STEM CELL TRANSPLANTATION AS A TREATMENT FOR ACUTE MYELOID LEUKEMIA

Does the age of the donor and recipient make a difference in clinical outcome?

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Abstract

Acute myeloid leukemia is the most common type of acute leukemia found among the elderly. After an induction treatment with chemotherapy to reach a remission of the leukemia, hematopoietic stem cell transplantation is seen as the number one treatment to possibly cure the leukemia. Several studies showed that for these stem cell transplantations, the use of younger stem cells is preferred over the use of older ones. This post-remission treatment, however, is not used for every patient, since not every patient reaches a complete remission and for some patients the induction therapy will be too heavy. Treating the older patients with a transplantation was for a longer time not desirable, but since the important introduction of the reduced-intensity conditioning it was also possible to treat the elderly. Two out of three studies showed promising results, in which no difference in overall-survival and progression-free survival was seen between the younger and older patients receiving a hematopoietic stem cell transplantation. When a patient is in need for stem cells, but no matching donor can be found, unmatched stem cells from the umbilical blood seems to be a promising alternative for stem cells from bone marrow or peripheral blood, since these stem cells can be easily stored and are directly available.

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1. Introduction

In the Netherlands around 2000 new people are diagnosed with leukemia every year. Around 650 of these patients are diagnosed with the subtype acute myeloid leukemia (AML) (KWF kankerbestrijding, kanker.nl, 2017).This heterogenous type of blood cancer is caused by mutations in stem cells of the bone marrow, leading to the formation of a leukemic stem cell which will give rise to a lot of undifferentiated blood cells, also called blasts. These blast cells don't function very well and so AML will result in bone marrow failure and leukocytosis, which is an increased number of white blood cells in the blood (de Kouchkovsky & Abdul-Hay, 2016). The treatment of AML consists of a combination of 2 chemotherapies, anthracycline and cytarabine, and is given in 2 different periods. The goal of the first period, also called induction therapy, is to reach a complete remission. The second period, also called consolidation therapy, is to remain the gained remission (de Kouchkovsky & Abdul-Hay, 2016).

After reaching the first complete remission, the choice of post-remission therapy will depend on the characteristics of the disease and the fitness of the patient. The number one post-remission treatment to potentially cure AML is a hematopoietic stem cell transplantation (HSCT), but this treatment is not directly given to all patients (Cornelissen, et al., 2014). The transplantation can often be postponed to a second remission in patients with favorable cytogenetics. Besides that, unfit patients cannot undergo a HSCT because the treatment will be too heavy (Dombret & Gardin, 2016). During a HSCT, the patient will either receive stem cells from its own healthy tissue or from another donor. Receiving cells from the patient itself is called an autologous stem cell transplantation, while receiving stem cells from another is called an autologous stem cell transplantation. Most of these stem cells are collected from the bone marrow or the peripheral blood circulation, but a more recent technique makes use of blood out of the umbilical cord (Panch, Szymanski, Savani, & Stroncek, 2017).

The so-called umbilical cord blood transplantation makes use of stem cells which are collected during birth out of blood of the umbilical cord and the placenta. These stem cells are seen as very young stem cells, which didn't pass a lot of cell divisions. The placental stem cells should induce a reduced immune reaction in allo-HSCT and be more potent than stem cells derived from bone marrow (Ballen, Gluckman, & Broxmeyer, 2013). The application of these stem cells will be discussed later in this review.

While hematopoietic stem cell transplantation is seen as the number one treatment as a possible cure for AML, it is not used in every patient with AML. Most of the treatment plans are made for the younger patients, while there is no clear treatment plan for the older AML patients (Dombret & Gardin, 2016) (de Kouchkovsky & Abdul-Hay, 2016). This brings us to a problem since AML is the most common acute leukemia among adults with a median age of 68 (Griffiths, Carraway, Chandhok, & Prebet, 2020).

The aim of this review is to take a look into the treatment outcome of allogeneic stem cell transplantation among AML patients. The first question which will be answered is if the treatment outcome depends on the age of the donor. The second

question which will be answered is if the treatment outcome depends on the age of the recipient.

2. The role of stem cell transplantation in AML

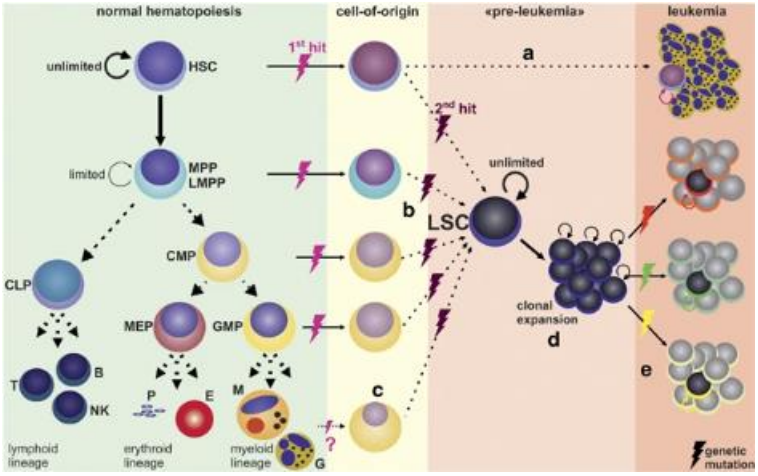
2.1. Haematopoietic stem cells

All stem cells in the body have two things in common, they will be able to renew themselves and they can differentiate in different types of cells. This makes it possible to replace old or damaged cells. Stem cells which will ultimately form blood cells are the so-called hematopoietic stem cells (HSCs). Stem cells are often classified by the potency they have to become other cells. HSCs are classified as multipotent stem cells, since they can give rise to all different blood forming cells, but can't give rise to other type of cells anymore. When an HSC divides, it will either form a new HSC or a multipotent progenitor, which has a limited potency to self-renewal but still can give rise to all blood cell types. This multipotent progenitor will either form a common lymphoid progenitor or a common myeloid progenitor. The lymphoid progenitor will give rise to the white blood cells, which will form the T-cells, B-cells, NK-cells and innate lymphoid cells. The myeloid cell progenitors will give rise to the rest of the cells which you will find in the blood, among which the erythrocytes, platelets and cells which form the innate immune system (Riether, Schürch, & Ochsenbein, 2014).

2.2. AML

Normally, the process of differentiation and self-renewal of HSCs is tightly balanced, but in leukemia this process is out of balance. It is believed that AML can be explained by a two-hit-hypothesis, which is shown in figure 1 (Takahashi, 2011). This hypothesis relies on the fact that a progenitor cell of the myeloid lineage will undergo two mutations which will result into a clonal expansion of blasts. Class one mutations will make the cells more proliferating, while class two mutations cause an abnormal hematopoietic differentiation. If these two mutations both occur, a leukemic stem cell will be formed which will be abnormally proliferative, giving rise to a lot of undifferentiated leukemic blast cells (Bonnet, 2005). These blast cells will push away the healthy cells, causing bone marrow failure and leucocytosis. If a patient will not be treated fast enough, death will occur in weeks to months because of an infection or a bleeding (de Kouchkovsky & Abdul-Hay, 2016).

Figure 1. The formation of leukemic stem cells during haematopoiesis (Riether, Schürch, & Ochsenbein, 2014)



Abbreviations: HSC, hematopoietic stem; MPP, multipotent progenitor; LMPP, lymphoid-primed multipotent progenitor; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte-macrophage progenitor; MEP, megakaryocyte-erythrocyte progenitor; LSC, leukemic stem cell; T, T-cell; B, B-cell; NK, NK-cell; P, platelet; M, macrophage; G, granulocyte

The first goal of the treatment of AML is to kill all the blast cells, which can be done by chemotherapy. If a complete remission is achieved, which means less than five percent blasts in the bone marrow, the consolidation therapy can start. This therapy depends on the risk profile of the patient, the treatment response and the toxicity of the therapy (Cornelissen, et al., 2014). Good risk patients will get another series of chemotherapy or sometimes an autologous stem cell transplantation. Poor risk patients will be recommended to do an allogenic stem cell transplantation. Patients within the intermediate risk group don't have a clear recommended treatment and so this should be discussed with the patient (Koreth, et al., 2009).

2.3. Stem cell transplantation

Stem cell transplantation is a fitting treatment for AML since it makes it possible to restore the function of the bone marrow by replacing the leukemic stem cells and blasts with healthy stem cells. This can either be done by autologous stem cells or allogenic stem cells. The difference between those two is that autologous stem cells are collected from the patient itself, while allogenic stem cells are collected from a donor. Which type of stem cells are going to be used is determined by the risk profile of the patient. While the autologous stem cell transplantation will only be carried out in good and intermediate risk patients under specific conditions, allogenic stem cell transplantation can be carried out in all risk categories (HOVON-leukemiewerkgroep, 2018). Almost one third of all allogeneic stem cell transplantations is on indication of AML, while the autologous stem cell transplantation in AML patients only covers 2,2 percent of all performed stem cell transplantations (Niederwieser, et al., 2016).

Before an allogeneic transplantation can take place, a fitting donor has to be found, which means that the HLA-system is compatible with the patient. This is most important for transplantations which make use of stem cells from the bone marrow or the peripheral blood, since these transplants cover a high number of T-cells. These T-cells can cause a graft-versus-host disease (GVDH), in which the donor T-cells recognize the host cells as foreign (Passweg, et al., 2012). When a patient receives an umbilical blood transplant, the HLA-type is less important, since the T-cells found in the umbilical blood are often naïve and don't cause this type of rejection (Wagner, et al., 1996) (Panch, Szymanski, Savani, & Stroncek, 2017). Although the chance to cause GVDH is the smallest in umbilical blood transplants, the time of engraftment is shown to be the longest because of the low concentration of CD34+ stem cells (Panch, Szymanski, Savani, & Stroncek, 2017).

When a fitting donor is found, in case of the allogeneic transplantations, the stem cells have to be transplanted into the recipient. Before the transplantation can take place, the recipient has to be treated with chemotherapy to make place for the new stem cells. The best way to do this from historical perspective was to give the recipient a high dose of chemotherapy, also called marrow-ablative chemotherapy, and a total body irradiation to kill all the cells in the bone marrow (Jethava, et al., 2017). This method works very effective and is still used to treat the younger and fitter patients with AML. However, the biggest disadvantage of this regimen is the treatment-related mortality (Webster & Pratz, 2017).

To make this pre-transplantation treatment less toxic, reduced intensity conditioning has been introduced to replace the myeloablative therapy. This therapy uses just enough chemotherapy to make place for the new stem cells, but doesn't kill them all. While the toxicity of the treatment is lower, the relapse rate is higher (Jethava, et al., 2017).

3. Types of stem cells

3.1. Sources of haematopoietic stem cells

HSCTs use hematopoietic stem cells which can be found and collected in 3 different types of tissue: bone marrow, peripheral blood and cord blood.

The traditional way to collect stem cells is by bone marrow aspiration. Stem cells are collected most of the time from the iliac crest, but can also be harvested from the sternum. During the procedure of collecting the stem cells, the donor has to be under general anaesthesia. This is the reason why today most of the stem cells are harvested out of the peripheral blood rather than bone marrow (Panch, Szymanski, Savani, & Stroncek, 2017).

To harvest haematopoietic stem cells from peripheral blood, the donor should first be treated with granulocyte colony-stimulating factor (C-GSF). This compound mobilizes the stem cells from the bone marrow into the blood, which makes it possible to collect the stem cells via apheresis. The biggest benefit of this method is the amount of stem cells which are collected. The high amount of stem cells causes a shorter engraftment time and so a shortened time for the patient to recover from the transplantation. Another advantage is that this method is more donor friendly. All these benefits make that this way of collecting haematologic stem cells is the most preferred and used (Panch, Szymanski, Savani, & Stroncek, 2017).

A third source of stem cells is the umbilical blood. Different research found that this type of stem cells could easily be collected after birth, without harming the baby or mother. After collecting stem cells out of the blood, these can be cryopreserved for over twenty years. Injection of these stem cells in a new recipient gave rise to a new functional haematopoietic system and so this technique can also be used in the clinic today (Ballen, Gluckman, & Broxmeyer, 2013). While HLA-compatibility with the donor is often preferred in case of hematopoietic stem cell transplantation, this compatibility plays a less significant role in the transplantation of umbilical cord stem cells (Panch, Szymanski, Savani, & Stroncek, 2017). This feature of stem cells could make it possible to treat patients for whom no compatible donor can be found.

3.2. Treatment outcome by using different kind of stem cells

Does the treatment outcome depend on the age of the donor? This question could be answered from two perspectives. The first one is to look into the outcome of transplantations with different types of stem cells. Stem cells from the umbilical blood can be seen as younger stem cells than the hematopoietic stem cells from the bone marrow and the peripheral blood. Because stem cells from umbilical blood are used as an alternative treatment for patients who have no relatives, the treatment outcome is often compared with unrelated haematopoietic stem cell transplantation.

A study from 2010 presented the outcome of 1525 patients, which either underwent a stem cell transplantation from umbilical blood, bone marrow or peripheral blood (Eapen, et al., 2010). What they found was that the leukemia-free survival was comparable between the three sources, but the therapy-related mortality was higher in the patients treated with stem cells from umbilical blood. Besides that, they found out that the acute and chronic GVDH were lower in patients treated with stem cells from umbilical blood compared to those out of the peripheral blood. Only the chronic GVDH was lower in umbilical stem cell treated patients, compared to those treated with bone marrow derived stem cells.

Another study done had some comparable outcome as the previous study (Chen, et al., 2012). In this study researchers compared the outcome of patients who were first treated with a reduced-intensity conditioning and then were then either transplanted with stem cells from umbilical blood or unrelated stem cells from bone marrow or peripheral blood. The difference with the previous study is that these researchers used data from patients who were transplanted with a double umbilical transplant. This technique is more commonly used in adults, since the amount of stem cells in umbilical blood is not enough to provide a fully functioning bone marrow (Panch, Szymanski, Savani, & Stroncek, 2017). They also found that the GVDH was less common in the patients treated with stem cells from umbilical blood. However, the 2-year cumulative incidence of non-relapse mortality was higher in patients treated with umbilical blood. Progression-free survival and overall-survival were not significantly different from each other.

A study from Rocha, et al. (2004) compared the outcome of 682 adults, who either received unrelated stem cells from cord blood or bone marrow. 94% of the cord blood transplants were HLA mismatched, while the recipients of the bone marrow were HLA-matched. Acute GVHD was lower after a transplantation with umbilical blood, while the recovery of neutrophils was delayed. The chronic GVHD, transplant-related mortality (TRM), relapse rate (RR) and leukemia-free survival (LFS) were all not significantly different between the two groups.

The complete outcome of the studies is also presented in table 1.

Table 1. Clinical outcome of different studies comparing the source of stem cells

No. evaluable patients	Disease	Source of stem cells	Acute GVHD	Chronic GVHD	TRM	RR	LFS	Conclusion	Study
1525	AML: 880 ALL: 645	UCB: 165 PBPCs: 888 BM: 472	4–6/6 matched UCB: 30,2% 8/8 matched BM: 38,9% 7/8 matched BM: 46% 8/8 matched PBPC: 48,1% 7/8 matched PBPC: 52,3%	4–6/6 matched UCB: 24,2% 8/8 matched BM: 39,8% 7/8 matched BM: 36,4% 8/8 matched PBPC: 51,7% 7/8 matched PBPC: 44,1%	4–6/6 matched UCB: 33,3% 8/8 matched BM: 22,9% 7/8 matched BM: 32,9% 8/8 matched PBPC: 23,6% 7/8 matched PBPC: 36,3%	4–6/6 matched UCB: 26,1% 8/8 matched BM: 33,7% 7/8 matched BM: 30% 8/8 matched PBPC: 33,1% 7/8 matched PBPC: 30,1%	4–6/6 matched UCB: 59,4% 8/8 matched BM: 56,6% 7/8 matched BM: 57,1% 8/8 matched PBPC: 56,6% 7/8 matched PBPC: 66,4%	These data support the use of UCB for adults with acute leukemia when there is no HLA-matched unrelated adult donor available, and when a transplant is needed urgently	(Eapen, et al., 2010)
285	AML: 95 Non-HL: 49 MDS: 43 CLL/SLL/PLL: 38 HL: 27 Other: 33	UCB: 64 PBSCs: 214 BM: 7	dUCB: 14,1% UD: 20,3%	dUCB: 21,9% UD: 53,9%	dUCB: 26,9% UD: 10,4%	dUCB: 42,7% UD: 49,8%	X	dUCB is a suitable alternative for patients undergoing RIC HSCT without an HLA-matching donor	(Chen, et al., 2012)
682	AML: 362 ALL: 320	UCB: 98 UBM: 584	UCB: 26% UBM: 39%	UCB: 30% UBM: 46%	UCB: 44% UBM: 38%	UCB: 23% UBM: 23%	UCB: 33% UBM: 38%	Cord blood from an unrelated donor is an alternative source of hematopoietic stem cells for adults with acute leukemia who lack an HLA-matched bone marrow donor.	(Rocha, et al., 2004)

Abbreviations: UCB, umbilical cord blood; PBPCs, peripheral blood cells; BM, bone marrow; UBM, unrelated bone marrow; UD, unrelated donor; dUCB, double umbilical cord blood; non-HL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; CLL, chronic lymphoid leukemia; SLL, small lymphocytic lymphoma ; PLL, prolymphocytic leukemia;

3.3 Treatment outcome by using donors of different ages

Another way to investigate if the donor age matters for the treatment outcome, is to compare the outcome of recipients who either received stem cells from an old donor or a younger donor.

Bastida, et al. (2015) wanted to see if the outcome of an allogeneic transplantation depended on the age of the donor. Therefore, they analysed 197 patients, who did receive an allogeneic stem cell transplantation. The older donors were specified as fifty years or older, and the younger donors were below the age of fifty. The clinical outcome of this study was defined in overall survival, progression free survival, therapy related mortality and relapse risk. They showed that an older donor resulted in a lower overall survival, higher therapy related mortality, higher relapse rate and lower disease-free survival.

Another research published in Bone Marrow Transplantation found that stem cells from a younger unrelated donor resulted into a better outcome than stem cells from an older related donor (Ayuk, et al., 2013). The recipients treated with stem cells from the younger donor showed a higher 5-year overall survival and also a lower treatment related mortality compared to the older related donors. The relapse rate in this study was not significant between the two groups.

Compared to the previous studies, the study of Craig Kollman and his colleagues used a lot more patients in his retrospective analysis (Kollman, et al., 2001). They looked into different donor characteristics on the outcome of the recipient. This research categorized the age of the donors into 18-30, 31-40 and older than 40. What they found out was that the five-year overall survival was higher in recipients treated with younger stem cells, compared to the recipients receiving older stem cells. However, recipients of mismatched donors had a lower 5-year overall survival compared with matched donors. Also, the GVDH was more common seen in the group treated with stem cells of the older donor.

Table 2 shows the complete outcome of the different studies.

Table 2. Clinical outcome of different studies comparing the age of the donor

No. of evaluable patients	Disease	Donor Age groups	Acute GVDH	Chronic GVDH	TRM	RR	OS	Conclusion	Study
169	AML: 117 MDS: 62	<50: 83 >50: 96	<50: 17% >50: 21%	<50: 61% >50: 59%	<50: 11% >50: 21%	<50: 25,5% >50: 28,8%	UD<50: 72% UD>50: 20% RD<50: 72% RD>50: 54%	OS and DFS are better for patients who receive hematopoietic stem cell transplantation from a younger donor	(Bastida, et al., 2015)
168	AML	UD<39: 60 UD>39: 40 RD<39: 25 RD>39: 43	UD<39: 33,3% UD>39: 37,5% RD<39: 32,5% RD>39: 30%	UD<39: 33% UD>39: 42,9% RD<39: 31,8% RD>39: 48,4%	UD<39: 12% UD>39: 26% RD<39: 13% RD>39: 35%	UD<39: 23% UD>39: 37% RD<39: 35% RD>39: 33%	UD<39: 66% UD>39: 41% RD<39: 65% RD>39: 34%	Donor age and cytogenetic risk group are the only factors significantly influencing 5-yr OS	(Ayuk, et al., 2013)
6978	CML: 2469 AML: 1373 ALL: 1359 Other: 1777	18-30: 1923 31-45: 3924 >46: 1131	UD18-30: 30% UD31-45: 41% UD>46: 40% RD18-30: 29% RD31-45: 30% RD>46: 30%	UD18-30: 41% UD31-45: 43% UD>46: 50% RD18-30: 45% RD31-45: 50% RD>46: 51%	X	X	18-30: 39% 31-45: 38% >46: 32%	The use of younger donors may lower the incidence of GVHD and improve survival after bone marrow transplantation. Age should be considered when selecting among comparably HLA-matched volunteer donors	(Kollman, et al., 2001)

Abbreviations: GVDH, graft-versus-host disease; OS, overall survival; TRM, transplant-related mortality; RR, relapse rate; UD, unrelated donor; RD, related donor; CML, chronic myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome

4. Stem cell transplantation among older patients

While the older population forms the largest group of patients with AML, an optimal treatment strategy has not been established yet. Most of these older patients show up with adverse cytogenetics and have often several comorbidities (Dombret & Gardin, 2016) (de Kouchkovsky & Abdul-Hay, 2016). Because myo-ablative chemotherapy was historically seen part of the HSCT, this treatment had such a great risk for the elderly that the HSCT was not preferred (Rashidi, Ebadi, Colditz, & DiPersio, 2016). This all changed with the introduction of the reduced intensity conditioning. Instead of killing all the cells in the bone marrow, a reduced amount of chemotherapy is given to the recipient to prepare the patient for a transplantation. Because several research has found out that there is no difference in leukemia-free survival and overall survival between both pre-transplantation treatments, the allogeneic stem cell transplantation could be a fitting treatment for elderly too (Webster & Pratz, 2017). With the knowledge that we now have of these less heavy conditioning regimens, does the treatment outcome depend on the age of the recipient or can we use allogeneic stem cell transplantations for all elderly patients with AML? Is there an age limit in which the treatment toxicity is higher than the chance to cure an elderly patient?

A research from 2010 looked at the clinical outcome of haematopoietic stem cell transplantation among different age groups and compared them in overall survival, disease-free survival, transplant-related mortality, GVDH and neutrophil recovery time (McClune, et al., 2010). The patients were split up in the following age-cohorts: 40-54, 55-59, 60-64 and >65. They showed in their study that there was no significant difference between the outcome factors among the different age groups. However, other factors like a mismatching HLA and adverse cytogenetics resulted in a lower overall survival and a higher transplant-related mortality.

Another research did also look at the outcomes of allogeneic haematopoietic stem cell transplantation among different age groups, which received reduced-intensity conditioning before transplantation (Aoki, et al., 2016). First, they divided the patients into the following age-cohorts: 50-54, 55-59, 60-64 and >65. They looked into the overall survival, relapse rate, non-relapse mortality and acute and chronic GVHD. All these factors did not differ significant among the different age groups and so they concluded that age was not a contraindication for older patients undergoing an allogeneic hematopoietic stem cell transplantation.

A study from last year compared the outcome of allogeneic hematopoietic stem cell transplantation between patients aged >70 and patients aged 50-69 (Ringdén, et al., 2019). While the study investigated both the outcome of MDS, which is another haematological disease, and AML patients, only the outcome of the AML patients is presented in table 3. They found out that there was no significant difference in acute and chronic GVHD and relapse between the two groups, but the non-relapse mortality, overall survival and leukemia free survival were significantly worse in the group patients >70. They also saw that patients >70 with a higher Karnowski Performance score (a score that says something about the fitness of the patient) showed an improved outcome after the transplantation.

The outcomes of the three different studies can also be found in table 3.

Table 3. Clinical outcome of different studies comparing the age of the recipient

No. of evaluable patients	Disease	Recipient age groups	Acute GVHD	Chronic GVHD	TRM	RR	OS	Conclusion	Study
1080	AML: 545 MDS: 535	40-54: 201 55-59: 149 60-64: 132 >65: 63	40-54: 33% 55-59: 35% 60-64: 35% >65: 33%	40-54: 41% 55-59: 49% 60-64: 43% >65: 53%	40-54: 25% 55-59: 22% 60-64: 32% >65: 34%	40-54: 28% 55-59: 29% 60-64: 29% >65: 25%	40-54: 44% 55-59: 50% 60-64: 34% >65: 36%	With these similar outcomes observed in older patients, we conclude that older age alone should not be considered a contraindication to HCT.	(McClune, et al., 2010)
757	AML	50-54: 89 55-59: 249 60-64: 301 >65: 118	50-54: 35,1% 55-59: 36,1% 60-64: 37,6% >65: 31%	50-54: 35% 55-59: 37,4% 60-64: 39,6% >65: 38%	50-54: 24% 55-59: 22,8% 60-64: 29,2% >65: 27,6%	50-54: 36,9% 55-59: 37,6% 60-64: 36,6% >65: 35,7%	50-54: 47,8% 55-59: 45,2% 60-64: 37,9% >65: 36,6%	These results suggested that advanced patient age is not a contraindication for RIC allo-HSCT in elderly AML patients	(Aoki, et al., 2016)
17374	AML	50-69: 16661 >70: 713	50-69: 25% >70: 23%	50-69: 41% >70: 43%	50-69: 24% >70: 34%	50-69: 32% >70: 33%	50-69: 50% >70: 38%	Patients age ≥70 years with active disease should be offered the opportunity to undergo HSCT. A KPS score ≥80% was associated with improved outcome of HSCT in these patients.	(Ringdén, et al., 2019)

Abbreviations: GVDH, graft-versus-host disease; TRM, transplant-related mortality; RR, relapse rate; OS, overall survival; MDS, myelodysplastic syndrome; KPS, Karnofsky Performance Status; RIC, reduced-intensity conditioning; allo-HSCT, allogeneic hematopoietic stem cell transplantation

5. Discussion and Conclusion

More and more people are getting older these days. This process of ageing is related to a lot of different diseases, among which acute myeloid leukemia. To potentially cure this disease, a hematopoietic stem cell transplantation could be offered to a patient. Several studies showed that not every patient can benefit from this treatment because of the treatment-related mortality. It is important to know for which patients the treatment can be offered and which stem cells could best be used. Therefore, the aim of this study was to look at treatment outcome of patients, who underwent a stem cell transplantation to potentially cure their AML. To specify the treatment outcome three questions have been asked: does the treatment outcome depend on the type of stem cells used, does the treatment outcome depend on the age of the donor and does the treatment outcome depend on the age of the recipient.

Comparing the outcome using different kind of stem cells, all the three mentioned studies came together with the same conclusion: umbilical blood seems to be a potential source of stem cells if the recipient can't find an HLA-fitting donor (Eapen, et al., 2010) (Chen, et al., 2012) (Rocha, et al., 2004). While the acute and chronic GVDH are often lower in patients treated with stem cells from umbilical blood, it is remarkable that the transplant-related mortality is often higher. If this problem could be solved, this type of stem cells could be used more widely.

The comparison between the use of stem cells from an older donor versus stem cells from a younger donor showed that stem cells from younger donors resulted in a higher overall survival. This is why all three studies concluded that the use of younger stem cells is preferred over the use of stem cells from older donors. Most interesting was that the study from Ayuk, et al. (2013) showed that the use of unrelated younger donor cells show a better outcome in patients than using related stem cells from an older donor. This might implicate that the age of stem cells from a donor could be a more important factor to select stem cells than the relatedness between donor and recipient.

While older age of the patient has long been seen as a contraindication for performing a HSCT, the three studies mentioned in this review concluded that this is not the case. While the studies of McClune, et al. and Aoki, et al. found no significant differences in transplant-related mortality and overall survival between the older and younger patients, Ringdén, et al. did show a significant worse survival for elderly patients. All three studies mentioned that performance score plays an important role in the outcome of transplantations, where the lower performance score was associated with worse outcome. This implicates that not only age should be used to decide if a patients will benefit from a transplantation, but that performance score should also be determined.

Especially on the front of the umbilical stem cells, a lot of research can be done. First of all, the cohorts of patients treated with stem cells from umbilical blood are relatively small. In order to get a better view on the outcome of those patients, more studies have to be done with greater amounts of patients. Future research could also look at explanations for the higher transplant-related mortality in patients treated with stem cells from umbilical blood. If this mortality can be decreased, the

application of stem cells from umbilical blood could more widely be used. While most studies make use of incompletely-matched umbilical stem cells, there is little known about patients treated with fully HLA-matched stem cells. If these results are comparable to the outcome of treatments with stem cells from the bone marrow or peripheral blood, the amount of stem cells will be expanded and more patients could receive matched stem cells.

In conclusion, hematopoietic stem cell transplantation is a fitting treatment to potentially cure patients with AML, even in patients of higher age. For these transplantations the use of stem cells from a younger donor are preferred over stem cells from an older donor. If a fitting donor can't be found, the use of umbilical stem cells is a promising alternative for unrelated stem cells from bone marrow and peripheral blood. This last source of stem cells is relatively new and should be more investigated to get a more complete view on the application of these stem cells.

5. Citations

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