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REVIEW ARTICLE

The FLAMSA concept—past and future

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Abstract

The FLAMSA reduced intensity (RIC) concept, also known as "sequential therapy", is a conceptual platform for the treatment of leukemia separated in several parts: induction therapy, a sequence of antileukemic and immunosuppressive conditioning for allogeneic stem cell transplantation, and immune restitution supported by donor lymphocyte transfusions. The antileukemic part consists of fludarabine, cytosine arabinoside, and amsacrine (FLAMSA); non-cross reactive agents like fludarabine and amsacrine have been successfully used in cases of refractoriness and relapse. Immunosuppressive conditioning and transplantation follow after only 3 days of rest. This way, the toxicity of allogeneic transplantation could be reduced and the anti-leukemia effects by using allogeneic immune cells could be optimized. This review summarizes available data on efficacy and toxicity of this approach. Further, possible strategies for improvements are discussed in order to provide better chances for elderly and frail patients and patients with advanced and high-risk disease. Among others, several new agents are available that target molecular changes of leukemia for induction of remission and allow for bridging the time after transplantation until adoptive immunotherapy becomes safe and effective.

Keywords AML · MDS · Transplantation · Conditioning · FLAMSA · DLI · Graft versus leukemia · Targeted therapy

Introduction

Originally, total body irradiation (TBI) and rescue with marrow transplantation were used for the treatment of hematopoietic malignancies including leukemia [1]. Although irradiation was effective in suppressing leukemia, it rarely could eradicate the disease. The combination of TBI with cyclophosphamide (CY) and other chemotherapy with allogeneic transplantation was effective in some patients with advanced and otherwise refractory disease. Mostly, allogeneic hematopoietic cells were essential for the cure of leukemia [2], allogeneic transplantation has always been a form of adoptive immunotherapy, but GVHD is the major obstacle of allogeneic transplantation [3]. Depletion of T cells from the graft has been the most effective way of prevention in animal experiments [4] and in human patients [5, 6]. However, rejection of the graft, delayed immune recovery, and an increased incidence of relapse have been the drawbacks of "ex vivo" T cell depletion [7]. Treatment of the recipient with anti-thymocyte globulin (ATG) and monoclonal T cell antibodies prior to transplantation could prevent rejection and GVHD by depletion of grafted T cells "in vivo" by persistent antibodies in the patient.

However, relapses were not prevented; leukemia and residual hematopoietic cells of the host survived despite "myeloablative" conditioning. Obviously, T cells were necessary for the elimination of residual lymphocytes of the host and leukemia cells [8, 9]. In animal experiments with dogs, mixed chimerism was produced by transplantation of T cell-depleted marrow [10]. In these, the transfusion of lymphocytes from the marrow donor could convert mixed into complete chimerism. Importantly, the transfusion of lymphocytes had to be delayed for 2 months after transplantation in order to prevent GVHD.

Donor lymphocyte transfusions induced sustained remissions in patients with relapse of chronic myelogenous leukemia (CML) after transplantation [11]. Beneficial effects were

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also observed in patients with recurrent acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), and multiple myeloma (MMY) as well as in some patients with acute lymphoblastic leukemia (ALL) [12–14]. The beneficial effect of donor lymphocytes gave a chance for reducing the intensity of conditioning, but the role of donor lymphocytes and conditioning remains to be defined for various diseases and stages of disease. Non-myeloablative conditioning and conditioning with reduced intensity have already allowed the inclusion of elderly and frail patients [15, 16].

The aim of the FLAMSA-RIC regimen in patients with advanced or genetically high-risk acute myeloid leukemia (AML) and preleukemic myelodysplastic syndrome (MDS) was the sequential application of a short and intensive chemotherapy followed by reduced intensity conditioning without waiting for a remission to be confirmed. Conditioning treatment with FLAMSA-RIC has primarily been restricted to elderly patients (over 60 years of age) and patients with high-risk AML. Most patients had intensive induction chemotherapy with and without remission and incomplete recovery of blood counts. As a rule, patients with high-risk MDS did not have prior intensive chemotherapy, but they were treated with azacytidine, decitabine, or low-dose cytosine arabinoside (ARA-C). The majority had refractory or relapsed disease [17].

Antileukemic conditioning

The FLAMSA-RIC concept was designed for patients with advanced acute myeloid leukemia (AML) and preleukemic myelodysplastic syndrome (MDS); the disease stage was either primary refractory, in relapse or with high risk of early relapse. The first part of the treatment consists of intermediate doses of cytosine arabinoside (Ara-C 2 g/m^2) preceded by fludarabine (30 mg/kg) and followed by amsacrine (100 mg/m^2) on each of 4 successive days followed by 3 days of rest prior to the second part of treatment with 4 Gy TBI on day − 4, antithymocyte globuline (ATG) on days − 3, − 2, and − 1 and cyclophosphamide (CY) on days − 3 and − 2 prior to transplantation [17]. The first part is directed to proliferating leukemia cells, whereas TBI is toxic to stem cells and kills quiescent and slowly proliferating leukemia stem cells besides normal stem cells (cf. below). This protocol is highly effective and well tolerated. The addition of fludarabine (FLU) prior to Ara-C enhances the production of Ara-CTP [18]. Amsacrine was applied instead of anthracyclines, because it belongs to another class of DNA intercalating drugs and inhibitors of topoisomerase II, it is not cross resistant with anthracyclines [19] and less cardiotoxic [20]. In countries where amsacrin is not available, mitoxantrone (10 mg/m^2 × 3 days) and idarubicin (10 mg/m^2 × 3 days) have been used with some success. FLAMSA has also been used in patients with recurrent AML after allogeneic transplantation for remission induction followed by blood stem cells from the original donor. These patients did not receive immunosuppressive conditioning, if significant chimerism persisted. The leukemia treatment block has been changed by some centers and clofarabine has been substituted for fludarabine. Clofarabine is very effective in acute leukemia, but is associated with considerable toxicity. The dose of ARA-C should be reduced, if clofarabine is substituted for fludarabine (M. Mohty personal comm.) [21].

Immunosuppressive conditioning

This part of the conditioning was reduced intensity consisting of 4 Gy TBI, ATG and CY. TBI has a strong myelosuppressive effect; its immunosuppressive effect is moderate. Cyclophosphamide (CY) is strongly immunosuppressive, but it fails to eliminate myeloid stem cells. The combination of TBI with cyclophosphamide is sufficiently immunosuppressive and allows prompt engraftment and permanent chimerism [22]. Prevention of GVHD is best achieved by depletion of T cells from the graft. Treatment of the patient with ATG is superior to ex vivo T cell depletion because the immune suppression of the host prevents rejection; ex vivo treatment of the graft only prevents GVHD. ATG given to the host prior to transplantation suppresses the host's immune reaction against the graft and the graft-versus-host reaction by "in vivo" T cell depletion. In patients given sufficiently large doses of ATG (30 mg/kg × 4 days), T cell antibodies were found in the peripheral blood up to 4 weeks after the last dose [23]. Antibody levels fell suddenly around 30 days post treatment, most likely because antibodies against ATG are formed that eliminate residual activity. CY and ATG doses were adjusted to the donor source, HLA-identical sibling transplant: ATG 10 mg/kg × 3 days, CY 40 mg/kg × 2 days, HLA-matched unrelated transplants: ATG 20 mg/kg × 3 days, CY 60 mg/kg for 2 days.

CY exerts strong immunosuppression, but mucositis and cystitis are serious side effects, particularly in elderly patients. Possibly, CY could be reduced without a critical reduction of immune suppression [24]. In a previous study in patients with CML, reduction of the dose of TBI did not change day 100 non-relapse mortality, whereas the reduced CY dose decreased early mortality significantly [25].

In principle, TBI was applied as part of the immunosuppression, but it also induces prolonged hematopoietic aplasia. It has strong effects on stem cells, normal hematopoietic and leukemia stem cells [26], 99% of progenitor cells are eliminated at 4 Gy. In general, leukemia stem cells have a similar radiosensitivity as normal stem cells. However, the radiosensitivity of leukemia may vary with the stage of the leukemia; in advanced stages, a greater resistance of apoptotic mechanisms can develop. The results of transplantation are

best for patients transplanted in remission; the results are worst, if several lines of chemotherapy have failed. In primary refractory patients, the results are better, if they had less chemotherapy before transplantation [17, 27]. Allogeneic transplantation in refractory patients should therefore be scheduled as soon as one or two cycles of induction chemotherapy have failed.

The effect of TBI can be enhanced by prior chemotherapy with fludarabine and amsacrine, but it is not known whether the effect of other stem cell toxic agents as busulfan, treosulfan, melphalan, and BCNU are also enhanced. Substituting TBI with busulfan for 2 days has been well tolerated by elderly patients, but its anti-leukemia effect may be lower [28]. Treosulfan at a dose of 10 g/m^2 was substituted for TBI with a similar outcome in elderly patients [29].

A prospective randomized study in Great Britain did not find better results with FLAMSA-busulfan than with other regimens including fludarabine-busulfan [30]. However, 155 patients were in remission and only nine patients in primary refractory disease, and treatment for remission induction and time until transplantation were not reported. In contrast, a retrospective analysis of the EBMT Acute Leukemia Working Party showed a lower relapse incidence and better relapse-free survival of FLAMSA TBI than treosulfan-fludarabine and FLAMSA Busulfan, but no major impact on overall survival [31]. A benefit of low dose of TBI was also described in patients with MDS conditioned with fludarabine and treosulfan [32]; the relapse incidence was lower with an additional dose of 2 Gy TBI without increased toxicity.

Adoptive immunotherapy with transfusions of lymphocytes of the donor

Transfusion of donor lymphocytes is an integral part of the FLAMSA-RIC concept and of allogeneic stem cell transplantation with any form of T cell depletion for prevention of GVHD. An important variable is the time after transplantation in order to avoid GVHD. In animal experiments, it had been shown that 2 months after transplantation of T cell-depleted marrow lymphocytes of the donor could be transfused without producing GVHD [8, 33]. These animals were mixed chimeras and became complete chimeras after donor lymphocyte transfusions. Immune responses were improved in transfused animals and donor immunity could be transferred. These animals could be given large amounts of lymphocytes without producing GVHD. However, GVHD did occur in animals that received donor lymphocytes following a T cell-depleting treatment [34].

In humans, donor lymphocyte transfusions were effective in the treatment of relapses of CML, AML, and myeloma as well as in some patients with ALL [11–14]. However, sustained remissions were observed mainly in patients with recurrent CML; the majority of patients with acute leukemia and myeloma disease relapsed again without further treatment. Long-term remissions were preferably seen in CML patients treated simultaneously with low-dose interferon-a (IFN-a) or IFN-a and GM-CSF [35]. Success was also due to the slow pace of the disease in CML, and GVHD could be avoided by starting with a low dose and escalating doses with repeated transfusions [36, 37]. In AML, relapse could be controlled with low-dose Ara-C, mobilized stem cells, and GM-CSF after transfusion, if the relapse occurred more than 6 months after transplantation [38]. GVHD was more frequent than in CML patients.

Prophylactic donor lymphocyte transfusions (DLI) were given to high-risk AML patients more than 120 days after transplantation. The requirements for prophylactic DLI were absence of GVHD, infections, and relapse; immunosuppressive therapy had to be suspended for at least 30 days [17]. A matched pair analysis of FLAMSA patients treated in Germany demonstrated superior survival of patients given DLI as compared to those not given DLI (Fig. 1) [39]. However, the control of early relapses is difficult by DLI from normal donors; they have been excluded by a landmark analysis in 180-day survivors. This analysis compared patients transplanted in remission and patients transplanted in active disease with their respective historical control. Remission patients had an excellent survival and relapse patients an improved survival as compared to historical controls. Of course, retrospective analyses can be biased by the improvement of treatment modalities not adjusted for.

Acute GVHD was seen in about 50% of patients given large doses of DLI; in most patients, severe GVHD could be prevented by starting with a low dose of donor T cells (1×10^6–1×10^7/kg body weight (BW) for HLA-identical transplants) and increasing the dose every 4–6 weeks, if there is no GVHD. In HLA-mismatched and HLA-haploidentical transplants, the starting dose should be no more than 1×10^5/kg BW. This dose of T cells in the graft did not produce acute GVHD neither in DLA-mismatched dogs [40] nor in HLA-mismatched human patients [41] . However, GVHD can develop, if lymphocyte-depleting treatment is given prior to DLI and/or infection is occurring. Infections, particularly viral infection, induce interferon and expression HLA class II antigens in non-hematopoietic tissue. Prevention of infection by prevention of exposure and prophylactic treatment with antibiotics, antivirals, and antifungals is indicated. As a rule, acute GVHD can be controlled, if treated early and with adequate intensity [42].

Chronic GVHD can develop in some patients; a mild degree may be acceptable, because it is associated with a strong graft-versus-leukemia effect. More severe chronic GVHD is deleterious and should be treated with all available methods. Progressive involvement of the lungs and the gut has to be treated vigorously.

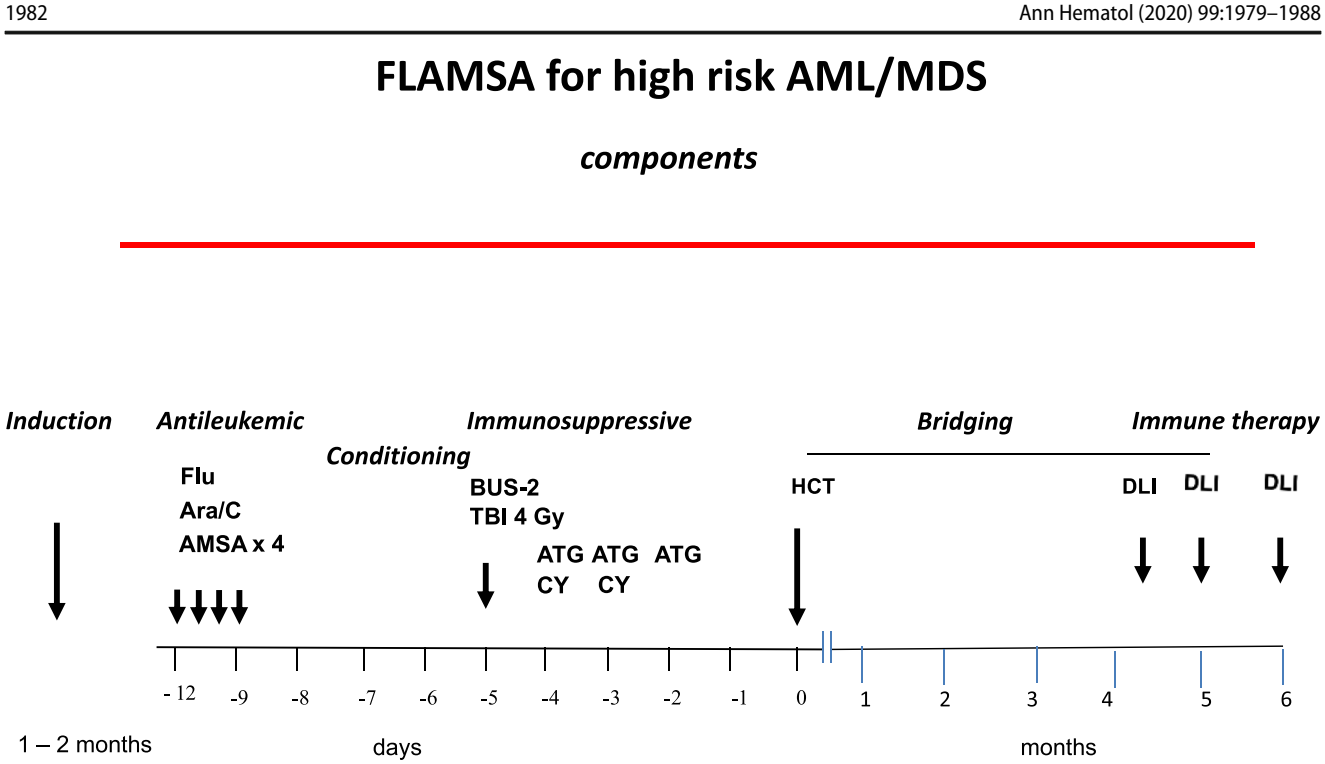

Fig. 1 FLAMSA regimen and its components. Flu: fludarabin 30 mg/m^2, AraC: cytosine arabinoside 2000 mg/m^2, AMSA: amsacrine 100 mg/m^2; BUS2: busulfan 4 × 0.8 mg/kg × 4 per day × 2 days; TBI: total body irradiation 4 Gy; ATG: antithymocyte globulin 20 mg/kg or 10 mg/kg (in case of HLA-identical sibling donor) per day × 3; CY: cyclophosphamide 60 mg/kg (40 mg/kg for HLA-identical sibling donor); HCT hematopoietic cell transplantation, DLI: donor lymphocyte transfusions in escalating doses starting with 1 × 10^6/kg CD3+ T cells escalating to 5 × 10^6 and 10^7/kg or 10^8/kg

The sequential treatment with DLI in the FLAMSA-RIC study has been designed for the prophylaxis of leukemia relapse in patients with high-risk AML and MDS after T cell depletion at transplantation; the use of DLI in patients with minimal residual disease after transplantation is discussed.

Current problems and future directions

Prophylactic and preemptive treatment with donor lymphocytes

Prophylactic treatment is indicated in patients with active disease and high-risk leukemia. Particular high risks are associated with primary refractory leukemia, early relapses of leukemia, and remissions without recovery of blood counts (CRi). Alternatively, post-transplant treatment with DLI may be preemptive in patients with minimal residual disease after transplantation. These patients have a particular high risk of relapse [43]. Cells with a mutated genotype for NPM1, CBFB-MYH11 (inv 16), and RUNX/RUNX1 can be detected by PCR with a sensitivity of 10^{-5} malignant cells [43]. An even better sensitivity can be reached by next-generation sequencing (NGS) [44]. Patients with MRD were treated with DLI or IL-2 depending on the availability of the DLI donor; DLI reduced relapse and improved survival in a multicenter study [45, 46]. These studies differ from others in several ways: the transplant consisted of G-CSF-mobilized bone marrow and blood cells, DLI were G-CSF-mobilized PBSC preceded in most cases by a cycle of intensive chemotherapy, GVHD prophylaxis was given after DLI for 2–4 weeks, and IL-2 was administered for stimulation of DLI. Most importantly, DLI were started whenever MRD was positive, as early as day 30 or 60 after transplantation.

The delay of DLI to day 120 after transplantation reflects the preconditions of absence of immunosuppressive treatment, absence of GVHD, and infections as well as the exclusion of early relapses. In addition, the effect of DLI from normal non-immunized donors on residual host hematopoietic cells is an ongoing effect over several months [8], in patients with CML clinical response took often 6–8 weeks after DLI and the median time until molecular response was 6 months and later responses were seen after more than 1 year [35, 47]. Therefore, it is conceivable that DLI from normal donors may not show immediate effects unless the donor is immune to an antigen presented by the leukemia or DLI are activated by host dendritic cells after transfusion.

Stimulation of the response

Most experience in stimulating a response has been gained from treating relapses after transplantation. In CML dendritic

cells of leukemia origin present antigen directly [48], presentation can be stimulated by treatment with low-dose interferon-alpha (IFN-a) and GM-CSF [49]. In AML, direct antigen presentation and stimulation of T cells can be induced with GM-CSF [50, 51]; the role of IFN-a is disputed [52]. Clinical trials have shown divergent results; better results are expected from pegylated IFN-a. [52]. Patients with relapse of AML were treated with low-dose Ara-C, G-CSF-mobilized blood cells, and GM-CSF. Treatment of the patients with GM-CSF that started at week 2 and continued every month for 1 week has enabled leukemia-free survival in some patients. Patients with a late relapse had a better prognosis and some patients survived with sustained long-term remissions. Long-term survival of some patients has also been reported with the combination of azacytidine and DLI [53]. Early relapses are often associated with a FLT3-ITD. They rarely responded low-dose Ara-C; they could be treated with sorafenib or the first part of the FLAMSA regimen; in these, mobilized peripheral blood stem cell DLI and GM-CSF carried a high risk of acute GVHD.

There are several ways of immune escape of AML cells as summarized in recent reviews [54, 55]. Increased anti-inflammatory cytokines as IL-10 and TGF-ß, decreased inflammatory cytokines, and immunosuppressive enzymes as IDO and others are well known. Immune check point ligands and genes of the proliferative machinery (FLT3-ITD, KRAS) have gained interest with new inhibitory agents. In HLA-haploidentical transplantation, the genetic loss of heterozygosity of HLA class I in AML cells was an important finding [56]. Recently, variables for immune escape of AML cells were investigated in patients with relapse after allogeneic transplantation as compared to those after chemotherapy [57, 58]; the spectrum of gained and lost mutations at relapse as compared to those at diagnosis was similar in both groups [57]. Firstly, HLA class II antigens were downregulated in the majority of patients, a change that can be reversed with IFN-gamma.

Check point inhibitors have a great success in the treatment of lymphoma [59] and some solid tumors; they have been used for the treatment of leukemia relapse after allogeneic stem cell transplantation [60, 61]. The risk of GVHD has to be considered, and results are controversial. In patients with residual disease prior chemotherapy may be justified; this results in the depletion of lymphocytes prior to DLI [45] and damage associated activation giving a high risk of GVHD. These patients should be treated with prophylactic immune suppression for a short time [62]. However, immune suppression is a hindrance to recognize antigens on leukemia cells and it may result in the failure of GVL effects.

Bridging between transplantation and DLI

Obviously, donor lymphocytes transfused after more than 120 days cannot prevent early relapses, the time for recognition, and immune reaction may need another month so that 180 days as a landmark is a relevant time point for the evaluation of the effects. Therefore, bridging of the time until DLI is an important task.

Azacytidine has been given as post-transplant maintenance [63, 64] in combination with DLI in patients with recurrent AML/MDS [53, 65]. Complete responses were seen, and some responses were durable [63]. In combination with valproate, azacytidine can induce CD8-positive T cells against the tumor antigen MAGE [64]. Azacytidine was effective for the treatment of relapse after transplantation in a multicenter study and DLI did not improve the results of azacytidine [66]. However, there was no common schedule of DLI and most received DLI after failure of azacytidine. Favorable factors for response were late relapse—after more than 6 months—and low blast count in the marrow (< 20%) [66]. A multicenter study of azacytidine for mixed chimerism (RELAZA trial) demonstrated improved survival [63]. Recently, an oral preparation of azacytidine was tested as maintenance drug with good results, best results with 14 days of treatment rather than the usual 7-day schedule [67]. Another hypomethylation drug is decitabine that has been used in combination with DLI for the treatment of relapses after transplantation [68]. Long-term survival was achieved by second transplants.

In patients with FLT3 ITD, sorafenib was successful for remission induction pre- and post-transplant [69]; patients achieving molecular remissions have a chance of long-term survival [70]. Maintenance treatment with sorafenib post-transplant has improved relapse-free survival without significant added toxicity [71]. Midostaurin given with chemotherapy and after transplantation did have a positive effect [72]; more specific FLT3 inhibitors are quizartinib and gilteritinib [73]. Presently, it is not known whether these have the same immune effects as sorafenib [74].

Another interesting drug is the histone deacetylase inhibitor panobinostat as maintenance treatment [75] that was tested in 42 patients starting between 60 and 147 with a median of 95 days. There was no increase of GVHD, not even after DLI; panobinostat does not prevent the development of immunological tolerance; it has an immune-modulating effect as vorinostat, another deacetylase inhibitor [76], without weakening the graft-versus-leukemia effect. The major problem of these targeted therapies is hematological side effects so that treatment can only be started late after 1–2 months. Similarly, the bcl2 inhibitor venetoclax has excellent activity against leukemia, but the hematological side effects prohibit prophylactic treatment for bridging.

Similarly, the CD33 antibody treatment either charged with the drug ozogamycin or as bispecific CD33 × CD3 T cell engager (BITE) has a limited role as bridging because of myelosuppression. The cytostatic-loaded antibody had severe side effects with veno-occlusive disease of the liver; it has been reintroduced for high antileukemic efficiency at a lower dose.

Remission induction

A major problem of the treatment of AML and preleukemic MDS is the high age and physical condition of the patients; many patients are not fit enough to stand several cycles of intensive chemotherapy without complications. Most regimens for remission induction are intensive chemotherapy with Ara-C and Daunomycin (7 + 3) [77] or FLAG-Ida [78]. They are associated with severe side effects like infections, diarrhea, and cardiac problems. Less intensive regimens can de designed for elderly and frail patients. Low-dose ARA-C was conventionally given with 20 mg/m^2 twice per day for 10 days; toxicity was low as were remission rates [79]. Conventional regimens of low-dose ARA-C are not very effective, but treatment of elderly patients with 10 mg/m^2 twice per day for 21 days produced the same survival as intensive chemotherapy with less side effects [80]. Gastrointestinal toxicity can limit the duration of treatment; otherwise, treatment over 4 weeks may even improve responses in patients with preleukemic MDS or smoldering leukemia and slow progression (personal obs.). Recently, combinations of low-dose ARA-C with cladribine in alternating cycles with decitabine have achieved objective responses in 58% of patients and a median overall survival of 13.8 months [81]. New regimens of low toxicity and good efficacy have been described; they include CPX351 and combinations of venetoclax with either Ara-C or azacytidine. CPX351 is a liposomal preparation of a fixed combination of Ara-C and daunorubicin that permits the slow release of the drugs with low toxicity and high efficiency [82]. CPX351 was compared to the conventional 7 + 3 regimen; it showed improved survival and gave the chance of long-term remissions following allogeneic transplantation [83]. Venetoclax is a bcl2 inhibitor that combines very well with low-dose Ara-C or azacytidine [84]. These less toxic induction therapies increase the chances of elderly and frail patients for transplantation. Sequential conditioning with FLAMSA may be sufficient to induce long-term remissions in patients treated with low intensity induction therapy.

Conclusions

The FLAMSA-RIC concept is a time sequential therapy that includes sequential anti-leukemia therapy with reduced intensity conditioning including in vivo T cell depletion and delayed transfusion of donor lymphocytes. The anti-leukemia part of conditioning is highly effective; the conditioning part consists of myelosuppressive 4 Gy TBI, BUS, or Treosulfan, and immunosuppressive ATG/CY. In countries where amsacrine is not available, idarubicin or mitoxantrone has been used instead. TBI appears superior anti-leukemic, BUS, and Treo less toxic in elderly patients. The use of melphalan and thiotepa has not yet been reported in this context. Toxicity of CY may be decreased by lower doses or protracted application (3 × 20/40 mg/kg). Immune therapy with donor lymphocytes is effective in patients treated with T cell depletion in vivo or ex vivo. ATG or alemtuzumab should be given in doses sufficient for in vivo T cell depletion. Donor lymphocytes rarely produce a GVL effect before 4–8 weeks unless the patient is lympho-depleted by prior therapy, or lymphocytes are stimulated by IFN-a and /or GM-CSF, intermittent infections or lymphocytes are from immune donors. The indication of DLI may be restricted to patients with minimal residual disease (MRD) or given to every patient with high-risk MDS/AML. Bridging the time interval between transplantation and DLI is most important, azacytidine and lenalidomide or panobinostat have been used with success, sorafenib for FLT3 mutated AML. The indication of allogeneic transplantation has been expanded to patients of 70 years and older. In patients, primary induction should be limited to one or two cycles of chemotherapy; in elderly patients, new less intensive regimens should be preferred like venetoclax-azacytidine [85] or CPX 351 [86].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Kolb Consulting UG has consulting contracts with Novartis, Therakos and Eurocept without impact on the presented review.

Research involving human participants All procedures performed in studies involving human patients were in accordance with the standards of the institutional review boards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants for the treatment as well as the scientific use of the data.

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