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ORIGINAL ARTICLE

An immunological approach to acute myeloid leukaemia☆

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UL16-binding proteins 1-4 (ULBP 1-4)

Abstract
Introduction: Acute myeloid leukaemia (AML) is the second haematological malignancy in the paediatric population, and one of the leading causes of childhood cancer mortality. Survival is currently around 60%, with no improvement in last decades, suggesting that new therapeutic approaches are needed. The anti-leukaemia effect mediated by the lymphocytes and natural killer (NK) cells of the immune system has been established in haematopoietic stem cell transplantation, and also as adoptive immunotherapy after consolidation chemotherapy schemes.
Patients and methods: A retrospective study was conducted on the clinical characteristics of patients diagnosed and treated for AML in our centre from 1996 to 2014. The mean fluorescence intensities of HLA-I, MICA/B and ULBP1-4, ligands for NK cell receptors, were also analysed in ten new diagnosed leukaemia cases, five myeloid and five lymphoid.
Results: A total of 67 patients were used in this analysis. With a median follow up of 25 months, the event-free survival was 62% (95% CI: 55–67). Secondary AML, non-M3 phenotype, and the absence of favourable cytogenetic markers had a lower survival. The probability of relapse was 38% (95% CI: 31–45). The expression of HLA-I and ULBP-4 was significantly lower in myeloid than in lymphoid blast cells.
Conclusions: Our clinical results are similar to those described in the literature. Survival did not significantly change in recent decades, and the likelihood of relapse remains high. Myeloid blasts might be more susceptible to the cytotoxicity of NK cells through their lower expression of HLA-I. NK therapy strategies in minimal disease situation could be effective, as reported by other groups.

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PALABRAS CLAVE
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Células natural killer;
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Aspectos inmunológicos de la leucemia mieloblástica aguda

Resumen
Introducción: La leucemia mieloblástica aguda (LMA) constituye la segunda hemopatía maligna en la población pediátrica y una de las principales causas de mortalidad por cáncer infantil. La supervivencia se sitúa alrededor del 60% sin haber mejorado en las últimas décadas, por lo que son necesarios nuevos enfoques terapéuticos. El efecto antileucémico ejercido por los linfocitos y las células natural killer (NK) del sistema inmunológico está bien establecido en el trasplante de células madre hematopoyéticas pero también como estrategia de inmunoterapia adoptiva tras la quimioterapia de consolidación.
Pacientes y métodos: De manera retrospectiva, se analizan las características clínicas de los pacientes diagnosticados de LMA en nuestro centro durante el período 1996–2014. Además en 10 leucemias agudas, 5 linfoides y 5 mieloides, se analizaron la intensidad media de fluorescencia de HLA-I, MICA-B, ULBP1-4, ligandos para los receptores de las células NK.
Resultados: Un total de 67 pacientes formaron parte de este análisis. La supervivencia libre de eventos con una mediana de seguimiento de 25 meses fue del 62% (IC del 95%, 55–67). Las LMA con menor supervivencia fueron las secundarias, las no M3 y las carentes de marcadores citogenéticos favorables. La probabilidad de recaída fue del 38% (IC del 95%, 31–45). La expresión de HLA-I y ULBP-4 fue significativamente menor en los blastos mieloides que en los linfoides.
Conclusiones: Nuestros resultados clínicos son similares a los descritos en la literatura. No se ha modificado significativamente la supervivencia en las últimas décadas y la probabilidad de recaída sigue siendo elevada. Los blastos mieloides podrían ser más susceptibles a las células NK al expresar menos HLA-I, por lo que estrategias de terapia celular podrían ser eficaces tal y como reportan otros grupos.

Introduction

Acute myeloid leukaemia (AML) accounts for 20% of childhood leukaemias.[1] Approximately 60 cases are diagnosed each year in Spain. Current therapeutic approaches are based on the administration of polychemotherapy, combining high-dose cytarabine with anthracyclines and topoisomerase inhibitors.[2] Furthermore, patients that respond poorly to induction therapy, patients considered to be high-risk from the outset (with secondary AML or unfavourable cytogenetic characteristics), or intermediate-risk patients that have a HLA match related donor are candidates for allogeneic haematopoietic stem cell transplantation (HSCT) for AML in first complete remission.[3,4]

The survival of patients with AML has improved considerably in the past 40 years, mostly due to advances in supportive care. However, survival has plateaued at 60% in recent decades. Our knowledge of the genetic heterogeneity of AML and its importance in prognosis is increasing by the day.[5,6] There are cytogenetic changes that carry a good prognosis, such as t(8;21)(q22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(15;17)(q22;q12), the presence of which corresponds to an 80% survival with chemotherapy alone, while unfavourable changes such as 5q, t(6;9)(p23;q34), monosomy 7 and complex karyotypes are refractory to chemotherapy and have survival rates of no more than 40% even with HSCT.[6–8]

Thus far, the potential of these genetic changes as therapeutic targets has not had a significant impact on survival.[9,10] Recently, and complementing advances on genetic and epigenetic phenomena, an immunobiological approach to AML is being developed.[11,12] Such an approach is supported by different observations: (a) the crucial role of HSCT[3,13]; (b) the success of cellular adoptive immunotherapy with post-transplant donor lymphocyte infusions against minimal residual disease and/or mixed chimerism[14,15]; and (c) the favourable clinical and preclinical experience with antibodies such as gemtuzumab ozogamicin (anti-CD33) and bi-specific T-cell engagers (CD33/CD3, AMG 330).[16,17]

In this regard, the Perugia group led by Dr Velardi demonstrated the antileukaemic effect of haploidentical HSCT in adult patients with AML through the donor-derived natural killer (NK) cells.[18,19] Later on, the St Jude group confirmed these findings in childhood AML and pioneered an NK cell infusion regimen for consolidation therapy in patients with low-to-intermediate risk AML.[20] We know that the antileukaemic activity of NK cells is regulated by the recognition by inhibitory and activating receptors of their ligands in blast cells.[21] These ligands correspond to human leucocyte antigen class I (HLA-I) for inhibitory receptors, and major histocompatibility complex (MHC) class I-related chain A/B (MICA/B) and UL16-binding proteins 1-4 (ULBP 1-4) for activating receptors.[22]

This study offers a retrospective review of our experience in the management of childhood AML and describes the expression of NK cell receptor ligands in 10 cases of acute leukaemia (5 myeloid and 5 lymphoid), comparing this expression in both types of acute leukaemia with the