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## Editorial

### Neoplasia in Lung Transplants

#### Neoplasias en el trasplante de pulmón

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The number of immunocompromised patients has increased in recent decades, as a result of the AIDS epidemic, advances in cancer chemotherapy and organ transplants. The incidence of neoplasia is increased when there are changes in the immune system, basically in cases of AIDS<sup>1</sup> and solid organ transplantation,<sup>2</sup> owing to the intensity of immunodepressive treatment and the reactivation of viruses implicated in oncogenesis, for example the Epstein-Barr virus (EBV), and the human herpes type 8 and papilloma viruses.

The incidence of neoplasias in lung transplantation (LT) is not really known because survival rates are low and follow-up times short. We might expect the incidence to be high, if we take into account the fact that immunodepression is more intense than in the case of transplantation of other solid organs and, furthermore, the recipient often has risk factors for the development of solid neoplasias, chiefly lung cancer.

The registry of the International Society for Heart and Lung Transplantation (ISHLT) has reported that the incidence of neoplasias during the first year after LT is 3.6%, 50% of this figure corresponding to lymphoproliferative diseases, and that 27.8% of patients who survive for 10 years after a transplant develop tumours, mainly affecting the skin.<sup>3</sup> Apart from the ISHLT data, there are few studies that evaluate the risk factors, prognosis, and incidence of this complication. Many studies have been conducted entirely in 1 centre and the incidence cannot be evaluated because only cases with neoplasias were recorded.<sup>4</sup> The Spanish Heart Transplantation Tumour Registry,<sup>5</sup> which covers a period of 20 years (average post-transplant follow-up period of 5.2 years), found the frequency of neoplasias to be 14.4%.

The principal risk factors for developing tumours include immunodepressants.<sup>6,7</sup> In particular OKT3 induction has been

implicated in the increase in post-transplant lymphoproliferative disorders,<sup>8</sup> although there are studies which fail to corroborate this link. These differences may be attributed to the fact that the way OKT3 was used—the dose and duration of treatment—was different. However, the individual role of each immunodepressant is very difficult to evaluate because treatment regimes include various drug combinations and controlled trials specifically designed to investigate this aspect have not been carried out. It might also be the case that the intensity of immunodepression is more important than the actual agent used. Recently new immunodepressants, such as interleukin-2 receptor antagonists, which, according to the data that is currently available, do not increase the risk of any type of neoplasia and m-TOR (*mammalian target of rapamycin*) inhibitors, which could have a role in protecting patients against the development of post-transplant neoplasias, have been introduced.<sup>9</sup>

Other factors implicated in the increase in neoplasias are viruses which are potentially carcinogenic. The risk of lymphoproliferative disorders after transplantation is especially high in EBV-negative recipients who receive an organ from an EBV-positive donor, reaching an incidence of up to 33% compared to 1.7% in EBV-positive recipients.<sup>10</sup> This would explain the higher frequency in children and patients with cystic fibrosis which has been described in some series. The introduction of anti-viral prophylaxis using aciclovir or ganciclovir to lower the risk of infection with herpes viruses, especially cytomegaloviruses, probably reduces neoplasias linked to viruses, such as Kaposi's sarcoma, lymphoproliferative disease, or squamous-cell cancers. The lower incidence of lymphomas in series that include prophylaxis supports this hypothesis.<sup>11</sup> Thus, the administration of OKT3 and antithymocytic globulin in patients who have not received aciclovir is associated with an increased risk of all types of neoplasias, whilst, in patients who received prophylaxis, OKT3 induction only increased the risk of tumours that were neither cutaneous nor lymphoproliferative. This is why, when the carcinogenic risk of immunodepressant agents is considered, we

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need to consider the use of anti-viral drugs, given that the same regime using aciclovir or ganciclovir during the first 3 months reduces the risk of lymphoma.

Other variables which must be taken into account include the individual risk of the recipient, as, although this risk is initially independent of immunodepression, we do not know whether it may be modified by a transplant. Thus, age, masculine sex, genetic factors, and exposure to certain diseases, for example chronic obstructive pulmonary disease and pulmonary fibrosis, may also contribute to increased risk of neoplasias.

The transmission of malignant cells via the donor is exceptional, but it can occur and metastases of tumours from donors have been described in recipients.<sup>12,13</sup> The tumours which pose the greatest risk of transmission (about 25%) are melanomas, choriocarcinomas, bladder carcinoma, renal carcinoma, sarcomas, and myelomas. Cases of transmission of lung cancer have also been documented<sup>14</sup> and this could have important implications with respect to the liberalization of the criteria for donors over the age of 55 and with a smoking load of over 20 pack-years, as the detection of lung cancer in donors is difficult. There are no specific markers and, when donors are evaluated, other tests, such as high-resolution computerized tomography, are not included.

The proper identification of recipients with a known history of neoplasia is also relevant to achieving a decrease in the incidence of neoplasias in patients with solid organ transplants. Although guidelines have been drawn up to homogenize the criteria, depending on the type of neoplasia and the time which has elapsed since its curation, there is no definitive clinical evidence and sometimes these criteria even depend on the availability of organs. A special case is LT in patients with haematological neoplasias who, having been treated with a bone marrow transplant and cured, develop bronchiolitis obliterans or another subsidiary transplant complication. The risk of recurrence of haematological disease or the appearance of other lymphoproliferative syndromes is difficult to evaluate in these cases.

Also neoplasias which are not detected in the recipient, especially in explanted lungs, can complicate transplant results in the short and long term.<sup>15,16</sup>

The most common types of neoplasia in patients with solid organ transplants are lymphoproliferative neoplasias during the first year following transplantation and skin tumours other than melanomas (principally spinocellular carcinoma) after the fifth year. However, this varies depending on the organ which has been transplanted: the incidence of post-transplant lymphoproliferative disorders is highest in LT (ranging from 1.8% to 20% depending on the series<sup>8,17,18</sup>), while renal transplant has the lowest incidence. This variability depends on the centre, type of transplant, risk factors for the transplant population (children, EBV status), and anti-viral and immunodepressive prophylaxis regimes, as well as follow-up time. 80% of the cases which present post-transplant lymphoproliferative disorders are positive for EBV and the most common types of lymphoma are diffuse large B-cell lymphoma and Burkitt's lymphoma.<sup>19</sup> T-cell lymphomas are uncommon, tend to appear later after transplantation and are normally EBV-negative.<sup>20</sup> As a rule the lymphoma is preferentially located in the transplanted organ. Early-stage lymphomas, which are often positive for EBV and polymorphic, are more likely to respond to the immunodepression reduction strategy, while late-stage monoclonal lymphomas are associated with a poorer prognosis.

The incidence of skin neoplasias varies in different geographical regions, depending on sun exposure and, although they are more aggressive than in immunocompetent patients, the prognosis is good. One of their peculiarities is that they occur in unusual parts of the body,<sup>21</sup> particularly areas which are protected from the sun.

In the early decades, when transplants were introduced, the most common tumours in the general population, such as lung, breast, prostate and colon cancer, only showed slight increases because the

recipients were younger and survival was shorter. However, we might expect that, as a result of the rise in the age of recipients, less restrictive transplant criteria and increased survival, these tumours will become more common. Lung cancer deserves special mention: although we might expect a high incidence, owing to the coexistence of smoking and immunodepressive treatment, its frequency is 0%–3.4% after transplantation of one lung, increasing to 2%–4% if we only take patients with emphysema and fibrosis into consideration.<sup>22–24</sup> These values are very similar to the figure of 1%–3% found in screening studies on high-risk populations.

LT has certain special peculiarities with respect to other organs which can contribute to the development of neoplasias, but generally we have few patients at our disposal who have been monitored long enough to evaluate neoplasias that appear in the longer term. Nevertheless, the introduction of a series of measures, such as systematic prophylaxis with antiviral agents, the monitorization of EBV-negative recipients, the modification of induction regimes that replace OKT3 with interleukin-2<sup>3</sup> receptors and the introduction of m-TORs together with a better knowledge of how neoplasias behave in this population group, would bring about significant changes and contribute to earlier diagnosis.

Although the exact repercussions of these measures has yet to be determined, it is to be hoped that they will manage to reduce the incidence of lymphoproliferative neoplasias in the first year after transplantation, but, as survival becomes more prolonged, solid neoplasias may increase. Supporting this view, in the Spanish Heart Transplantation Tumour Registry<sup>5</sup> only 10% of the tumours observed in different localizations were lymphoid tumours and 39.6% solid tumours, an experience shared by Spanish LT groups and confirmed by the data supplied by all the transplant groups at the last SEPAR Congress (unpublished data).

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