

Is there a Future for Haematopoietic Cell Transplants?

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Summary

Recent advances in anti-cancer chemotherapy and in targeted and immune therapies raise the question whether there is a future for haematopoietic cell transplants. I discuss their importance but in the end the magnitude of these improvements is modest. I point out the efficacy of immune therapy is predominately restricted to B-cell cancers and that many if not most successful immune therapy recipients eventually receive an allogeneic haematopoietic cell transplant, especially those with acute lymphoblastic leukaemia (ALL). I also discuss most allotransplants are done for cancers not treated with current immune therapy. Randomized trials show an autotransplant is better than new drugs

in young persons with plasma cell myeloma. Considerable data indicate much of the efficacy of allotransplants results from a non-cancer-specific allogeneic effect not expected to operate with current immune therapies. Lastly, I discuss a role for donor-derived chimeric antigen receptor (CAR)-T-cells in persons relapsing after an allotransplant for B-cell cancers. The sum of these considerations suggest an ongoing role for haematopoietic cell transplants in diverse settings.

Keywords

Hematopoietic stem cell transplantation, targeted drugs, immune therapy, (CAR)-T cells, efficiency.

This paper is based on the lecture held at the R. Gorbacheva Memorial Meeting in Hematopoietic Stem Cell Transplantation and Gene Therapy (Sept 19, 2020, St. Petersburg, Russia)

Background

Haematopoietic cell transplants are increasingly done to treat blood and bone marrow cancers, bone marrow failure and genetic disorders. In the US there were about 14,000 autotransplants and 9,000 allotransplants in 2018. Global autotransplants in 2019 were about 28,000 and allotransplants, about 17,000 with a total of about 45,000. These rates are expected to increase. In the US most autotransplants are for plasma cell myeloma (PCM) and non-Hodgkin lymphoma (NHL) whereas most allotransplants are for acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS). Relatively few allotransplants were done for acute lymphoblastic leukaemia (ALL) or myelo-proliferative neoplasms

(MPNs; Table 1). This distribution is important as most immune therapies are for cancers not currently treated with haematopoietic cell transplants as I discuss below.

Table 1. Indications for haematopoietic cell transplants in the US 2018
(<https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx>)

Plasma cell myeloma	9,000	Autotransplant
NHL	3,500	Autotransplant
AML	3,500	Allotransplant
MDS/MPN	2,000	Allotransplant
ALL	1,500	Allotransplant

Discussion

Recent interventions which might compete with haematopoietic cell transplants include new anti-cancer chemotherapy and targeted and immune therapies. Several new drugs used to treat blood and bone marrow cancers are listed in Table 2.

Table 2. Some new drugs for blood and bone marrow cancers

Venetoclax
CC-486
Glasdegib
Nelarabine
Calasparginase
Clofarabine
Vyexos
Bendamustine
Omacetaxine mepesuccinate
Bortezomib
Carflizomib
Ixazomib

Although progress in developing new drugs is encouraging the magnitude of benefit with several of these drugs is modest. An example of the impact of azacitidine and venetoclax in newly diagnosed persons with AML judged inappropriate to receive intensive chemotherapy is shown in Figure 1. Although adding venetoclax to azacitidine significantly improved survival, 65% of subjects died by 2.5 years.

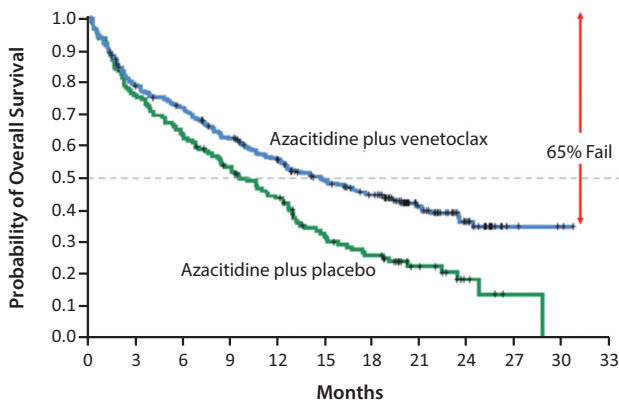


Figure 1. Results of a randomized trial of azacitidine with or without venetoclax in persons with newly diagnosed AML judged inappropriate to receive intensive chemotherapy [1]

Table 3 shows the 5-year survivals of persons with AML and PCM treated in 1999-2003, and treated 2010-2016. These data indicate only a modest improvement with about 70 percent of persons with AML and 45 percent of those with PCM dying before 5 years.

Examples of targeted therapies for myeloid cancers, especially AML are shown in Table 4 along with the target gene.

Table 3. 5-year survivals of persons with AML and PCM by therapy interval (<https://seer.cancer.gov/>)

	1999-2003	2010-2016
AML	21%	29%
PCM	43%	54%

Table 4. Some targeted therapies for myeloid cancers

Midstarin	FLT3
Gilteritinib	FLT3
Sorafenib	FLT3
Enasidenib	IDH2
Ivosidenib	IDH1
Ruxolitinib	JAK2
Fedratinib	JAK2

An example of the impact of targeted *FLT3* mutation therapy in AML is shown in Fig. 2 [2]. Although adding midostaurin to cytarabine and daunorubicin improves survival, 55 percent of subjects died by 5 years and many survivors also received an allotransplant in 1st remission. These data indicate a modest impact of targeted therapy in AML.

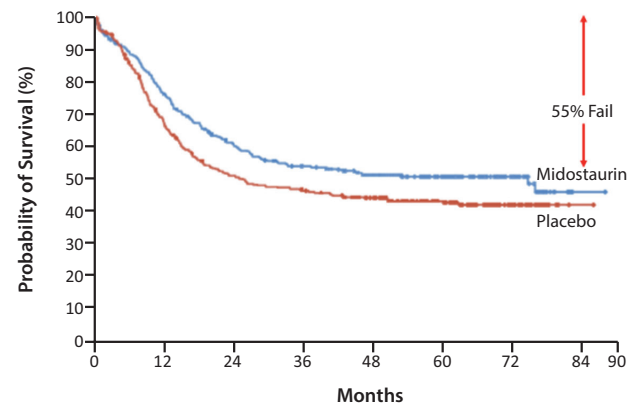


Figure 2. Cytarabine and daunorubicin with or without midostaurin in newly-diagnosed AML [2]

Fig. 3 displays the estimated impact of targeted therapies on survival of persons with acute myeloblastic leukemia (AML) [3]. It seems only about 10 percent of people will benefit.

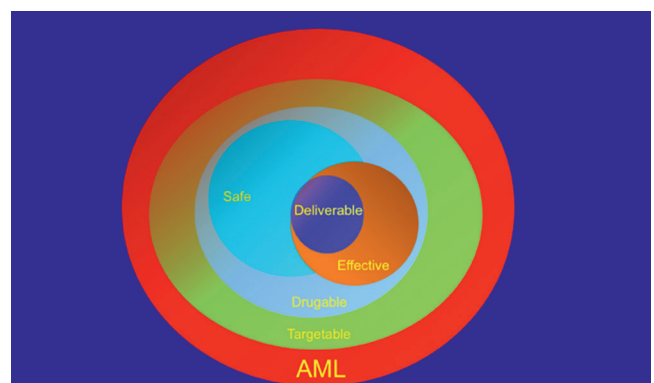


Figure 3. Estimated benefit of targeted therapy in AML [3]

Immune therapy is another new therapy of blood and bone marrow cancers. Some examples are displayed in Table 5.

Table 5. Some examples of immune therapies in blood and bone marrow cancers

Immune Therapy Breakthroughs	
Monoclonal antibodies	Rixtuxumab CD20, Daratumumab BCMA
Antibody-drug conjugates	Brentuximab vedotin CD30
Bi-specific (BiTE) antibodies	Blinatumomab CD20/CD30
CAR-T-cells	CD19, CD20, BCMA
Checkpoint inhibitors	PD-1, PD-1L, CTLA-4

However, these therapies are effective only in B-cell cancers and are lineage- but not cancer-specific (Fig. 4). Other than gemtuzumab ozogamicin, an anti-CD33 monoclonal antibody, there is no proved safe and effective therapy of myeloid cancers.

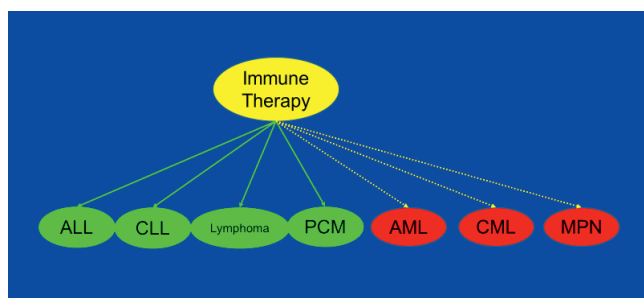


Figure 4. Scheme of immune therapy of lymphoid and myeloid cancers

CAR-T-cells are an important advance in therapy of lymphoid cancers with high response rates. However, often responses are not sustained unless a subsequent allogeneic haematopoietic cell transplant is done. An example of event-free survival (EFS) in children and young adults with advanced ALL is shown in Figure 5 with a failure rate of 40 percent at 1.5 years in complete responders [4].

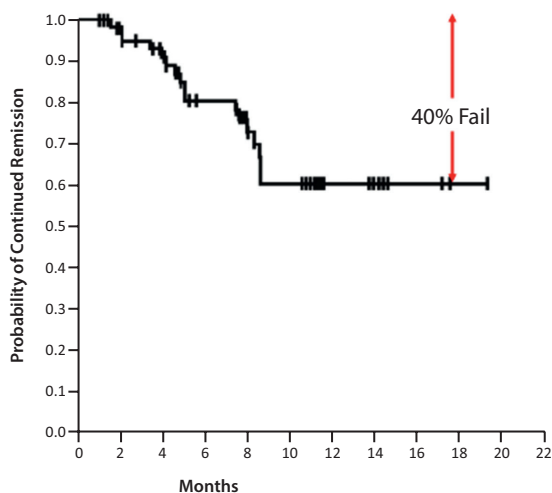


Figure 5. Event-free survival in children and young adults with advanced ALL after successful CAR-T-cell therapy [4]

Similarly, there are high rates of therapy-failure after successful CAR-T-cell therapy of diffuse large B-cell (DLBCL; Figure 6), follicular (FL) and marginal zone lymphomas (MZL; Fig. 7). [5] (https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8008).

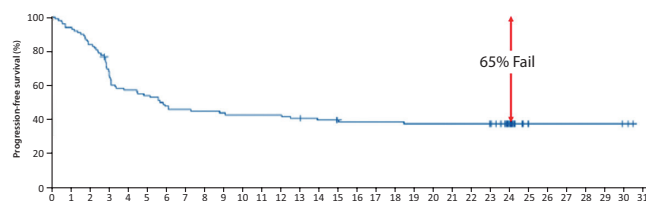


Figure 6. PFS after successful CAR-T-cell therapy of DLBCL [5]

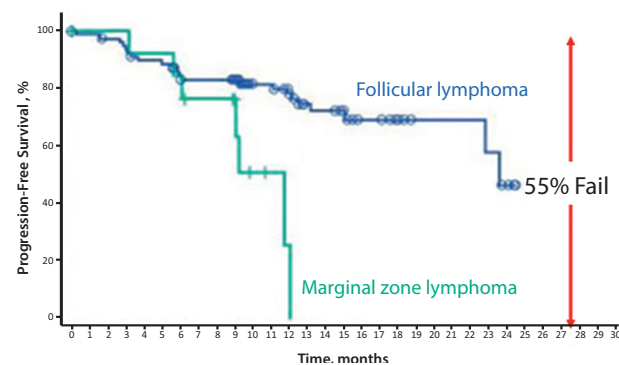


Figure 7. PFS after successful CAR-T-cell therapy of FL and MZL (https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.8008)

The argument CAR-T-cell therapy serves predominately as a *bridge* to an allotransplant is unconvincing as there are no strong data survival of persons with ALL transplanted in 2nd remission are better than those transplanted in relapse when all subjects are accounted for. Consequently, the best approach to someone responding to CAR-T-cell therapy is controversial. It may be reasonable to consider an allotransplant in persons with ALL and in those with MZL after responding to CAR-T-cell therapy, but wait for therapy failure in those with DLBCL and FL (Fig. 8).

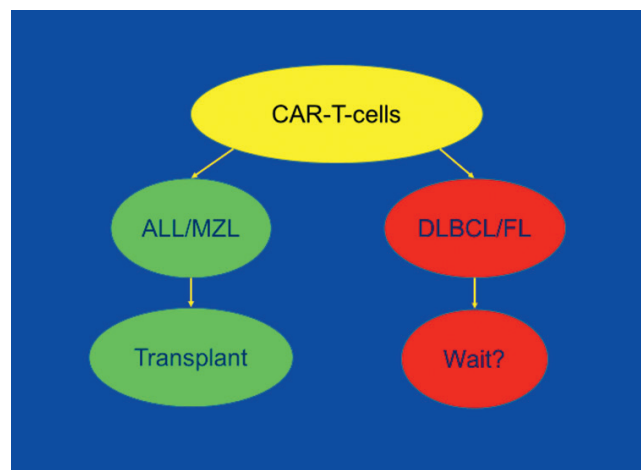


Figure 8. Possible roles for allotransplants is persons receiving CAR-T-cell therapy

It is also important to recall much of the efficacy of allotransplants results from an allogeneic anti-cancer effect so far difficult to distinguish from graft-versus-host disease (GvHD) [6]. These data are displayed in Fig. 9. For example, whether there is a specific anti-leukaemia effect is controversial, as reviewed in [7].

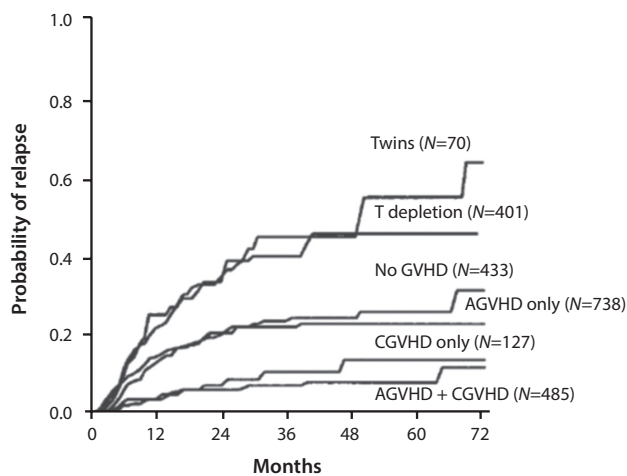


Figure 9. Actuarial probability of relapse in recipients of bone marrow transplants for AML [6]

Some data suggest the potential use of donor-derived CAR-T-cells in persons relapsing after an allotransplant for B-cell cancers [8].

Conclusion

Advances in treating ALL, AML, lymphomas and PCM are important and exciting but the magnitude of benefit is modest and few people are cured. Many persons with immune therapy successes go on to receive an allotransplant. Most cancers where immune therapy is effective are B-cell cancers whereas most allotransplants are done for myeloid cancers. Moreover, these immune therapies are lineage-, not cancer-specific and lack the allogeneic anti-cancer effect associated with allotransplants. In young persons with PCM, autotransplants are better than new drugs in randomized clinical trials. CAR-T-cell therapy of B-cell cancers is effective but mostly not a cure. Donor CAR-T-cells are a promising in persons relapsing after an allogeneic haematopoietic cell transplant. Transplants will remain an important therapy in the immediate future. Put in terms of food, although there is nouvelle cuisine Boef Stroganoff remains a classic and my 1st dinner choice at Chekhov restaurant in Petersburg.

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Conflict of interest

RPG is a consultant to BeiGene Ltd., Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Pharmaceuticals Inc. and CStone Pharmaceuticals; advisor to Antegene Biotech LLC, Medical Director, FFF Enterprises Inc.; partner, AZAC Inc.; Board of Directors, Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd.

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Есть ли будущее у трансплантации гемопоэтических клеток?

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Резюме

Нынешние успехи противоопухолевой терапии, таргетной и иммунотерапии подрывают вопрос о том, есть ли будущее у трансплантации гемопоэтических клеток (ТГСК). Я обсуждаю важность этого, но, в итоге, масштаб этих усовершенствований пока скром.

Я подчеркиваю, что эффективность иммунной терапии ограничена, преимущественно, В-клеточными опухолями, и что у многих, если не большинства больных, успешно леченных посредством иммунотерапии, может выполняться аллогенная ТГСК, особенно при остром лимфобластном лейкозе (ОЛЛ).

Я также обсуждаю то, что большинство аллотрансплантаций проводятся по поводу злокачественных заболеваний, которые не лечатся существующей иммунотерапией.

Рандомизированные испытания показывают, что аутотрансплантация – лучше, чем новые препараты при лечении молодых пациентов с плазмноклеточной миеломой. Значительное число данных указывает на то, что эффективность аллотрансплантации

обусловлена не опухольспецифическими аллогенными эффектами, которые, очевидно, не связаны с существующей иммунотерапией.

Наконец, я обсуждаю роль применения Т-клеток с донорским химерным антигенным рецептором (CAR-T) у лиц, рецидивирующих после алло-ТГСК при В-клеточных опухолях. В итоге можно предполагать и в последующем значительную роль трансплантации гемопоэтических клеток в различных клинических ситуациях.

Ключевые слова

Трансплантация гемопоэтических стволовых клеток, таргетные препараты, иммунная терапия, CAR-T клетки, эффективность.