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Immunotherapy prospects for acute myeloid leukaemia

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Summary

While chemotherapy is successful at inducing remission of acute myeloid leukaemia (AML), the disease has a high probability of relapse. Strategies to prevent relapse involve consolidation chemotherapy, stem cell transplantation and immunotherapy. Evidence for immunosurveillance of AML and susceptibility of leukaemia cells to both T cell and natural killer (NK) cell attack and justifies the application of immune strategies to control residual AML persisting after remission induction. Immune therapy for AML includes allogeneic stem cell transplantation, adoptive transfer of allogeneic or autologous T cells or NK cells, vaccination with leukaemia cells, dendritic cells, cell lysates, peptides and DNA vaccines and treatment with cytokines, antibodies and immunomodulatory agents. Here we describe what is known about the immunological features of AML at presentation and in remission, the current status of immunotherapy and strategies combining treatment approaches with a view to achieving leukaemia cure.

Keywords: AML, antibodies, cell therapy, vaccines

Background

In the 1970s it became apparent that the recently introduced chemotherapeutic agents daunorubicin and cytosine arabinoside could achieve remissions in a substantial number of patients with acute myeloid leukaemia (AML). However, unlike the experience with childhood acute lymphoblastic leukaemia, it was clear that remissions were not usually maintained by consolidation and maintenance treatments [1]. This was the incentive to explore the idea of preventing relapse by vaccinating patients against leukaemia at remission, when the disease was at a low residual level. One vaccine trial with bacille Calmette–Guérin (BCG) and irradiated autologous leukaemia cells did report prolonged remission and survival in the vaccinated group [2], but interest in vaccination waned with the development of high-dose therapy and stem cell transplantation (SCT) to sustain remissions. An important lesson from allogeneic SCT was that the donor immune system could confer a graft-*versus*-leukaemia (GVL) effect whose potency has been realized increasingly over the last few decades, supporting a role for both donor T cells and natural killer (NK) cells in the suppression and elimination of residual leukaemia after SCT [3]. Four decades after the initial attempts at vaccination for AML and with only small improvements in the long-term survival of AML patients, especially those aged over 60 years, interest in immune mechanisms controlling AML and immunotherapy for AML has been revived. Here we review the evidence for the interaction of the immune system with AML and results of recent vaccine trials and outline developing immunotherapeutic strategies.

Interaction of the immune system with AML

AML cells as targets for immune attack

There is abundant evidence that AML cells are susceptible targets of innate and adaptive immune responses. AML cells express both major histocompatibility complex (MHC) classes I and class II, making them susceptible to T cell recognition and attack. They also express major immunogene complex (MIC)-A/B, one of the ligands for the activating NK cell receptor NKG2D. T cells and NK cells exert cytotoxicity through perforin-granzyme release, interaction of TNF-related apoptosis-inducing ligand (TRAIL) with death receptors on the target causing apoptosis, and indirectly through cytokine production of inflammatory cytokines tumour necrosis factor (TNF) and interferon (IFN) [4–6].

Allogeneic anti-leukaemia reactivity

The most compelling data for the susceptibility of AML to immune attack comes from experience with allogeneic SCT, where both T cells and NK cells are implicated in the GVL effect [3]. Humanized severe combined immunodeficiency (SCID) mouse models demonstrate that T cell clones derived from patients after allogeneic SCT can prevent and control the emergence of human leukaemia *in vivo* [7,8]. *In vitro*, a number of studies show that AML cells are targeted by donor T cells after SCT and at least one minor histocompatibility antigen (mHAg) on AML cells has been characterized [9]. Allogeneic NK cells are cytotoxic to AML targets that do not express cognate human leucocyte antigen (HLA) molecules for the killer immunoglobulin-like receptor (KIR) on the donor's NK cell, protecting allorecipients from relapse [10]. Other allogeneic interactions between NK cells and targets that do not follow the 'missing self' rule also occur in HLA-identical SCT. Notably, donors possessing KIR groups of the B haplotype confer protection against relapse in both HLA matched unrelated [11] and related SCT [12]. Transplant data suggests that NK mediated GVL is very specific for myeloid leukaemias.

Autologous anti-leukaemia reactivity

Cytotoxic interactions also occur between autologous lymphocytes and AML cells. It has been known for many years that fresh autologous leukaemic blasts are lysed by cytokine-activated NK cells [13,14]. AML expression of NK ligands, including MHC class I molecules and CD44, determines their susceptibility to NK attack. A high expression of HLA-G, HLA-Bw4 and HLA-C protects AML cells from NK lysis and is associated with poorer outcome after chemotherapy [15,16]. T cells recognizing autologous AML cells have been generated *in vitro* in prolonged culture where the T cells are restimulated with AML antigen-presenting cells [17,18] and T cells specific for several antigens expressed on AML cells (WT1, PR1, PRAME) are often detected in patients with AML compared with infrequent low levels of expression seen in healthy individuals [19,20].

The AML stem cell as a target for immune attack

It is generally accepted that cure of AML can only be accomplished by eliminating the leukaemic progenitor responsible for maintaining remission. Using SCID-Hu mouse models, Dick and colleagues showed that only 1/250 000 AML $CD34^+CD38^-$ cells were capable of establishing leukaemic haematopoiesis in the recipient [21,22]. These cells could be targeted by alloreactive T cells recognizing minor antigens on the leukaemia stem cells [7,8]. These models should be interpreted with caution, as the xenogeneic milieu of the recipient mouse underestimates the number of cells capable of self-renewal and do not provide clear evidence that long-lived AML progenitors are subject to the same degree of immune attack. Furthermore, they do not identify whether all subtypes of AML have comparable hierarchies of long-lived progenitors. Indeed, an alternative model of leukaemia cure is that a sustained T cell response to the progeny of the AML stem cell but not the small stem cell pool itself could contain the leukaemia at a minimal disease level, resulting in a functional cure [3].

Immune surveillance (IS) in AML

Although the concept of immune surveillance is well accepted, evidence for IS specifically in AML is largely indirect, revealed through relationships between treatment outcome and immune parameters and adaptive changes made by the leukaemia favouring immune evasion, unlike viral-induced malignancies. Perhaps the most compelling evidence for a significant role of immune control of AML comes from several observations indicating that lymphocyte recovery following induction chemotherapy is strongly predictive for outcome. T cells are reduced after chemotherapy but have a rapid clonogenic potential which allows a swift T cell recovery [23]. Patients achieving the highest lymphocyte counts within 6 weeks of chemotherapy have the lowest relapse rates [24–26]. Long-term survival in AML is also favoured by normalized lymphocyte counts [27]. These data all suggest that an intact immune system can protect against relapse of disease, but do not define whether the effect is mediated through T cells or NK cells.

How AML evades immune control

There are diverse abnormalities in AML at presentation and relapse that suggest how the leukaemia may develop despite immunosurveillance and how an established leukaemia may acquire new characteristics to defeat immune control. Figure 1 depicts the interactions between AML cells and the immune environment. Genetic features are emerging that may favour the development of AML in the presence of an intact immune system. There is an increased frequency in AML of a particular genotype of the co-stimulatory molecule cytotoxic lymphocyte antigen -4 (CTLA-4) [28]. The inhibitory KIR molecule KIR 2DL2 is expressed more frequently in AML, again suggesting a predisposition for AML through some form of immune escape [29]. There is also strong evidence that an established AML can mutate to escape immune control. The most dramatic example of this comes from studies after SCT where relapsed leukaemias have been found to down-regulate co-stimulatory molecules, become resistant to NK cell-mediated lysis [30] and, after haploidentical SCT, down-regulate the entire mismatched HLA haplotype to avoid powerful GVL effects through mismatched CTL [31]. AML cells at presentation of disease show a number of abnormalities suggestive of

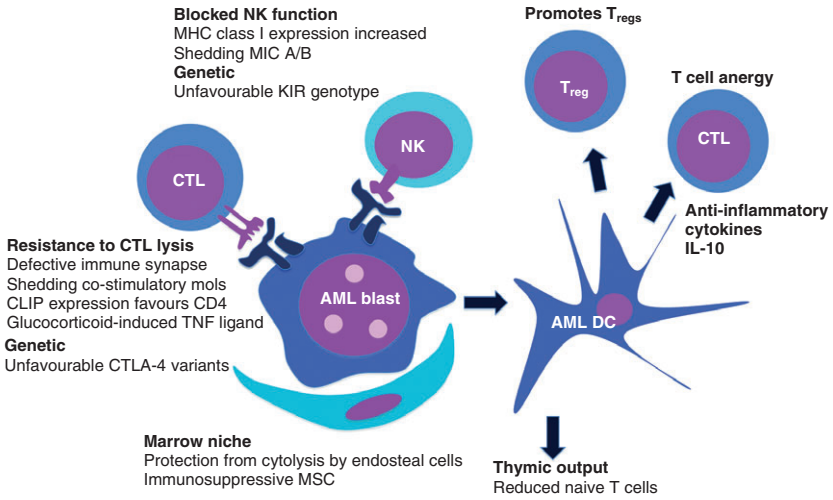

Fig. 1. Interactions between acute myeloid leukaemia (AML) cells with the immune milieu.

immune pressure to select variants that evade immune surveillance. AML can express the ligand for the glucocorticoid-induced tumour necrosis factor-related protein (GITRL), which can block NK function through triggering GITR on the NK cell directly or through soluble GITRL [32]. AML blasts often weakly express co-stimulatory molecules which may favour their escape from T cell-mediated killing, and the probability of remaining in remission is greatest in patients who express both CD80 and CD86 [4]. AML cells can shed ligands for co-stimulatory molecules such as the 4-1BB ligand, which may allow the leukaemia to block T cell attack by the binding of soluble ligand to the T cell [33]. The class II-associated invariant chain self-peptide (CLIP) is expressed variably in AML. CLIP down-regulation can increase antigenicity of AML cells (by unblocking MHC class II loading with self-antigen) and increase CD4 responses. Patients whose AML blasts have less CLIP bound to HLA-DR molecules have prolonged remissions [34]. AML cells secrete soluble factors which may be responsible for a variety of defects observed in T cell and NK cell function [35,36]. Through their myeloid-lineage affinity, AML cells can generate leukaemic dendritic cells (DC) *in vitro* and *in vivo* which function as antigen-presenting cells (APC). However, AML DC are distinctly abnormal [37]. They can inhibit the induction of CTL, inducing T cell anergy [38–40] and favouring the generation of regulatory T cells [41] which are increased in AML [42]. Probably as a consequence of the leukaemia, T cells in AML show several abnormalities: recent thymic emigrants are reduced, suggesting defective thymic function [43]. In a detailed study of T cells in AML Le Dieu and colleagues found T cells with abnormal phenotypes and genotypes that formed defective immune synapses with AML blasts [44]. Finally, the AML microenvironment may favour AML survival – mesenchymal stromal cells in leukaemias can provide an immunosuppressive milieu [45] and the protective endosteal region of the marrow favours the survival of leukaemic stem cells [46].

Developments in immunotherapy of AML

Treatment strategies

Whether the goal of immunotherapy in AML is to boost the patient's immune system or to confer immunity with T cells, NK cells or monoclonal antibodies, immune treatment is usually planned as a means of sustaining remission once the disease has been bulk-reduced with chemotherapy. Animal models of AML have proved useful in providing the basis for adoptive T cell and NK cell therapy [47], exploring the combination of immunotherapy with chemotherapy [48] and defining the role of regulatory T cells in preventing full efficacy of leukaemia-specific cytotoxic T cells in a mouse AML model [49]. The development of robust human leukaemia models in immune deficient mice has helped to identify MHag, CD44 and WT1 as targets for immune attack that result in the elimination of human AML transferred into non-obese diabetic (NOD)-SCID or the more permissive NOD/LtSz-scid IL2Rgammac null (NSG) mice [50–53]. These studies have helped to pinpoint treatments and factors which improve elimination of AML progenitor cells, but are limited by the artificial environment of the mouse which, despite immune deficiency, may not represent a sufficiently permissive environment for human AML to proliferate. In man, clinical immunotherapy trials have variously explored cytokines, vaccines to boost T cell immunity, treatments to increase susceptibility of the target as well as strategies to directly attack AML cells with antibodies, or lymphocytes (Fig. 2).

Cytokines

The availability of the lymphokine interleukin (IL)-2 for clinical use in the 1980s precipitated a number of clinical trials exploring its potential to boost both T cell and NK cell function to prevent relapse after induction therapy for AML.

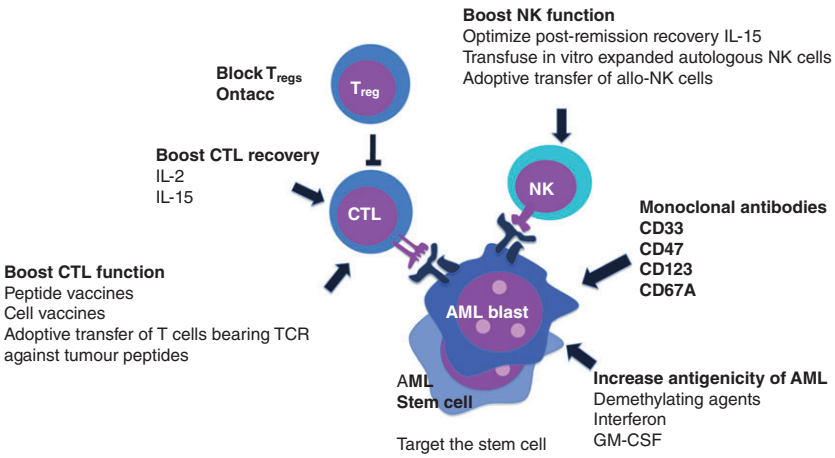

Fig. 2. Immunotherapeutic strategies for acute myeloid leukaemia (AML).

Results have been variable [54–59]. Some trials demonstrated a prolongation of remission. However monocytic leukaemias can express the IL-2 receptor, which carries a theoretical risk of IL-2 induced relapse [60]. Most recently Romero *et al*. used low-dose IL-2 in conjunction with histamine dihydrochloride, which enhances NK killing through conserving expression of the activating receptors NKG2D and NKp46 [61]. Interleukin-15 is another lymphokine targeting the common gamma chain of the IL-2 receptor, which is emerging as a critical factor for growth of T cells and NK cells after lymphoablative chemotherapy as well as promoting NK cytotoxicity [62]. When IL-15 becomes available for clinical trial it will be of major interest to explore its application early after remission induction to expand the lymphocyte compartment rapidly to reduce relapse. Other cytokines of potential interest in AML are granulocyte–macrophage colony-stimulating factor (GM–CSF), which can increase antigen presentation by the leukaemia, and interferon, which can increase lymphocyte cytotoxicity, up-regulate MHC expression on the tumour and suppress malignant cell proliferation [63,64]. However, in contrast to the wide experience of IFN in CML, it has been rarely employed in AML except in the context of leukaemic relapse after stem cell transplantation.

Monoclonal antibodies

Monoclonal antibodies can kill leukaemic cells via a variety of mechanisms and have emerged as promising therapeutic tools, due both to their specificity and potential for reduced toxicity compared to chemotherapy. AML cells express several surface molecules that have been explored as targets for monoclonal antibody therapy. These include CD33, CD123 (IL-3 receptor alpha chain) [65], CD47 (integrin-associated protein) [66,67], C-type lectin [68] and CD64 (high-affinity Fc gamma receptor) [69]. Most experience has been obtained with antibodies targeting CD33, a surface glycoprotein found on more than 80% of myeloid leukaemias but not on normal haematopoietic stem cells or mature granulocytes. Thus anti-CD33 antibodies eliminate malignant myeloid cells selectively while sparing normal stem cells [70]. The first humanized CD33 molecule approved by the Food and Drug Administration (FDA) was conjugated with calicheamycin (gemtuzumab). Trials exploring single-agent use of gemtuzumab have achieved remission only in the in the range of 15%, but gemtuzumab used together with other agents to treat relapsed or refractory leukaemia are promising [71–77]. The most significant toxicity reported is liver injury, occurring most commonly when gemtuzumab is used in combination with thioguanine or in the setting of allogeneic stem cell transplantation [78]. Antibody treatment has been reviewed recently [79].

Whole cell vaccines

AML cells are weak stimulators of T cells and often possess mechanisms that prevent induction of T cell response and induce resistance to cytotoxicity (see above). Simple vaccination with irradiated blasts with BCG or other cytokines resulted in prolongation of remission but with no improvement in survival [1]. To increase the susceptibility of AML to immune attack, investigators have sought to improve antigenicity of the leukaemia by transfection of genes for co-stimulatory molecules such as 4-1BB ligand [80], combinations of CD80 and IL-2 [81] or by differentiating the blasts into leukaemic DC. In a study of 22 AML patients, DC were generated successfully in five and used to treat patients in remission. However, only two of these patients were long-term survivors [82]. Alternatively, DC have been generated from AML patients in remission and made more antigenic by fusion with AML blasts [83], exposure to AML lysates or peptide antigens or transfection with RNA [84]. A clinical trial with a monocyte-derived DC loaded with mRNA for Wilms tumour-1 (WT1) antigen is under way [85]. Although immune responses to AML can be enhanced *in vitro* with

these approaches, clinical data are scanty and clinical responses in small diverse patient series is still very preliminary (reviewed in [86]).

Antigen-specific vaccines

A recent review listed more than 14 candidate leukaemia-associated antigens expressed by AML, some of which have formed the basis for developing antigen-specific vaccines using DNA or peptides [87]. Most widely researched and developed as peptide vaccines in clinical trials are the HLA-A2 peptide epitopes of WT1 ($WT1_{126}$), proteinase 3 (PR1) and hyaluronan-mediated motility receptor (RHAMM)/CD168 (receptor for hyaluronic acid mediated motility), and an HLA A24-specific epitope of WT1 [88]. Vaccines have been combined with the BCG-based adjuvant, montanide, keyhole limpet haemocyanin (KLH) or incomplete Freund's adjuvant, with or without concurrently administered GM–CSF [89]. All these peptides induce immune responses with increases in tetramer-positive T cells producing gamma-interferon after peptide stimulation. A number of clinical trials have been carried out with peptide vaccines: Oka *et al*. described 12 AML patients in CR and two MDS patients vaccinated with 0·3–3·0 mg of a modified HLA-A24–binding WT1 class I epitope emulsified in Montanide. There were clinical responses with reduction in leukaemic blasts associated with immune responses to WT1 in some patients but no complete remissions [89]. Keilholz *et al*. described 17 AML patients in CR and two patients with refractory anaemia with excess blasts (RAEB) receiving a median of 11 vaccinations of $WT1_{126}$ peptide, with KLH adjuvant and GM–CSF. Ten AML patients had stable disease and there was a reduction in leukaemic blasts in the two patients with RAEB [90]. Molldrem and colleagues serially vaccinated 66 patients with CML, AML and MDS at various stages of disease progression with the PR1 peptide at doses ranging from 0·25–1·0 mg with Montanide and GM–CSF. Stable disease and some complete remissions were observed associated with induced immune responses to PR1. Event-free survival was prolonged significantly in the patients who showed an immune response [91]. Rezvani and colleagues treated eight patients with AML in remission or stable MDS with a single dose of a combined PR1 and WT1 vaccine and observed immune responses to either PR1 or WT1 in all patients, associated with a transient fall in WT1 mRNA residual disease [92]. Greiner recently reported the results of high-dose RHAMM peptide vaccination given bi-weekly. Four of nine patients had immunological responses and three showed clinical responses – reduction of leukaemic marrow blasts and improved blood counts [93]. It is difficult to draw firm conclusions from this diverse group of patients treated with different vaccines and schedules, but it is possible to conclude that immune responses were nearly always necessary for a clinical response or reduction in leukaemia burden measured by WT1 mRNA. Clinical responses, assessed differently in each study, ranged from reduction in marrow blasts, improved blood counts and impressive continuous complete remissions in some high-risk patients, to complete remissions in perhaps 5% of evaluable patients. While these data are promising, the studies are too small and diverse to draw any meaningful conclusions about the true efficacy of peptide vaccination in AML. Currently, T cell responses to peptide vaccines are limited to single MHC class I epitopes. A broad range of peptides spanning most common HLA molecules and including MHC class II epitopes would not only extend the applicability of these vaccines to more patients but would also recruit CD4 T cell help that could sustain CD8 T cell responses over a longer period. As an alternative, some researchers have focused upon developing DNA vaccines incorporating the entire sequence of the antigen [20].

NK cells

NK cells with the potential for alloreaction use the inhibitory killer cell immunoglobulin-like receptors (KIRs) to sense the missing expression of self-MHC class I molecules. Therefore, NK cell alloreactions are generated between individuals that are KIR ligand mismatched [47]. NK cells are relatively easy to select from apheresis donations, but although typically approximately 5×10^8 cells can be obtained relatively pure, this may not represent a sufficient number for clinical efficacy [94]. Miller and colleagues therefore sought to expand transfused NK cells *in vivo*. Selected NK cells from HLA identical donors were transfused into 19 patients with high-risk AML after conditioning with low-dose total body irradiation or a combination of fludarabine and cyclophosphamide. The conditioning induced a rise of IL-15 and circulating NK cell numbers which showed enhanced cytotoxicity to leukaemia lasting more than 3 weeks. Five patients achieved complete remission [95]. Other investigators have developed clinical-grade strategies to expand NK cells *ex-vivo* using B cell lines [96] or modified K562 cells [97]. Such techniques can yield 20–200-fold expansion of pure but activated NK cells over several weeks. Expanded cells are fully functional and kill leukaemia and tumour targets. Clinical trials using expanded NK cells have not yet been reported. Future developments may include combined *ex-vivo* and *in vivo* expansion approaches.

Adoptive T cell therapy

Allogeneic T cells can be raised against mHag by peptide-pulsed DC or AML cells and are being used in treatment of relapsed leukaemia after stem cell transplantation. Outside the context of SCT, the occurrence in patients of CTL specific for AML supports the possibility of using expanded autologous antigen-specific CTL to attack AML [3,86]. Adoptive transfer of leukaemia-specific T cells presents different challenges according to whether the transfused T cells are

autologous or allogeneic in origin. Treatment with allogeneic T cells requires immunosuppression of the recipient to permit at least the short-term survival of the transfused cells. Two studies of allogeneic T cell transfer in non-transplant recipients have been reported [98,99]. Haploidentical donor lymphocyte transfusions were given to patients with diverse malignancies, including 13 patients with high-risk AML. Transfusion was followed by a cytokine storm without any sustained cellular engraftment, but there were tumour responses including five complete remissions in the AML patients [99]. Future developments will need to focus upon ways to achieve a short controlled engraftment sufficient to confer an anti-leukaemia effect perhaps by engineering T cells to escape immune attack, which may in turn require the co-insertion of a suicide gene as a safety precaution to prevent sustained persistence and expansion of the foreign T cell clone. Autologous T cell infusions can avoid the problems of alloreactivity of patient to donor or donor to patient. Here the problem is to generate sufficient numbers of T cells with powerful anti-leukaemia activity. A promising strategy is to sequence the high-avidity T cell receptor (TCR) from T cell clones recognizing leukaemia antigen targets and insert the TCR gene into T cells of the AML patient [52]. By choosing a long-lived central memory T cell population as the carrier, for example, specific for a DNA virus such as cytomegalovirus (CMV), it may be possible to achieve a sustained T cell control of AML. An alternative approach in early clinical trials in ALL is the insertion of a chimeric antigen receptor (CAR) into the host T cell [100]. The external portion of the CAR is an antibody site binding to a leukaemia-restricted surface molecule, while the intracellular portion triggers T cell activation pathways leading to a cytotoxic T cell response after the T cell binds to the leukaemia. However, despite the identification of leukaemia-specific T cells in patients with AML [17–19], there are many hurdles to overcome before adoptive autologous leukaemia-specific T cell transfer becomes a clinical possibility [101].

Optimizing immunotherapeutic approaches in AML

While current experience with antigen specific and cell-based vaccines supports the potential of such immunotherapy to control AML, response rates rarely surpass 20% and complete responses are uncommon and seldom sustained. To improve upon these results will require a combined approach to enhance all the components of the immune response to the leukaemia. We can now identify points in the pathway to AML cell destruction that could be enhanced to improve the therapeutic effect.

The immune milieu

It is now clear that lymphodepletion after immunosuppressive chemotherapy produces profound changes in the cytokine milieu favourable to both T cell and NK cell expansion and function, particularly in response to a rise in IL-15 [62,95]. The immune milieu after induction chemotherapy or after conditioning for SCT may thus be favourable to lymphocyte expansion and enhance the response to vaccination. Clinical trials giving vaccines early after immunodepleting therapy are therefore worth exploring. Alternatively, vaccines or lymphocyte transfer might be enhanced by administrating lymphocyte growth factors such as IL-15, which may soon become available for clinical use.

Regulatory T cells

While regulatory T cells (T_{reg}) perform a useful function in curtailing side effects from overaggressive T cell responses to infection, they limit the efficacy of vaccines. Animal studies confirm the improved anti-leukaemic effect of a DC vaccine given after T_{reg} have been depleted [102]. In man T_{reg} depletion can be achieved using Denileukin difitox (Ontacc), an IL-2-like molecule conjugated to diphtheria toxin which binds to the alpha chain of the IL-2 receptor and which is up-regulated on T_{reg} cells, killing the cell when the receptor is internalized. Given just before vaccination or T cell infusion (to avoid killing activated T cells) this agent can increase immune responses to vaccines in an animal model and is currently being explored in clinical vaccine trials [103].

Increasing cytotoxic susceptibility of AML

Although the administration of *ex-vivo* generation of leukaemic DC has not produced significant clinical responses, it is possible that the administration of appropriate cytokines such as GM–CSF, M-CSF and interferons could be useful in rendering the AML target a better antigen-presenting cell by maturing it towards a DC or by up-regulating MHC expression [86]. The demethylating agent 5 azacytidine can up-regulate cancer testis antigens (which includes WT1) [104]. NK cytotoxicity to AML can be enhanced by valproic acid and all-trans-retinoic acid which increases NKG2D ligand expression on the target [105], and by resiquimod, which up-regulated Toll-like receptors rendering cells more immunostimulatory [106].

Targeting the AML stem cells

Immunotherapy would clearly have its best chance of cure if the AML progenitors were targeted. In CML the expression of some tumour-specific antigens (TSA) is weak in the most primitive $CD90^{+}CD38^{-}CD34^{+}$ cell compartment. Treatment of CML cells with the proteasome inhibitor Bortezomib renders them more susceptible to NK killing by up-regulating TRAIL on the target. Such agents could therefore play a useful role in enhancing leukaemia elimination [107].

The future: co-ordinating immunotherapy with other treatments

It is unlikely that a single strategy could stand alone as the sole modality for successful treatment of AML. The role of induction chemotherapy in achieving leukaemia bulk reduction while at the same time resetting the immune clock by inducing lymphopenia is a logical prelude to giving immunotherapy to prevent further disease recurrence. We are only now beginning to appreciate the potential immunostimulatory capacity of chemotherapy. For example, fludarabine is not only an effective anti-leukaemic drug but causes lymphoablation which underpins the surge in IL-15 that stimulates NK and T cell recovery [23,95], and 5-azacytidine increases tumour antigen presentation [104]. Thus, thoughtful selection of induction regimens may allow synergy with subsequent immunotherapy. Critical to understanding the effectiveness of immunotherapy in AML is the monitoring of minimal residual disease and the immune response to leukaemia. These biological monitors are more likely to provide a reliable readout of the success of treatment rather than relying upon diverse clinical outcome measurements in diverse patient populations. In this regard, WT1 is rapidly becoming a standard target for MRD measurement in AML. Finally, immunotherapy approaches can be combined with autologous or allogeneic SCT to improve the curative potential of transplantation, which offers greater opportunity for leukaemia reduction through the myeloablative preparative regimen and the GVL effect [108].

Disclosure

AJB: none; KLB: none.

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