SECTION 1 Transplantation in lymphomas

CHAPTER 1

Lymphoma and transplantation: historical perspective

Andrew R. Rezvani

Brief history of hematopoietic cell transplantation

The concept of hematopoietic cell transplantation (HCT) dates back more than 100 years. Writing in the Journal of the American Medical Association in 1896, Quine credited Brown-Séquard and d’Arsonval with proposing the therapeutic infusion of bone marrow to treat leukemia, and summarized anecdotal reports of bone marrow infusion as an adjunct to then-standard treatments such as arsenic for pernicious anemia [1]. Quine also described the first case of inadvertently transmitted blood-borne infection (malaria) in a marrow recipient. Anecdotal reports of marrow infusion continued to appear in the literature, but often used only several milliliters of bone marrow and were unsuccessful [2,3]. Classified animal experiments were carried out by the US Atomic Energy Commission during World War II on the use of HCT to treat radiation exposure (later published in 1950), but these were similarly unsuccessful [4]. The era of modern HCT is generally understood to have originated with the 1949 publication by Jacobson et al. of the observation that mice could survive otherwise lethal irradiation if splenocytes were protected from the radiation and reinfused afterward [5,6]. Subsequent work by Lorenz et al. [7] showed that infusion of bone marrow had similarly protective effects in irradiated mice and guinea pigs. Hematopoietic recovery after marrow infusion was initially hypothesized to derive from a humoral or hormonal factor in the infusate, but in the mid-1950s Main and Prehn and others proved conclusively that donor hematopoietic cells engrafted and persisted in HCT recipient animals [8–11].

The first successful use of HCT to treat leukemia in murine models was reported by Barnes and Loutit in 1956 [12]. These authors outlined the central premises of modern allogeneic HCT: first, that high-dose myeloablative therapy could eliminate hematologic malignancies and, second, that donor hematopoietic cells could mount an immunologic response which would eradicate residual leukemia in the recipient. In 1957, these authors reported that leukemic mice treated with myeloablative irradiation and syngeneic HCT had hematopoietic recovery but died of recurrent leukemia, while mice receiving allogeneic HCT demonstrated eradication of leukemia but died of so-called “secondary disease,” a syndrome of diarrhea and weight loss which would today be recognized as graft-versus-host disease (GVHD) [13,14].

Early efforts at allogeneic HCT in humans were carried out nearly simultaneously by Thomas et al. in the 1950s [15]. However, as the immunologic basis of histocompatibility was poorly understood at the time, these patients did not engraft. In fact, a summary of the first approximately 200 human recipients of allogeneic HCT, published in 1970, found no survivors [16]. During this time, however, a number of breakthroughs in animal models of HCT laid the groundwork for the future success of this approach. Billingham et al. [17,18] described the biological basis of GVHD and alloimmune tolerance, and Uphoff [19] and Lochte et al. [20] described the use of methotrexate to prevent GVHD. Thomas et al. [21,22]
pioneered the use of canine models of allogeneic HCT. Perhaps most importantly, advances in the understanding of histocompatibility in both the human and the dog provided a basis for donor–recipient matching, a critical component of successful allogeneic HCT [23–25].

In the setting of these advances, allogeneic HCT in humans was revisited with greater success. By 1975, the Seattle group of investigators summarized the results of 110 patients with acute leukemias or aplastic anemia who had received allogeneic HCT from HLA-identical sibling donors. While deaths from recurrent leukemia, GVHD, and opportunistic infection were common, this report was the first to describe long-term survivors of allogeneic HCT [26,27]. Up to this point, allogeneic HCT had been reserved for patients with refractory leukemia; with the application of this approach to patients in first complete remission, substantial improvements in survival were seen [28]. With the advent of HLA typing, the first unrelated-donor transplant was performed using an HLA-matched volunteer donor in 1979 [29]. From these beginnings, HCT has become a fast-growing and increasingly widely used treatment approach for malignant and non-malignant hematologic disease [30].

Much of the benefit from allogeneic HCT derives from the immune effect of the graft against residual tumor (the graft-versus-tumor, or GVT, effect). In contrast, autologous HCT functions on the principle of dose escalation and relies entirely on high-dose, supralethal chemoradiotherapy to eradicate disease. Autologous hematopoietic cells are infused to rebuild the marrow and circumvent rejection, and GVHD. While a number of anecdotal reports and case series of autologous HCT appeared in the 1950s and 1960s, the first patients reported to be cured of otherwise lethal malignancies by this approach were described by Appelbaum et al. in 1978 [31,32]. Subsequent studies established autologous HCT as a potentially curative treatment for many lymphomas, and as an effective but not curative treatment for multiple myeloma.

**History of autologous HCT in non-Hodgkin lymphoma**

The curative potential of autologous HCT was first demonstrated in patients with non-Hodgkin lymphoma (NHL) [32,33], and this approach continues to form a cornerstone of management of relapsed NHL, as described in subsequent chapters. The central principles of autologous HCT for NHL were established in the 1980s. Specifically, chemosensitivity is a key determinant of benefit from autologous HCT; Philip et al. [33] reported as early as 1987 that disease-free survival rates were approximately 40% in patients with chemosensitive relapsed NHL, approximately 20% in those with chemotherapy-refractory disease, and nearly zero for patients with primary refractory NHL who had never achieved complete remission. The benefit of autologous HCT in relapsed aggressive NHL was confirmed in a randomized controlled clinical trial comparing standard-dose chemotherapy to high-dose chemotherapy with autologous HCT. The final results of this trial, reported in 1995, showed that both event-free survival (EFS) and overall survival (OS) were superior in the group undergoing autologous HCT (46% vs. 12% for EFS, and 53% vs. 32% for OS) [34]. On the basis of this convincing finding, autologous HCT has come to be considered the standard of care for eligible patients with chemotherapy-sensitive relapsed aggressive NHL.

Autologous HCT has also been studied in patients with indolent NHL, but the historical evidence for benefit is less definitive in this setting than in aggressive NHL. Several trials in the 1990s demonstrated prolonged disease-free survival and possible cure in a subset of patients with indolent NHL undergoing autologous HCT [35,36]. Likewise, a randomized controlled trial of 89 patients published in 2003 showed improved EFS and OS with autologous HCT as compared to conventional chemotherapy alone in patients with relapsed indolent NHL (58% vs. 26% for 2-year EFS, and 71% vs. 46% for 4-year OS) [37]. Despite the positive results of this randomized trial, autologous HCT remains controversial in indolent NHL. The curative potential of autologous HCT in indolent NHL is not universally accepted (in contrast to aggressive NHL), and so there may be greater reluctance to expose patients to the regimen-related toxicities and long-term risks of this approach, which include secondary myelodysplastic syndromes and acute leukemias, which can occur in up to 5% of patients [38]. Additionally, many of the trials supporting autologous HCT in indolent NHL were performed before the advent of rituximab and modern chemoimmunotherapy. For example, treatment with FCR (fludarabine, cyclophosphamide, and rituximab) chemotherapy can produce median disease-free survivals of more than 4 years in patients with relapsed NHL.
indolent NHL [39]. In the setting of highly active conventional chemotherapy regimens, the appeal of autologous HCT in indolent NHL is reduced. Nonetheless, historical data do support its efficacy as a treatment option, particularly for patients with short remission durations or suboptimal responses to conventional chemoimmunotherapy.

History of autologous HCT in Hodgkin lymphoma

While Hodgkin lymphoma (HL) is among the most curable forms of cancer with upfront treatment, the minority of patients who relapse or who have primary refractory HL have a grim prognosis with conventional chemotherapy alone. Reports of the successful use of autologous HCT in HL began to appear in the literature in the mid-1980s [40–44]. On the basis of these uncontrolled and generally single-institution studies, relapsed HL quickly became one of the most common indications for autologous HCT. As with NHL, chemosensitivity at relapse was felt to be one of the most important determinants of likelihood of cure after autologous HCT.

Since autologous HCT had already entered widespread use, two randomized controlled trials comparing conventional chemotherapy with autologous HCT were performed in the 1990s. The British National Lymphoma Investigation randomized a total of 40 patients with relapsed or refractory HL to receive either BEAM conditioning (carmustine, etoposide, cytarabine, and melphalan) followed by autologous HCT, or reduced-dose BEAM alone. The trial was initially intended to enroll a larger number of patients, but it proved impossible to accrue patients for randomization due to insistence on the part of both patients and physicians for autologous HCT. The trial was thus closed early and suffered from severely limited statistical power, with only 20 patients in each arm of the randomization. Upon publication in 1993, statistically significant differences were seen in EFS in favor of the transplant arm, although the difference in OS did not reach statistical significance [45].

Separately, the European Society for Blood and Marrow Transplantation (EBMT) conducted a randomized clinical trial comparing chemotherapy alone to autologous HCT in 161 patients with chemosensitive relapsed HL, published in 2002. As with the earlier randomized trial, the EBMT group reported significantly superior EFS, but not OS, with autologous HCT [46]. While neither study showed a statistically significant OS benefit with autologous HCT, the benefit in EFS was felt to be convincing and the studies were acknowledged to be limited in statistical power to detect differences in OS. Thus, on the basis of the earlier uncontrolled trials and these two randomized trials, autologous HCT has become an accepted standard of care for eligible patients with chemosensitive relapsed HL. Additional aspects of autologous HCT for HL, including more recent developments, are covered in more detail in Chapter 18.

History of allogeneic HCT in lymphoma

Historically, autologous HCT has been far more widely employed than allogeneic HCT in the treatment of lymphomas, in part because the earliest clinical trials were unable to definitively establish the existence of an alloimmune graft-versus-lymphoma effect [47]. Likewise, autologous HCT was viewed as more feasible in lymphomas than in leukemias because of the lower incidence of malignant bone marrow involvement in the former. Subsequent experience, however, indicated that tumor contamination of autografts in lymphoma patients contributed to post-transplant relapse [48], underscoring the potential benefit of tumor-free allogeneic grafts in these diseases. Even more importantly, further clinical trials confirmed the existence of potent graft-versus-lymphoma effects [49], underscoring the potential benefit of allotransplantation in lymphoma.

The initial experience with allogeneic HCT in NHL involved the use of myeloablative conditioning with high-dose total body irradiation (TBI) or the combination of busulfan and cyclophosphamide (BU/CY). As a consequence of the intensity of conditioning, allogeneic HCT was generally restricted to patients who were young and healthy enough to tolerate the regimen-related toxicities. These demographics included some patients with HL and aggressive NHL, but excluded the vast majority of indolent NHL patients, who tended to be older at the time of diagnosis. However, even in this young and relatively healthy population, the regimen-related toxicity and transplant-related mortality of allogeneic HCT was substantial, if not prohibitive, ranging from 25 to 50% [47,49–51]. This degree of transplant-related mortality was out of proportion to that seen in leukemia.
cohorts. Acute and chronic GVHD incidences were no higher than those seen with other transplant indications; the majority of non-relapse deaths in these early trials stemmed from pneumonitis and pulmonary injury, likely because many patients had previously undergone radiation therapy to the chest and were thus predisposed to further pulmonary compromise.

As noted above, the reliance on intensive myeloablative conditioning precluded the vast majority of patients with indolent NHL, who tended to be older and more heavily pretreated than patients with HL or aggressive NHL. In fact, as of 1990, only a total of seven allogeneic transplants for indolent NHL had been reported in the literature [52–54]. Allogeneic HCT was generally not performed for indolent NHL because of good results with conventional therapies, advanced patient age, and the prohibitively high risk of transplant-related mortality.

The most important development in the use of allogeneic HCT for lymphomas has been the introduction of reduced-intensity and non-myeloablative conditioning regimens. These regimens, pioneered by various groups including McSweeney et al. [55] in Seattle, Khouri et al. [56] at M.D. Anderson Cancer Center, and Lowsky et al. [57] at Stanford (among others), are based on the principle that immunologic graft-versus-lymphoma effects rather than conditioning agents are responsible for the majority of benefit from allogeneic HCT. While the specific agents used in reduced-intensity conditioning regimens vary, they are generally selected to permit donor hematopoietic engraftment with minimal regimen-related toxicity. These regimens have little or no intrinsic antitumor effect and instead serve the role of facilitating donor engraftment.

Lymphomas were a natural target disease for newly developed reduced-intensity conditioning regimens, given the older age of the patient population and the high transplant-related mortality seen with myeloablative approaches. Perhaps most importantly, reduced-intensity conditioning made it possible to perform safe allografting in patients who had previously undergone high-dose chemotherapy and autologous HCT (as is common in the course of lymphoma treatment). The prior experience in attempting myeloablative allogeneic HCT in lymphoma patients after a previous autograft was dismal, with a 2-year disease-free survival after allotransplantation of zero [58]. In contrast, non-myeloablative and reduced-intensity regimens quickly proved capable of producing donor engraftment with acceptable regimen-related toxicity in patients with prior autologous HCT.

Over the past 15 years, an extensive literature has arisen describing the successful use of non-myeloablative or reduced-intensity allogeneic HCT to treat lymphoma. These results are described in detail in later chapters, but the overarching theme is that allogeneic HCT is increasingly part of the treatment algorithm for patients with relapsed and refractory lymphomas. For most types of aggressive NHL and for HL, autologous HCT is still generally a standard of care for patients with a first chemosensitive relapse. However, some groups have incorporated allogeneic HCT into the upfront management of patients with indolent NHL because of good results with conventional therapies, advanced patient age, and the prohibitively high risk of transplant-related mortality.

Lymphomas were a natural target disease for newly developed reduced-intensity conditioning regimens, given the older age of the patient population and the high transplant-related mortality seen with myeloablative approaches. Perhaps most importantly, reduced-intensity conditioning made it possible to perform safe allografting in patients who had previously undergone high-dose chemotherapy and autologous HCT (as is common in the course of lymphoma treatment). The prior experience in attempting myeloablative allogeneic HCT in lymphoma patients after a previous autograft was dismal, with a 2-year disease-free survival after allotransplantation of zero [58]. In contrast, non-myeloablative and reduced-intensity regimens quickly proved capable of producing donor engraftment with acceptable regimen-related toxicity in patients with prior autologous HCT.

General historical considerations

No historical perspective on HCT would be complete without discussion of improvements in supportive care. Much of the improvement in outcomes with both allogeneic and autologous HCT over the past decades is due to the advent of more effective antimicrobials, surveillance strategies against opportunistic infection, blood-product support, and management of regimen-related toxicities. Common opportunistic infections in the post-transplant period include cytomegalovirus (CMV) reactivation and invasive fungal infections such as pulmonary aspergillosis. In the early days of HCT, these complications were feared and nearly universally fatal. Substantial progress has been made in monitoring CMV reactivation and in determining appropriate thresholds for preemptive antiviral therapy to prevent the development of CMV disease. Likewise, potent modern antifungals such as the triazoles and echinocandins have improved our ability to treat invasive fungal infections, while imaging and endoscopic diagnosis of these infections has improved our ability to detect them.
Substantial progress has been made in the prevention of acute GVHD, with a number of novel prophylactic regimens supplementing standard and proven approaches such as tacrolimus plus methotrexate. In contrast, chronic GVHD remains a poorly understood entity which has proven challenging to prevent or treat, despite decades of clinical investigation.

A recent analysis of transplant outcomes over time confirmed significant reductions in transplant-related mortality and improvements in overall survival over time [61]. Strikingly, the incidence of hepatic acute GVHD, one of the most lethal complications of allogeneic HCT, has declined dramatically over the past 10–15 years. Various explanations have been proposed for this decline, ranging from the increasing use of reduced-intensity and non-myeloablative conditioning regimens to better donor and patient selection to the now-wide-spread use of prophylactic ursodiol [62]. Regardless, from a historical perspective, improvements in supportive care have transformed HCT and significantly improved outcomes across the range of transplant indications [61].

References

1 Quine WE. The remedial application of bone marrow. JAMA 1896;26:1012–16.
3 Morrison M, Samwick AA. Intramedullary (sternal) transfusion of human bone marrow. JAMA 1940;115:1708–11.


