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Emerging immunotherapies in older adults with acute myeloid leukemia

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Abstract

Purpose of review—We summarize recent advances for acute myeloid leukemia (AML) in older patients, with a focus on immunotherapeutics. Although the recently updated US SEER data still show that the majority of older AML patients do not receive any therapy, this reality is slowly changing. Advances in our understanding of the biology of AML and in the field of immunology are facilitating the development of alternative therapeutic options for patients, affording more and novel opportunities for potentially curative treatment.

Recent findings—Data from multiple cooperative groups show that older patients benefit from the incorporation of gemtuzumab ozogamicin, an anti-CD33 mAb toxin, into induction regimens. The first prospective study for Reduced-intensity conditioning (RIC) Allogeneic Hematopoietic Stem Cell Transplantation in older AML patients was reported at ASH 2012; the approach was feasible and improved Disease-Free Survival over conventional chemotherapy. Proof-of-concept trials targeting specific antigens such as WT1 or novel unique leukemia-associated antigens are currently underway, as well as other trials using chimeric antigen receptor T cells or (Natural Killer NK/effector cells in nontransplantation settings.

Summary—Wider application of immunotherapies such as allogeneic hematopoietic stem cell transplantation with RIC have altered the landscape and offer potential for cure of an increasing number of older AML patients.

Keywords

immunotherapy; natural killer cells; older acute myeloid leukemia patients

Introduction

The incidence of AML increases with age, with an age-adjusted incidence of 3.6 cases per 100 000 people per year and a median age of 69 years at diagnosis. Older patients have poor survival due to an increased likelihood of intrinsic chemoresistance and concomitant medical comorbidities resulting in poor tolerance to chemotherapy. Long-term OS(Overall survival) is only 10% [1]. In a recent update of the US SEER experience of Medicare

patients with acute myeloid leukemia (AML) in the 1990s, only 33.8% of AML patients aged more than 65 years received treatment; the entire cohort had a median survival of only 2.4 months [2[•]] (Table 1). Furthermore, only 0.8% of these patients received what is emerging as the best option for cure, Reduced-intensity conditioning Allogeneic Hematopoietic Stem Cell Transplantation (RIC HSCT). However, over the course of the decade studied in the SEER dataset, the frequency of older AML patients actually receiving any treatment increased, probably in part due to availability of the hypomethylating agents and other options. RIC HSCT is also increasingly utilized in older AML patients.

Biology of Acute Myeloid Leukemia in Older Patients

Increasing knowledge about the molecular heterogeneity of AML holds the promise that each patient can be eventually treated in personalized fashion on the basis of unique biologic features. Advances in whole genome sequencing have shown the full spectrum of mutations that can occur at diagnosis and the acquisition of multiple new mutations over the course of clonal evolution [3^{••},4^{••}].

Cytogenetically Normal Acute Myeloid Leukemia (CN-AML) has been studied as a platform to identify novel mutations, and several genes have been identified with prognostic significance [5[•]]. *DNMT3A-R882* mutation occurs in 33.3% of older patients and is associated with shorter Disease-Free Survival (DFS) and OS [6]. In a cohort of 46 older patients treated with the hypomethylating agent decitabine, six out of eight patients with mutated *DNMT3A* achieved Complete remission (CR); this small dataset is interesting and needs further exploration [7]. Isocitrate Dehydrogenase 1 (*IDH2*) mutations occur in 19% of older patients and demonstrate resistance to induction chemotherapy (IC), as evidenced by lower CR rates (20 vs. 67%; $P=.005$) and 3-year OS rates (0 vs. 17%) when compared with *IDH1/IDH2* wild-type (wt) patients [8]. Similar to younger adults, Nucleophosmin 1 (*NPM1*) mutations have a favourable prognosis in older patients, especially those aged at least 70 years [9]. Recently, autologous CD4⁺ and CD8⁺ T cell immune responses were demonstrated in samples from *NPM1*-mutated patients, raising the possibility that *NPM1*-directed immune responses might result in the elimination of *NPM1*-mutated blasts [10]. Other genes associated with adverse outcome in older patients have high *Meningioma 1* (*MNI*) expression and Additional Sex Combs like 1 (*ASXL1*).[11,12]. Although the prevalence of Wilms Tumor 1 (*WT1*) mutations is lower in older patients, they are associated with lower rates of CR [13]. Vaccinations with peptides derived from *WT1* oncoprotein have induced T cell responses in older patients treated during maintenance of CR [14,15].

Hypomethylating Agents

Epigenetic silencing of structurally normal genes by abnormal DNA methylation, mediated by DNA-Methyl Transferase (DNMT) enzymes, has been shown to contribute to myeloid leukemogenesis [16]. Two azanucleoside DNMT inhibitors, azacitidine (5-Azacitidine; Vidaza; Celgene, Inc., Summit, New Jersey, USA) and decitabine (5-aza-2'-deoxycytidine; Dacogen; Eisai, Inc.,Tokyo, Japan), are approved in the United States for treatment of patients with Myelodysplastic Syndrome (MDS). A randomized trial showing OS benefit for

azacitidine in high-risk MDS also showed that azacitidine was effective in AML patients with bone marrow blasts of 20–30% [17]. A recent phase II study in 53 older AML patients using a novel schedule of decitabine as a single agent (a 10-day/cycle schedule with a subsequent response-adapted approach) yielded a CR rate of 47%, requiring a median of three cycles to achieve CR. Median OS was 55 weeks. This trial also showed that higher pretreatment levels of *miR-29b*, a microRNA known to target DNMTs, were associated with clinical response to decitabine [18]. Recently, bortezomib has been shown to upregulate *miR-29b*, which led to a phase I trial of decitabine and bortezomib, with a CR rate of 50% in a small group of previously untreated patients [19].

A multicentre, international, randomized, open-label phase III trial comparing decitabine (with the typical 5-day/cycle schedule) with Best Supportive Care (BSC) or low-dose cytarabine showed that decitabine improved response rates but did not improve OS [20]. The Alliance [formerly - Cancer and Acute Leukemia Group B (CALGB)] is conducting a phase II randomized trial of decitabine alone in comparison with decitabine and bortezomib [21] in patients aged at least 60 years using a modification of the published 10-day dosing schedule (Clinical-Trials.gov Identifier: NCT01420926).

GO

Antibody-directed therapy allows targeting of the cell population of interest, potentially augmenting the antileukemic effect while avoiding increased toxicity [22]. CD33 is expressed in 90–95% of AML patients; when attached to its ligand, it internalizes into the cell and constitutes a potent mechanism for drug delivery. Gemtuzumab Ozogamicin (GO) is a humanized anti-CD33 antibody linked to a calicheamicin derivative that is a potent DNA-damaging agent. It initially gained regulatory approval in 2000 but was voluntarily withdrawn from the market in 2010 citing safety concerns of toxicity when given in combination with IC.

However, modification of the dose may permit patients to benefit without increased toxicity. A recent randomized trial of 1115 untreated AML patients (median age 67 years, range, 51–84 years) compared the addition of a single low-dose (3 mg/m^2) of GO with IC [23]. Although clinical response and toxicity were similar between the GO and no-GO arms, the incidence of relapse (68 vs. 76%) was significantly lower and OS (25 vs. 20%) was significantly better in the GO arm at 3 years. These data showed that GO at 3 mg/m^2 administered simultaneously with daunorubicin (50 mg/m^2) and IC was well tolerated, significantly reduced risk of relapse and improved OS.

In another randomized trial for newly diagnosed patients aged 50–70 years, GO was administered at a dose of 3 mg/m^2 on days 1, 4 and 7 during IC and day 1 of each of the two consolidation chemotherapy courses. One hundred and forty patients each were assigned to the GO and control groups. Complete response with or without incomplete platelet recovery was similar between the two groups (81% in the GO group vs. 75% in the no-GO group, $P = 0.25$). Yet, 2-year survival results were significantly better in the GO group: EFS, 40.8% in the GO group vs. 17.1% in the no-GO group, $P = 0.0003$; OS, 53.2% in the GO group vs. 41.9% in the no-GO group, $P = 0.0368$; DFS, 50.3% in the GO group vs. 22.7% in the no-GO group, $P = 0.0003$. Persistent thrombocytopenia was more common in the GO group

than in the control group (16 vs. 3%, $P < 0.0001$), without an increase in the risk of death from toxicity. This trial showed that fractionated lower doses of GO allowed safe delivery of higher cumulative doses and substantially improved outcomes in AML patients [24^{***}]. For particularly aged or infirm patients not candidates for IC, a randomized trial evaluated the impact of addition of GO to low-dose Ara-C, with the goal of improving remission rate and survival [25]. In this trial of 495 patients, the addition of GO significantly improved the remission rate (30 vs. 17%) but did not impact the 12-month OS (25 vs. 27%).

RIC HSCT

Allogeneic transplantation is a potentially curative treatment option for AML patients. However, this option was not available for many older patients due to excessive toxicity with conventional ablative conditioning approaches. RIC HSCT emerged as a less toxic alternative, as it relies on graft-versus-leukemia (GVL) effects rather than cytoreductive effects of the conditioning regimen [26,27]. A meta-analysis by Sorror *et al.* [28^{*}] of 372 patients older than 60 years undergoing RIC HSCT showed 5-year OS of 35% and progression-free survival (PFS) of 35%. Interestingly, contrary to popular opinion about toxicity of HSCT in older adults, 54% of patients receiving matched unrelated donor (MUD) HSCT were either never hospitalized or hospitalized only overnight in the first 100 days after HSCT.

Farag *et al.* [29] retrospectively compared RIC HSCT with IC in patients aged 60–70 years with AML in CR1 and showed that at 3 years, RIC HSCT was associated with a significantly lower risk of relapse (32 vs. 81%, $P < 0.001$), higher NRM (36 vs. 4%, $P < 0.001$) and longer leukemia-free survival (LFS) (32 vs. 15%; $P = 0.001$). OS was longer for HSCT recipients, but the difference was not statistically significant (37 vs. 25% at 3 years; $P = .08$).

The Alliance and the BMT-CTN initiated a phase II prospective study in 2004 using a uniform conditioning regimen to HSCT recipients [30^{***}]. One hundred and thirty-two patients were registered at 21 centres and 123 were transplanted [MRD(matched related donor) (47%); URD (unrelated donor)(53%)]. All donor grafts were Granulocyte Colony Stimulating Factor (G-CSF) mobilized Peripheral Blood Stem Cells (PBSC). The median age of patients was 65 years (range 60–74 years). More than 90% entered transplant after achieving CR with standard '7+3' based induction. CR1 was achieved after one (59%) or two (41%) induction cycles. All but the initial eight MRD recipients were conditioned with the same regimen containing fludarabine (30 mg/m²/day × 5), busulfan (6.4 mg/kg intravenous total dose) and ATG (Anti-thymocyte globulin)(7.5 mg/kg total dose). The cumulative incidence of acute Graft-Versus-Host Disease (GVHD) Grades 2-4 was 9.4% and that of chronic GVHD was 26%; relapse incidence was 47% with TRM of 14%. OS at 2 years was 46% with DFS of 39%. This is the first prospective phase II study to show feasibility and effectiveness of RIC allo-HSCT using MRD or MUD grafts. The high relapse rate warrants research on mitigating risk of relapse after transplant. Table 2 summarizes results of recent trials of RIC allo-HSCT in AML.

Natural Killer Cells as Immune Effectors In Acute Myeloid Leukemia

Allo-HSCT has demonstrated convincingly the potential of allogeneic T-cells in causing sustained remissions in hematologic malignancies. However, toxicity of allo-HSCT precludes its application to a broader group of patients. An improved understanding of NK biology along with mechanisms of NK and T-cell mediated alloreactivity against leukemia has led to clinical immunotherapeutic strategies, which can be done in non-HSCT settings.

The role of NK cells in mitigating GVHD while preserving GVL was first demonstrated by Ruggeri *et al.* [31] in the setting of T-depleted Human Leukocyte Antigen (HLA)-mismatched transplantation. In a study [32] of 92 high-risk AML patients who received grafts from an HLA haplotype mismatched family donor, recipients lacking HLA ligands for donor Killer-cell Immunoglobulin-like receptor (KIR) were found to have a lower rate of rejection, relapse and GVHD (Fig. 1).

Ruggeri *et al.* [31] evaluated the mechanism for these effects in a mouse model of mismatched allo-HSCT. When alloreactive donor NK clones were infused pretransplant, a reduction of recipient (Antigen-presenting cells (APC) was noted in the bone marrow, spleen and gut. These data suggest that alloreactive NK cells prevent GVHD by elimination of recipient APCs, which are critical for initiating the GVHD cascade. Other postulated mechanisms include evidence that donor NK cells are capable of killing donor T-cells that mediate GVHD. In an major histocompatibility complex (MHC)-mismatched setting, mouse recipients of an allogeneic transplant who received donor NK cells and T-cells on day 0 along with T-depleted bone marrow had a longer survival and a lower incidence of GVHD than in controls who received donor T cells alone [33]. Donor T-cells exhibited less proliferation and decreased IFN- γ production in the presence of NK cells. Despite reducing GVHD, the GVL effects mediated by donor T-cells were retained. Another study by Noval Rivas *et al.* [34] showed the regulatory effect of NK cells on inhibiting expansion and infiltration of minor antigen-specific T-cells that mediate chronic GVHD.

The impact of improved understanding of mechanisms of NK alloreactivity has resulted in paradigm-shifting insights on donor selection in HSCT. KIR expressed on NK cells recognize disparate HLA molecules and is divided into two different haplotype groups: Group A haplotypes with a fixed number of genes coding inhibitory receptors with the exception of KIR2DS4; and Group B haplotypes with variable gene contents including additional activating receptor genes [35,36]. All individuals can be categorized as having the following KIR genotypes: A/A, which is homozygous for group A KIR haplotypes, or B/x, which contains either one (A/B heterozygotes) or two (B/B homozygotes) group B haplotypes. Recent studies [37,38] have suggested that donor's NK cells expressing group B haplotypes, compared with group A, yield significantly superior protection against leukemic relapses and improved DFS in patients undergoing T-cell depleted HSCT for AML.

Sivori *et al.* [39] showed that expression of KIR2DS1 confers a remarkable advantage in the ability of NK cells to kill allogeneic dendritic cells and blasts in the setting of haploidentical HSCT [35]. Venstrom *et al.* [40] demonstrated in 1277 patients receiving MUD HSCT that patients with AML receiving allografts from KIR2DS1-positive donors had a lower rate of

relapse than those receiving allografts from KIR2DS1-negative donors (26.5 vs. 32.5%; $P = 0.02$). Donor KIR2DS1 appeared to provide protection against relapse in an HLA-C-dependent manner. We now have compelling evidence from both the haploidentical and MUD transplants that donor KIR2DS1 and 2DS2 genotypes are associated significantly with a lower relapse rate [38,41,42]. These data have led to ongoing prospective trials evaluating KIR genotypes in addition to HLA typing to select the most favourable KIR genotype donor who would confer a lower relapse risk.

PD-1 blockade in solid tumours has shown that removal of inhibitory signals enhances effector function resulting in clinical responses in patients with solid tumours [43]. A similar approach using an anti-KIR mAb (IPH2101) that can block KIR-mediated inhibition of NK cells has been studied in AML [44,45]. A phase I study [44] of IPH2101 in 23 older patients in CR1 showed improved survival in a small group of patients treated at higher dose levels, but PFS for the entire group was not significantly different among the dose levels.

Natural Killer Infusions in Acute Myeloid Leukemia in Non-Hematopoietic Stem Cell Transplantation Setting

In an effort to maximize GVL effects and to minimize TRM, donor NK cell infusions in the non-HSCT setting have been explored. Miller *et al.* [46] first reported the transfer of haploidentical NK cells in the non-HSCT setting. Curti *et al.* [47] studied feasibility of KIR-mismatched alloreactive NK cell infusion with low-dose IL-2 in older AML patients as postremission therapy, following conditioning with fludarabine and cyclophosphamide. Three out of six patients in CR remain leukemia-free at 34, 32 and 18 months of follow-up. These data suggest that NK cell therapy has a potential clinical benefit in non-HSCT settings.

Novel Immunotherapeutic Approaches in Acute Myeloid Leukemia

Following the success of Chimeric antigen receptor (CAR) T-cells in chronic lymphocytic leukemia [48], similar approaches targeting CD123, a marker which is expressed differentially in high numbers on Leukemic Stem Cells (LSCs) while sparing normal HSCs, are being studied. Two groups have developed CD123-specific CAR and have demonstrated activity of these modified T-cells against primary AML samples [49,50]. Similar approaches using CAR transfected NK cells are also being investigated [51]. As trafficking to selective therapeutic niches is a significant barrier to adoptively infused cells, Chemokine receptor type 4 (CXCR4) transduced T-cells are being studied to improve homing of T-cells to the bone marrow [52]. These novel approaches are summarized in Table 3 [53–55]. Although the regulatory and manufacturing processes for translation of cell therapies takes longer than pharmaceutical agents, recent successes with CAR T-cells offers reason for optimism at the possibility of immunotherapeutic approaches that can be done in patients not eligible for allo-HSCT.

Conclusion

The treatment of older patients with AML is slowly but steadily changing from an emphasis on supportive care to an approach that increasingly utilizes potentially curative therapies such as RIC HSCT. Advances in prognostication with the characterization of new mutations will eventually help identify patients who will have a higher likelihood of response to specific therapies. After achievement of CR, RIC HSCT emerges as a feasible and effective approach for a broader group of older patients. The identification of new target antigens along with novel approaches such as WT1 vaccines, NK cell infusions, improved donor selection for allo-HSCT and development of effector cells engineered for targeted cytotoxicity, among others, hold promise for a variety of immunotherapeutic options for older AML patients in the future.

Acknowledgments

None.

References and Recommended Reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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Key Points

- Treatment of older patients is slowly but steadily changing from an emphasis on supportive care to potentially curative therapies such as allogeneic HSCT.
- Older patients have more alternatives to induction chemotherapy such as hypomethylating agents and gemtuzumab ozogamicin.
- RIC allo-HSCT is emerging as a feasible and effective option for older patients who attain complete remission.
- Improved understanding of NK biology has provided insights on donor selection in allo-HSCT and for providing immunotherapy options in non-HSCT settings.
- Novel immunotherapy approaches hold promise for variety of treatment options for older patients in the future.

Figure 1.

In 92 high-risk acute leukemia recipients who received grafts from an HLA haplotype mismatched family donor, recipients lacking HLA ligands for donor KIR were found to have a lower rate of rejection, relapse and GVHD.

Table 1
Summary of US SEER acute myeloid leukemia dataset

	2000–2007
Patients, <i>n</i>	5480
Median age, years (range)	78 (65–93)
Frequency of prior MDS (%)	17.5
Patients with CCI score of at least 1 (%)	45
Patients who were tested for cytogenetics (%)	34.9
Patients treated with chemotherapy (%)	38.6
Patients receiving hypomethylating agents (%)	10.7
Patients receiving allo-HSCT (%)	0.8
OS of all patients (months)	3
OS of patients receiving chemotherapy (months)	6
OS of patients receiving hypomethylating agents (months)	9
OS of patients receiving allo-HSCT (months)	22
Death within 2 months of starting chemotherapy (%)	36
Death within 2 months of starting chemotherapy (%)	18.7

CCI, Charleston comorbidity index; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; OS, overall survival.

Table 2

Reduced-intensity HSCT trials in acute myeloid leukemia

Study	Type of study	Number of patients	Age range (years)	Follow-up (months)	Incidence of relapse (%)	Nonrelapse mortality (%)	Disease-free survival (%)	Overall survival (%)
Sorror <i>et al.</i> [28*]	Retrospective	372	60-75	55	41	27	32	35
Farag <i>et al.</i> [29]	Retrospective	94	60-70	36	32	36	32	37
Koreth [26]	Retrospective	158	60-71	34	54.6	10	35	46
Chevallier [27]	Retrospective	600	60-65	23.7	25	32.3	46.2	49.2
Devine [30**]	Prospective	132	60-74	40	47	14	39	46

HSCT, Hematopoietic stem cell transplantation.

Table 3
Promising preclinical immunotherapy studies from the American Society of Hematology Annual Meeting, 2012

Author	Mechanism	Type of cells	
Mardiros [49]	Target markers on leukemic stem cells while sparing normal hematopoietic stem cells	CD123-specific CAR T cells	CD123-specific CAR expressed in healthy donor T cells has antileukemic activity against primary AML patient samples
Tettamanti [50]	Target markers on leukemic stem cells while sparing normal hematopoietic stem cells	CD123-specific cytokine-induced killer cells (T cells)	CD123-specific CAR expressed in healthy donor T cells has antileukemic activity against primary AML patient samples and spares normal HSCs, which express CD123 in lower numbers
Chu [51]	Infusion of donor CAR NK cells	NKs transfected with anti-CD20 CAR	CD20-specific CAR expressed in healthy donor NKs expanded with K562-mbIL15-41BBL cells for 1–2 weeks demonstrates antileukemia activity against cell lines
Carpenter [52]	Improve trafficking of T cells to therapeutic niches	CXCR4 transduced T cells	Murine studies showing CXCR4 transduced T cells migrate in higher numbers to bone marrow and demonstrate improved effector function and capacity to generate memory cells
Stickel [54]	Identify novel tumour-associated antigens for immunotherapy	HLA ligandome analysis of primary AML patient samples	Similar amounts of HLA Class I on both AML and autologous healthy monocytes. 10000 peptides identified from 6 AML patients, proving a pathway for peptide-based immunotherapy
Dahmani [53]	Overcome resistance by immunosuppressive cytokine TGF- β	Autologous T cell response to leukemia	Murine studies investigating whether concomitant TGF- β blockade improves outcome of adoptive immunotherapy
Casucci [55]	Safe targeting of CD44v6 (adhesion receptor widely expressed in AML) through the coexpression of a suicide gene in CAR-modified T cells for AML	CAR T cells transduced with a suicide gene to control off-target toxicities of T cells	Murine studies show that CD44v6 transduced CAR T cells are cytotoxic against AML and can be ablated at will due to concomitant expression of humanized suicide gene inducible caspase 9

AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CXCR4, chemokine receptor type 4; HLA, human leukocyte antigen; HSC, Hematopoietic stem cells; NK, natural killer cells; OS, overall survival; TGF, transforming growth factor.