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ORIGINAL ARTICLE

HSP-90 Expression as a Predictor of Response to Radiotherapy in Head and Neck Cancer Patients☆

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KEYWORDS
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Abstract
Introduction and objectives: HSP-90 is an intracellular protein that protects the cell from environmental stress situations. The overexpression of HSP-90 isoforms could serve as a mechanism of resistance to radiotherapy for tumour cells. We studied this effect in a sample of head and neck tumours.
Methods: We included 87 patients diagnosed with oral cavity, oropharynx, larynx and hypopharynx tumours. We studied the expression of the HSP-90 isoforms by real-time PCR on pre-treatment biopsy samples. We analysed the relationship between HSP-90 expression levels and local relapse of the tumour with CRT decision trees.
Results: The expression levels of the inducible cytosolic isoform (HSP90AA) allowed the definition of two groups of patients with different rates of local relapse. The group with a low expression level showed a 2.9% local relapse rate, while the group with a high expression level showed a 38.2% rate.

Survival curves showed differences in time to local relapse for both groups of patients. These differences did not reach statistical significance.
Conclusions: Radiotherapy response was related to expression levels of HSP-90 in a sample of head and neck cancer patients. This result could prove useful in the selection of treatments for this group of patients.

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PALABRAS CLAVE
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Expresión de Heat Shock Protein-90 (HSP-90) como factor predictor de la respuesta a radioterapia en pacientes con tumores de cabeza y cuello

Resumen
Introducción y objetivos: La HSP-90 es una proteína intracelular que protege la célula en situaciones de estrés ambiental. El objetivo de este estudio es valorar si la sobreexpresión de alguna de las isoformas de HSP-90 confiere resistencia a la radioterapia en una muestra de tumores de cabeza y cuello.
Métodos: Se incluyeron en el estudio 87 pacientes con tumores de cavidad oral, orofaringe, laringe e hipofaringe. En muestras de biopsia pretratamiento se analizaron mediante PCR en tiempo real la expresión de las isoformas de HSP-90. Se utilizaron árboles de decisión para estudiar la relación entre el nivel de expresión de HSP-90 y la recidiva local del tumor.
Resultados: La expresión de la isoforma citosólica inducible (HSP90AA) permitió definir 2 grupos con diferentes índices de recidiva local. El grupo con expresión baja presentó un 21,9% de recidivas frente al 38,2% del grupo con expresión alta.
Las curvas de supervivencia muestran diferencias en el tiempo libre de recidiva local entre ambos grupos, aunque estas diferencias no alcanzaron significación estadística.
Conclusiones: La respuesta de los tumores de cabeza y cuello a la radioterapia parece relacionada con la expresión de HSP-90. Este resultado podría ser de utilidad en la selección de tratamientos en este grupo de pacientes.

Introduction

Tumours of the head and neck are the fifth highest in incidence in Europe, affecting more than 100 000 people each year.[1] In recent years major advances have been made in the so-called organ-preservation therapies, which seek to avoid mutilating surgery as the first approach in the treatment of these patients.

These treatments are principally based on the application of external radiotherapy, associated or otherwise with chemotherapy, and have different schemes.[2,3]

There is the possibility of surgical rescue for the patients for whom these therapies fail, although with fewer possibilities of success than the initial surgery. This results in significantly decreased survival in this group of patients.[4]

Establishing predictive response factors to radiotherapy would enable treatment to be individualised, avoiding ineffective treatment and maximising the possibilities of controlling the disease for each patient. The expression of different proteins related to cellular response to radiotherapy has been investigated along these lines.[5,6]

The Heat Shock Protein-90 (HSP-90) is a protein which is present in all cells and whose mission is to fold and form a wide range of proteins termed ''client'' proteins. In situations of environmental stress (hypoxia, heavy metals, acidosis) the expression of HSP-90 increases to stabilise the intracellular proteins and prevent damage to the cell.[7]

An increased expression of HSP-90 in different types of cancers has been demonstrated. This might be explained as the cell's attempt to maintain its homeostasis in the hypoxic and acidotic environment of the tumour or as means of countering the presence of mutated proteins, the result of the genetic alterations of oncogenesis.[8]

Our study seeks to investigate the expression of HSP-90 in a sample of head and neck tumours treated with radiotherapy, and to assess whether the over-expression of HSP-90 gives the tumour cells any advantage in response to treatment.

Methods

This study was approved by the hospital's ethical committee and complies with the principles of the Helsinki declaration.

All the patients were assessed by a multidisciplinary oncological committee in order to select their treatment, which was determined following the centre's protocols.

A total of 87 patients were included, diagnosed in our centre with squamous carcinomas of the oral cavity, oropharynx, larynx and hypopharynx, who had undergone treatment with radiotherapy or chemo-radiotherapy, and from whom it had been possible to take a valid tumour sample. The clinical characteristics of the tumours can be seen in Table 1.

The presence of the HPV virus was studied in the samples of tumours of the oropharynx by PCR. The presence of HPV 16 was demonstrated in 3 of the 36 cases of tumours in this site.

The relevant clinical information was obtained from a database which gathered information prospectively from all the patients diagnosed and treated in our centre since 1985.[9]

Only patients with a minimum follow-up of 2 years were considered in this study.

RNA Analysis

Prior to any treatment, biopsy samples were taken in which the levels of expression of the 3 HSP-90 isoforms were determined by PCR in real time (RT-PCR): HSP90AA (inducible