Post-Transplant Lymphoproliferative Diseases in an Elderly Population Who Underwent Cardiac Transplantation: Role of Physical Activity Rehabilitation Program

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Short title: Post-Transplant Lymphoproliferative Diseases and Other Neoplasms In Elderly Cardiac Transplantation

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Abstract

The incidence of post transplantation lymphoproliferative disorders (PTLDs) and other neoplasms in organ transplant patients is higher than in the non-transplanted population. This event is more frequent in older subjects, due, at least in part, to the immune dysfunction induced by immunosuppressants administered to prevent rejection. Alterations of the immune system mechanisms of protection against carcinogenesis appear to be the key role in the pathogenesis of these neoplasms.

The data of our study on the incidence of neoplasms occurred during a long-term follow-up in an elderly population after they underwent cardiac transplantation. This study gives, also evidence of the favorable effect of physical activity programs on cardiorespiratory and psychomotor function.

Keywords: physical activity; elderly population; mediastinal lymphomas; cardiac transplantation

1. Introduction

The incidence of cancer in organ transplant patients is higher than in the non-transplanted population [1-5]. This event is more frequent in older subjects, due, at least in part, to the immune dysfunction induced by immunosuppressants [6-8] administered to prevent rejection. These dysfunctions would not allow the elimination of mutated cells due to some alterations in the mechanisms of genetic duplication [9], and, consequently, the task of monitoring mutated cells, could be lost. In addition, immunosuppressed patients are more likely to be susceptible to some viral infections that may promote the onset of cancer, namely human immunodeficiency virus, human T-cell lymphotropic virus, EBV [10-13]. The influence of the immune system on the mechanisms of protection against carcinogenesis is proven by numerous studies performed in patients with primary or secondary immunodeficiencies [14-19]. Lymphocytes with receptor killer

cell lectin-like receptor subfamily k, member 1 (KLRK1) detect and eliminate transformed or malignant cells [20]. Some KLRK1 ligands such as MICB and MICA are expressed by many carcinomas (kidney, breast, lung, ovary, prostate, liver, colon) and in turn their expression is induced by oncogenic growth factors acting through their receptors such as EGFR (epidermal growth factor receptor) [21-24]. It has been shown that activation of EGFR can regulate the immunological visibility of transformed cells. Alterations to these mechanisms appear to be the key role in reducing immunological surveillance against neoplasms [25-28]. The most frequently encountered neoplasms in patients undergoing solid organ transplantation are generally post transplantation lymphoproliferative disorders (PTLDs) (Plasmocytic hyperplasia, PTLD, Polymorphic PTLD, Monomorphic PTLD-B and T/NK cell types, classical Hodgkin lymphoma PTLD) [29], Kaposi sarcoma, NHL EBV related, cervical uterine and anal neoplasms related to papilloma virus, liver tumors (related to HCV, HBV) [30-31], and non-melanoma skin cancer [32-34]. After transplantation patients are very brittle both physically and psychologically [35]. The first step is a functional recovery and autonomy that is usually carried out in hospital with physiokinesiotherapy and psychological support [36]. Once discharged, the patients should start a psychophysical rehabilitation program aimed to improve the functional capacity the behavioral conditions and the quality of life. The type of program is different from a patient to another. The preliminary evaluation is multidimensional and should include general clinical conditions, functional state of different organs, psychic state, physical-motor capacity (strength, flexibility, muscular coordination), cardiovascular function under stress conditions, comorbidities and social conditions [37]. Each of these points is very important for a correct adherence to a rehabilitation program [38]. Training can produce extremely important effects, as older people use a considerable proportion of their functional capacity to perform even simple everyday activities [39]. Programs include aerobic exercise to increase muscle endurance, exercises to strengthen the extensor muscles of the legs (which support the ability to walk and get up from a chair), and the upper limbs, useful for carrying

out household chores and other activities of daily life [40]. Aerobic training can be gradually intensive for patients who have a faster recovery and a feeling of well-being after the transplant. In these cases, the physical activity should start from 30 minutes walking or cycling stationary at moderate intensity to be increased progressively [41]. Subsequently, a training program of 5 days a week should start consisting of 20 minutes of slow running in the open air three times a week and a moderate physical activity on the remaining two days of for least 20 minutes (cycling at a regular pace and carrying light weights) [42]. Our patients were evaluated by completing the Long Form International Physical Activity Questionnaire (IPAQ) at the starting point and at weeks 4, 8 and 12, 18 follow-ups [43]. The aim of this study was to assess the incidence of neoplasms in an elderly population of heart transplants patients who underwent transplantation at AO Dei Colli - V. Monaldi, Naples, Campania region, Italy.

2. MATERIALS AND METHODS

This is retrospective cohort analysis of 487 patients aged 2-70 years who received heart transplantation from March 1999 to July 2018 at AO Dei Colli - V. Monaldi, Naples, Campania region, Italy. After transplantation, patients were observed during a long-term follow-up to assess whether new neoplasms will occur. EBV, HBV, HCV, LDH, all functional hematochemist indexes have been tested at a 4-month interval after transplantation and abdomen and superficial lymph node ultrasound was performed [44-47]. Obviously, neoplasms occurred before transplantation were not considered in this study. Immunosuppressant drugs used after transplantations were anti-thymocyte globulin (ATG), ciclosporin, everolimus, mycophenolate, prednisone, tacrolimus [48]. During the first 5 days, ATG was administered, followed by methylprednisolone associated with cyclosporine and mycophenolate or cyclosporine and everolimus or, after 2008, tacrolimus [49].

Three-hundred and sixty were excluded from this analysis, 180 because not elderly (aged less than 60 years), 103 patients because they had a history of previous cancer, 48 patients because they were lost during the follow up and 29 because they died within one year after heart transplantation for heart complication. Complete data were available for the remaining 127 patients. The incidence obtained was compared with those recently reported from Campania region (AIRTum data) [50]. All procedures were performed in accordance with the Helsinki declaration and all data were used for clinical investigation anonymously, according with what established in the informed consent and with the role of the ethics committee.

3. RESULTS

We found 84 incident cases of neoplasms: 15 lung cancers, 4 liver cancers, 2 biliary tract cancer, 4 pancreas cancer, 14 colon-rectal cancer, 20 PTLDs (3 Hodgkin lymphomas (HL), 14 (non-Hodgkin lymphoma) NHL, 3 plasmacytic hyperplasia), 10 urinary tract tumors (3 bladder, 7 kidney), 3 thyroid cancer, 5 HPV cancer related (3 uterine cervix, 2 anal cancer) 3 Kaposi's sarcoma, and 4 EBV-related head and neck (Figure 1).

The incident neoplasms occurred from 1 year to 7 years since heart transplantation and 67.31% of 127 in male, 59.69% of 127 in female. (Figure 1). Until October 2019, 95 of the 127 patients were still alive, 47% of male and 53% of female.

4. DISCUSSION AND CONCLUSION

In this observational retrospective study, we have highlighted how the onset of new malignancies in elderly patients undergoing cardiac transplantation has increased like it has been observed in the elderly population in the Campania region (AIRTum 2019). The limit of our reported data is that they are most very full-bodied, but nonetheless in good agreement with the data

in literature. A high incidence of PTLDs has been observed, and also increasing are the neoplasm related EBV and HPV.

Physical activity has been very useful for the functional recovery of the patients. Having observed our patients a long follow up after heart transplantation, we have a clear perception that a correct lifestyle and systematic sporting activity are the basis for reducing the onset of cancer.

Legend to the figure

Figure 1 Type of incident cancer occurred in 84 out of 127 patients who underwent heart transplantation.

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