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Artículo de revisión

Autograft versus tumor effect

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RESUMEN

La ventaja terapéutica de los trasplantes alogénicos de células madre se atribuye al efecto contra tumor que producen las células efectoras de la inmunidad del donador para erradicar las células tumorales. Sin embargo, la respuesta inmunitaria que producen las células efectoras de la inmunidad del donador no es específica, lo que no sólo crea el efecto de injerto contra tumor, sino también efectos perjudiciales de la enfermedad de injerto contra anfitrión. Los estudios recientes reportan que la infusión de linfocitos "espectadores" de autoinjerto de células madre se correlaciona con la recuperación de linfocitos y los resultados clínicos de pacientes en proceso de implante autólogo de células madre; algo parecido al efecto de injerto contra tumor visto en el trasplante alogénico de células madre, sin los efectos negativos de injerto contra anfitrión. La evidencia de que las células efectoras de la inmunidad del huésped recogidas al mismo tiempo que las células madre pueden mejorar los resultados clínicos después del implante autólogo de células madre, sugiere que el autoinjerto puede considerarse no sólo una estrategia terapéutica para recobrar la función de la médula ósea después de aplicar altas dosis de quimioterapia, sino también como una intervención de inmunoterapia adoptiva capaz de erradicar las células tumorales en pacientes con cáncer. En este artículo se revisa la manera de mejorar la recolección de células efectoras de la inmunidad del anfitrión, las diferentes células efectoras de la inmunidad recolectadas e infundidas desde autoinjerto de células madre y su asociación con el resultado clínico después de implante autólogo de células madre.

Palabras clave: efecto contra tumor, autoinjerto, células madre.

ABSTRACT

The therapeutic benefit reported from allogeneic stem cell transplantation is attributed to the graft versus tumor effect produced by the infused donor immune effector cells to eradicate tumor cells. However, the immune response produced by the donor immune effector cells is not specific creating not only the graft versus tumor effect, but also the detrimental effects of graft versus host disease. Recent reports have shown that the infusion of collected "bystander" lymphocytes from the stem cell autograft correlates with lymphocyte recovery and clinical outcomes in patients undergoing autologous stem cell transplantation (ASCT), similar to the graft versus tumor effect seen in the allogeneic stem cell transplantation without the adverse effects of graft versus host disease. The discovery that host immune effector cells collected at the same time as the stem cells can improve clinical outcomes post-ASCT, suggest that autograft can be viewed not only as a therapeutic maneuver to recover bone marrow function after deliver high-dose chemotherapy, but also as an adoptive immunotherapeutic intervention capable of eradicating tumor cells in cancer patients. In this article, we review how to enhance host immune effector cells collection, the different immune effector cells collected and infused from the stem cell autograft, and their association with clinical outcome post-ASCT.

Key words: Graft versus tumor effect, stem cell.

Graft versus tumor effect created by the infusion of allo-reactive donor immunocompetent cells is the mechanism of action used in allogeneic stem cell transplantation to eradicate tumor cells.[1] Thus, allogeneic stem cell transplantation is viewed more as an immunotherapy rather than a cytotoxic therapeutic modality limited to high-dose chemotherapy.[1] However, the allogeneic immune response is not specific as the infused donor immunocompetent cells producing graft versus tumor effect are also responsible for the development of graft versus host disease.[2] The transplant-related mortality documented in allogeneic stem cell transplantation has been reported between 20 to 50%; in contrast to 3% observed in the autologous stem cell transplantation (ASCT).[2] Therefore, current research attention in allogeneic stem cell transplantation is targeted at eliminating graft versus host disease and maximizing graft versus tumor effect.

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In comparison to allogeneic stem cell transplantation, the high-dose chemotherapy used in ASCT is considered to be the sole mechanism of action to eliminate resistant tumor clones that survived standard chemotherapy because of the presumed lack of an autologous graft (autograft) versus tumor effect that parallels the graft versus tumor effect reported in allogeneic stem cell transplantation.[2] However, our published studies reporting that the recovery of absolute lymphocyte count (ALC) post-ASCT is associated with superior clinical outcomes without the development of the detrimental effects of graft verus host disease suggest the possibility of an autograft versus tumor effect.[3] In addition, the discovery that the early ALC recovery post-ASCT, as a surrogate marker of host immunity in ASCT, is directly dependent on the absolute amount of infused bystander lymphocytes (immune effector cells) harvested during CD34+ stem cells collection leads to the conclusion that manipulation of the immunocompetent effector cells in the autograft can affect not only immune recovery but also clinical outcomes in the post-ASCT setting.[4, 5] In this article, current evidence for an autograft versus tumor effect in ASCT is reviewed.

Table 1. Diseases associated with superior survival by absolute lymphocyte recovery post-autologous stem cell transplantation

I. Leukemia		
	A) Acute myelogenous leukemia	
II. Lymphomas		
	A) B-cell non-Hodgkin's lymphoma	
		1) Diffuse large B-cell lymphoma
		2) Mantle cell lymphoma
	B) T-cell non-Hodgkin's lymphoma	
	C) Hodgkin lymphoma	
		1) Classical
III. Plasmaproliferative disorders		
	A) Multiple myeloma	
	B) Primary systemic amyloidosis	
IV. Solid tumors		
	A) Metastatic breast cancer	
	B) Ovarian cancer	

Lymphocyte count recovery post-autologous stem cell transplantation

We studied the absolute lymphocyte count (ALC) recovery, as a surrogate marker of host immunity, in the post-ASCT setting and its association with clinical outcomes. We were the first to report superior overall survival and progression-free survival in patients with multiple myeloma and non-Hodgkin lymphoma that recovered higher ALC on day 15 (ALC-15) after ASCT.[6] We subsequently reported similar observations in patients with other hematological malignancies[7-10] and solid tumors.[11] Our findings were then confirmed by independent groups (see Table 1).[12-17] The association between ALC-15 and superior survival post-ASCT suggests, for the first time in the autologous stem cell transplant literature, that patients own (autologous) immunity has anti-tumor activity that is not disease specific.[2,3] More importantly, ALC-15 was not associated with the development of GVHD favoring a more-specific immune response against the tumor and not the host in the ASCT setting.[2,3] We confirmed the prognostic ability of ALC-15 for survival post-ASCT prospectively.[18]

Sources of lymphocyte recovery post-autologous stem cell transplantation

The source of hematologic and immune cells recovery post-allogeneic stem cell transplantation is the donor infused stem cells and immune effector cells. In ASCT, the hematologic recovery is directly dependent on the infused CD34 + stem cells. However, we published that the infused CD34+ stem cells do not correlate with ALC-15 post-ASCT, suggesting another possible source for immune recovery in the ASCT setting. Two possible sources for ALC-15 recovery post-ASCT can be divided into two categories: a) the host lymphocytes surviving the high-dose chemotherapy and b) the infused of bystander lymphocytes collected from the stem cell autograft.[2] The host lymphocytes surviving high-dose chemotherapy most likely do not contribute to ALC-15 recovery post-ASCT because without stem cell rescue these patients remained with myelosuppression for a prolonged period of time. To identify host lymphocytes is more difficult in comparison with Allo-SCT where the development of mixed chimerism in allogeneic stem cell transplantation allows discrimination of host versus donor lymphocytes. Such

discrimination is currently not possible in ASCT in the absence of marking studies for host lymphocytes.

The second possible source for ALC-15 recovery post-ASCT is the bystander lymphocytes collected and infused from the stem cell autograft.[2] We reported a strong correlation between the infused autograft lymphocyte numbers [autograft absolute lymphocyte count (A-ALC)] and ALC-15 recovery. Patients infused with autograft containing higher A-ALC recovered greater numbers of ALC-15, resulting in better survival post-ASCT.[19,20] An infused A-ALC $\geq 0.5 \times 10^9$ lymphocytes/kg was associated with a superior survival post-ASCT. This finding has been supported by other investigators.[21]

These data suggest, for the first time, that the ASCT stem cell autograft should not be viewed only for bone marrow rescue procedure to harvest CD34 stem cells necessary for hematologic engraftment, but also an adoptive immunotherapeutic maneuver in which autograft lymphocyte content directly affects tumor-related clinical outcomes in multiple clinical settings.

The association between A-ALC and ALC-15 provides the first clinical evidence of an autograft versus tumor effect as the infusion of autograft lymphocytes has a direct impact on immune reconstitution and survival post-ASCT, similar to the graft versus tumor effect observed in allogeneic stem cell transplantation from the infused donor immune effector cells.[3] Therefore the identification of the specific immune effector cell(s) infused from the autograft could be used as an immunotherapeutic strategy to improve immune recovery and survival post-ASCT.

Immune effector cells collected in the autograft

Until the discovery that A-ALC affects ALC-15 recovery translating into clinical outcomes post-ASCT, the stem cell autograft in ASCT was only viewed as the means to collect enough stem cells to achieve hematologic rescue (hemoglobin, white blood cells and platelets) post-ASCT. However, the reported superior clinical outcomes based on the infusion of A-ALC collected in the autograft suggest that the autograft can be used as an immunotherapeutic modality to improve survival in patients undergoing ASCT. Therefore, the identification of the immune effector cells collected in the autograft will aid to tailor immune therapies to improve immune recovery and survival post-ASCT.

Schmidmaier et al[22] reported better event-free survival in multiple myeloma (MM) patients infused with higher numbers of $CD4^+$ helper T lymphocytes (HTL). Patients with a high percentage of HTL infused experienced a prolonged event-free survival (EFS) (2179 ± 170 versus 1670 ± 212 days, $P < 0.003$). CD4 + T-cells with low HLA-DR expression compared with those that were HLA-DR+ produced a better EFS and overall survival. Infusion of multiple myeloma cells from the autograft did not affect survival, suggesting that the relapse post-ASCT is due to the number of malignant cells surviving the high-dose chemotherapy in the host and not due to the malignant cells infused from the autograft.[23]

The infused autograft $CD8^+$ T cells have been associated with early lymphocyte recovery (ELR) post-ASCT. Defining ELR as an ALC ≥ 500 cells/µl at day 12 post-ASCT, Atta et al[24] reported a faster ELR in patients infused with a $CD8^+$ autograft lymphocyte dose of 0.1×10^9/kg. The authors stated that the autograft $CD8^+$ lymphocyte dose can be used as a marker of a faster ELR, thus translating in better clinical outcomes post-ASCT.

Natural killer (NK) cells have shown to be the earliest lymphocyte subset that recovered early post-allogeneic stem cell transplantation and post-ASCT.[2] We reported that the dose of infused autograft NK cells directly correlated with day 15 absolute NK cells counts (NK-15) post-ASCT.[25] Patients with an NK-15 ≥ 80 cells/µl experienced superior OS and PFS compared with those who did not (median OS: not reached versus 5.4 months, $p<0.0001$; and median PFS: not reached vs 3.3 months, $p<0.0001$, respectively).[18]

Dendritic cells (DC) are the antigen-presenting cells required for priming of naïve T-cells. DCs that express CD11c are classified as DC1 and they have a myeloid morphology and, when stimulated with tumor necrosis factor, produce high levels of interleukin-12 causing antigen naïve $CD4^+CD45RA^+$ T-cell differentiation to Th1 cells.[27] DC2, known as plasmacytoid DCs, has a CD11c-/CD123+ phenotype and they are the precursors of lymphoid DCs and serve to stimulate antigen naïve $CD4^+CD45RA^+$ T cells to differentiate into Th2 cells.[26] Dean et al[26] reported that the total number of collected and infused DCs affect survival post-ASCT. For patients infused with a DC dose $\geq 9.10 \times 10^6$/kg, the median OS was not reached compared with a median OS of 11.5 months for patients infused with a DC dose $< 9.10 \times 10^6$/kg ($p< 0.022$).[27] More interesting, for patients infused with DC1 ≥ 4.00×10^6/kg, the median OS was also not reached versus

11.3 months for patients infused with a DC1 dose < 4.00 x 10^6/kg. No association with survival was observed with infused DC2.[26] This finding suggests that the polarization of the host immunity towards an anti-tumor Th1 response (DC1) conveyed a superior survival than a Th2 anti-tumor down regulating immune response (DC2).

A great variety of immune effector cells are collected in conjunction with stem cells in the autograft providing a platform for research endeavors to create immunotherapeutic trials to improve clinical outcomes in ASCT.

Autograft immune effector cells collection

The collection of CD34 stem cells through the peripheral blood is directly dependent on the available circulating CD34 stem cells at the time of collection. Therefore, it is logical to assume that the collection of A-ALC will depend on the peripheral blood ALC at the time of collection (PC-ALC). We identified a positive correlation between PC-ALC and A-ALC.[20,21] Thus, any interventions that might result in pre-collection lymphopenia may negatively impact on A-ALC collection. This has been shown in multiple myeloma patients. Multiple myeloma patients' cells mobilized with granulocyte-colony stimulating-factor (G-CSF) and cyclophosphamide collected less A-ALC compared with multiple myeloma patients' cells that were mobilized with G-CSF alone.[27]

However, the combination of other cytokines with G-CSF may translate into higher numbers of circulating lymphocytes leading to higher numbers of A-ALC with the hope of faster immune recovery and improved clinical outcomes post-ASCT.

Interleukin-2 (IL-2) has been used in combination with G-CSF to mobilize NK cells to collect in the autograft. Sosman et al[28] found higher NK cell recovery by day 14 post-ASCT in patients in the IL-2 + G-CSF group. Other combinations of NK cells specific cytokines such as interleukin-15[29] and interleukein-21[30] could be studied to assess their ability to mobilize NK cells for harvesting in the autograft. Plerixifor is a CXCR4 inhibitor that has been approved for stem cell mobilization. In addition, we reported that Plerixifor can also enhance lymphocyte mobilization for harvesting with the hope to improve immune recovery post-ASCT.[31] The number of apheresis collections is determined by the target dose of collected CD34 stem cells. Similarly, patients that had ≥ 4 apheresis collection harvested more lymphocytes compared with those who collected in less than 4 apheresis collection.[27] Thus the number of collection could be used as a strategy to achieve a target dose of A-ALC to maximize immune recovery and survival post-ASCT.

Another maneuver to enhance lymphocyte collection during apheresis is to reset the apheresis machine to not only collect enough $CD34^+$ stem cells but also high numbers of A-ALC. Three apheresis machines have been used for stem cell collection in the ASCT setting including the COBE Spectra, the Fenwall CS 3000, and the Baxter Amicus. We identified that patients collected by the COBE Spectra collected more A-ALC than the other two machines and better survival post-ASCT was observed in patients collected by the Spectra machine compared to the others.[32] The survival benefit observed by the Spectra machine was not due to the machine itself; instead it was due to the fact that the Spectra machine collected more A-ALC. We are currently studying if modifying the apheresis machine settings not only collect enough CD34 stem cells, but also more A-ALC to affect survival post-ASCT.

Figure 1 summarizes strategies to optimize and deliver autologous immune effector cells. The first is to develop specific autologous immune effector cells mobilization regimens in conjunction with stem cell mobilization. The second is to modify the autograft collection process to collect a targeted A-ALC.

CONCLUSIONS

The superior clinical outcomes post-ASCT reported by the A-ALC affecting ALC-15 introduce a new understanding of stem cell autograft as an adoptive immunotherapeutic

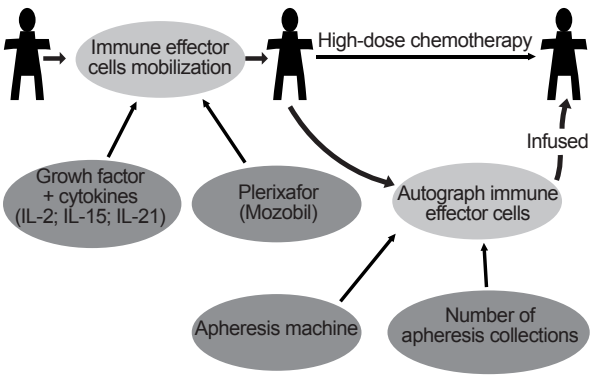

Figure 1. Schematic representation depicting strategies to engineer and deliver autologous immune effector cells.

strategy with direct impact on survival post-ASCT. Furthermore, the autograft versus tumor effect produced by the infused autograft immune effector cells is tumor specific as none of the detrimental side effects of GVHD have been reported. Further studies are warranted to understand how the host immunity improves survival post-ASCT.

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