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ORIGINAL ARTICLE

The Role of New Immunosuppressive Drugs in Nonmelanoma Skin Cancer in Renal Transplant Recipients☆

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KEYWORDS
Immunosuppression;
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Abstract
Introduction: Nonmelanoma skin cancer (NMSC) is the most common malignancy in patients who have received a solid organ transplant. Multiple factors are involved in the onset of posttransplant NMSC.
Objectives: To analyze the relationship between new immunosuppressive drugs and the onset of NMSC in renal transplant recipients.
Method: This was a combined retrospective and prospective observational study in which we studied 289 patients who received a kidney transplant between January 1996 and December 2010 at Hospital Universitario Doctor Peset in Valencia, Spain.
Results: Seventy-three patients (25.2%) developed 162 NMSCs over a median follow-up of 72 months. There were no statistically significant differences in the onset of NMSC on comparing different induction therapy strategies involving monoclonal and polyclonal antibodies. NMSCs occurred less frequently in patients treated with mammalian target of rapamycin (mTOR) inhibitors than in those treated with other immunosuppressive regimens, although the differences were not statistically significant. Three of 5 patients with recurrent NMSC who were switched from calcineurin inhibitors to mTOR inhibitors developed additional NMSCs despite the change.

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Conclusions: Induction therapy with monoclonal and polyclonal antibodies in renal transplant recipients is not associated with an increased risk of NMSC. While mTOR inhibitors are associated with a lower risk of posttransplant NMSC, it remains to be determined whether a switch to these drugs is useful in the management of patients who develop multiple NMSCs.

PALABRAS CLAVE
Inmunosupresión;
Inhibidores mTOR;
Trasplante renal;
Cáncer cutáneo

Papel de los nuevos agentes inmunosupresores en el cáncer cutáneo no melanoma en pacientes trasplantados renales

Resumen

Introducción: El cáncer de piel no melanoma (CCNM) es la neoplasia maligna que se presenta con más frecuencia después de un trasplante de órgano sólido. La etiología del CCNM tras el trasplante es multifactorial.

Objetivos: Analizar la relación entre los nuevos agentes inmunosupresores y la aparición de CCNM en pacientes trasplantados renales.

Método: Estudio observacional. Se examinaron una combinación de datos retrospectivos y prospectivos. Incluimos en el estudio 289 pacientes que habían recibido trasplante renal desde enero de 1996 hasta diciembre de 2010 en el Hospital Universitario Doctor Peset de Valencia.

Resultados: Tras una mediana de seguimiento de 72 meses 73 pacientes (25,2%) desarrollaron 162 CCNM. No hubo diferencias estadísticamente significativas en la incidencia de CCNM al comparar las distintas estrategias de inducción con anticuerpos mono o policlonales. La incidencia de tumores en pacientes con inhibidores mTOR fue menor que con el resto de tratamientos, aunque sin mostrar diferencias estadísticamente significativas. De 5 pacientes con CCNM recurrente que pasaron a tratarse con inhibidores mTOR (tras ser tratados previamente con inhibidores de la calcineurina), 3 continuaron presentando CCNM a pesar del cambio de tratamiento.

Conclusiones: La utilización de anticuerpos mono o policlonales en la terapia de inducción en pacientes trasplantados renales no se asocia a un mayor riesgo de CCNM. Si bien los inhibidores mTOR muestran menor riesgo de aparición de CCNM postrasplante queda por determinar si el cambio de tratamiento a inhibidores mTOR es un buena opción en el manejo de pacientes con múltiples CCNM.

Introduction

Nonmelanoma skin cancer (NMSC) is the most common malignancy in patients who have received a solid organ transplant.[1–3] Multiple factors are involved in the onset of posttransplant NMSC. In addition to ultraviolet UV radiation, other factors such as infection with human papillomavirus, genetics, and immunosuppressive therapy play an important role in the onset of these tumors.[4–6]

Immunosuppressive therapy is widely recognized as a risk factor in the etiology and pathogenesis of NMSC. Skin cancer arises as a result of decreased immunologic activity as well as direct oncogenic effects linked to certain immunosuppressive agents, although it is difficult to determine which mechanism is predominant.

Several studies have suggested that calcineurin inhibitors (tacrolimus and ciclosporin) have oncogenic properties, primarily linked to the production of cytokines that promote tumor growth and angiogenesis.[7–9] Treatment with azathioprine photosensitizes human skin to UV radiation[10] by promoting mutagenic DNA changes through 6-thioguanine, a metabolite of the drug. However, studies in humans[11,12] have demonstrated that the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus exert antineoplastic effects through multiple mechanisms: blocking of angiogenesis, inhibition of cell replication, inhibition of interleukin 10, and induction of apoptosis. mTOR inhibitors have thus been shown to have a preventive action against skin carcinogenesis as well as antitumor effects after the onset of malignant cutaneous tumors.

Immunosuppressive therapy in renal transplant recipients must be understood as a dynamic process that is constantly adapted to the characteristics of the patient's disease progression. In this context, immunosuppressive therapy is considered to be an induction therapy—i.e., introduced immediately following a transplant—and also a long-term maintenance therapy. Because of the increased risk of acute rejection during induction therapy, immunosuppressive therapy must be more powerful and intense during this period. The combination of immunosuppressive drugs used is essential. Induction therapy can involve monoclonal antibodies (muromonab-CD3 [OKT3] and basiliximab [Simulect]) or polyclonal antibodies (equine antithymocyte globulin [ATGAM] or rabbit antithymocyte globulin [Thymoglobulin]). These drugs are administered intravenously, generally during the first 10 to 15 days after the transplant, together with