)]. These patients, with a 6/6 HLA-compatible sibling donor, received induction chemotherapy (VAD in the years 2001 to 2007 and bortezomib-dexamethasone in the years 2008-2010). Patients without progressive disease received an autologous hematopoietic stem cell transplant conditioned with melphalan at a high dose. After resolution of side effects, patients received a nonmyeloablative allogeneic transplant conditioned with fludarabine and cyclophosphamide. The prophylaxis of graft-versus-host disease (GVHD) included mycophenolate mofetil and tacrolimus weaned quickly in the absence of GVHD. Despite the fact that these patients received induction chemotherapy that would be considered suboptimal today, and the fact that these patients did not receive consolidation or maintenance therapy after their

transplants, impressive results have been observed.

Indeed, the response rates following autologous transplantation after allogeneic transplantation are significantly improved: very good partial response or better from 54% to 86% and partial response or better from 82% to 94%. After a median follow-up of 7 years, the probability of overall survival and progression-free survival at 10 years was 64% and 44%, respectively. The cumulative incidences of grade II-IV acute and extensive chronic GVHD were 9% (95% CI: 4-15%) and 85% (95% CI: 75-91%), respectively. The cumulative incidences of nonrelapse mortality and progression were 10% (95% CI: 3-22%) and 47% (95% CI: 37-58%), respectively. In survivors, the probability of being independent from immunosuppressive treatment was 61% at 5 years and 85% at 10 years.

Thus our strategy of nonmyeloablative allogeneic transplantation in tandem post autologous hematopoietic stem cell transplantation is safe despite significant rates of extensive chronic GVHD which nonetheless seems to have a protective effective on recidivism. The overall survival at 10 years of 44%, as well as progression-free survival of 64%, are notable results. There are areas for improvement, however, such as recurrences, which remain frequent.

Research program

Building on our current experience in allogeneic hematopoietic stem cell transplantation, we focus our research program on the development of cellular therapy for multiple myeloma.

Thanks in part to the fruits of the Chair, a new **research protocol** including nonmyeloablative allogeneic transplantation for multiple myeloma will be opened in the coming months. This is a prospective phase II study with 30 patients ages 65 and

under with newly diagnosed multiple myeloma with a poor prognosis, evaluating the impact of post-allogeneic-transplant bortezomib; the patients will have previously received optimal induction chemotherapy with bortezomib and an autologous transplant of hematopoietic stem cells. The hypothesis of the study is that bortezomib administered after allogeneic transplantation of nonmyeloablative hematopoietic stem cells for poor-risk patients may offset the unfavorable impact on the prognosis of these patients, reduce recurrence, and reduce the incidence of severe chronic GVHD. Indeed, bortezomib is one of the most active agents against multiple myeloma, and recent studies have shown a protective effect against GVHD. The aim is to improve the clinical outcome of patients with a poor prognosis.

The primary objective is to determine the progression-free survival of these patients at 2 years. Secondary objectives include: 1) determining the incidence of toxicity, 2) determining the incidence of acute and chronic GVHD, 3) assessment of response rate and quality of response after allogeneic transplantation and after bortezomib, 4) determining the mortality associated with the allogeneic transplant and the nonrelapse mortality at 100 days and 2 years, 5) determining the overall survival and the incidence of relapse at 2 years, 6) evaluation of minimal residual disease using multi-parameter flow cytometry and 7) prospective evaluation of quality of life after the allogeneic transplantation.

The population will include *newly* diagnosed multiple myeloma patients (according to IMWG criteria) with a measurable disease: 1) paraprotein ≥ 10 g / L, and/or 2) Bence-Jones proteinuria ≥ 200 mg/day, and/or 3) measurement of serum free light chain ≥ 100 mg/L and an abnormal κ/λ ratio. These patients should have a poor-risk disease based on genetics, a high ISS or plasma cell leukemia. Patients ≤ 50 years old, regardless of risk, will also

be included. Patients must also have a compatible donor, related or not. Recruitment for this study will take place from November 2014 to November 2017, and the study will end once the patients have been followed for a period of at least 4 years after the allogeneic transplantation of hematopoietic stem cells.

The future

Despite effective new agents against multiple myeloma, recurrence is the rule. Over the coming years, the guiding thread of the Myeloma Canada Chair’s research on multiple myeloma will revolve around cellular therapy involving these promising new treatment agents as proposed in the above study. The hematopoietic stem cell transplantation team of Hôpital Maisonneuve-Rosemont as well as the proximity of Center of Excellence for Cellular Therapy (CETC) will facilitate collaboration for this kind of project.