SHORT REVIEW

Recent advances in the biology of germ cell tumors: Implications for the diagnosis and treatment

P. Chieffi¹, S. Chieffi², R. Franco³, and A.A. Sinisi⁴

¹Department of Psychology, Second University of Naples, Caserta; ²Department of Experimental Medicine, Second University of Naples; ³Istituto Nazionale dei Tumori “Fondazione G. Pascale”; ⁴Department of Cardiothoracic and Respiratory Sciences, Second University of Naples, Naples, Italy

ABSTRACT. Testicular germ cell tumors (TGCT), are the most frequent solid malignant tumors in men 20-40 yr of age, and the most frequent cause of death from solid tumors in this age group. TGCT can be subdivided into seminoma and non-seminoma germ cell tumors (NSGCT), including embryonal carcinoma, choriocarcinoma, yolk sac tumor, and teratoma. Seminomas and NSGCT do not only present distinctive clinical features, but they also show significant differences as far as therapy and prognosis are concerned. Many novel markers have given further advantages to discriminate between histological subgroups. In addition, therapeutic approaches for the treatment of TGCT have been proposed: humanized antibodies against receptors/surface molecules on cancer cells, inhibitors of serine-threonine, and tyrosine kinases, and others. The review will focus on the recent advances in the research of molecular alterations identified in TGCT and on novel targeted anti-neoplastic strategies that might help to treat chemotherapy-resistant TGCT.

©2012, Editrice Kurtis

INTRODUCTION

Testicular germ cell tumors (TGCT) represent the most common malignancy in young men in western industrialized countries, being a major cause of death attributable to cancer in this age group (1-4). TGCT are histologically classified into two major groups, namely, seminomas (SEM) and non-seminomas (NSEM), including embryonal carcinoma (EC), yolk sac tumor (YST), choriocarcinoma, and teratoma. YST and and teratoma occur mainly before puberty and have an annual incidence of 0.12/10,000. SEM and NSEM have an incidence of 6/100,000 per year in males aged 15-34 yr. The incidence of TGCT varies between different countries and races, being greater in Scandinavian and Switzerland than Asia and Latin America, and in Caucasians Americans compared to African Americans. The incidence in western countries has been increasing over the last decades, probably because an increased exposure to etiologic factors. Remarkably, differences in incidence between adjacent countries such as Sweden and Finland are still largely unexplained, calling for further studies. Urogenital development abnormalities (such as intersex syndrome, cryptorchidism, hypospadias, testicular dysgenesis) and clinical conditions, such as infertility and microlithiasis, are associated with higher risk of TGCT (5, 6). Both clinical and epidemiological evidences strongly suggest that genetic and environmental factors play an important role in the genesis and development of TGCT. Several genes are implicated in the pathogenesis of TGCT, but the involvement of other genetic factors remains unknown. Susceptibility genes and environmental factors may deregulate normal differentiation processes of primordial germ cells (PGC). In fact, TGCT have an invasive phenotype and are believed to be derived from a common ancestor, carcinoma in situ (CIS), where the generation and expansion of tumor cells is limited to within the seminiferous tubules (1-5). NSEM, such as EC and teratoma, contain stem cells as well as cells that have differentiated toward somatic lineages to various degrees, thus giving rise to a morphologically pleiotropic appearance (5, 7). In contrast, SEM have a rather uniform appearance, at least at the histological level. Due to this apparently homogenous cell composition, SEM are particularly suitable for investigations of tumor-associated alterations in gene expression. In addition, the cells that constitute SEM resemble the PGC and/or the cells in the CIS. Thus, gene expression profile in SEM is interesting not only with regard to understanding their oncogenesis, but it also may be useful for research into PGC. SEM are radio- and chemo-sensitive tumors, virtually completely curable (8). NSEM tumors are usually treated with surgery and chemotherapy, with different cure rates depending on the disease stage (9). The cure rate reaches up to 99% in the early stages of NSEM tumors, although in advanced disease decreases from 90% in patients with good prognostic category to 50% in patients with poor prognostic features (9). The rapid growth and progression of post-pubertal TGCT cause early lymph-node metastases and/or distant metastases. At the time of diagnosis about 25% of SEM patients and up to 60% of the NSEM patients suffers from metastatic disease (10), posing a therapeutic problem since in metastatic disease the treatment achieves modest results.

Key-words: Aurora B, gonocytes, GPR30, HMGA, PATZ1, seminoma, teratoma, testis, testicular cancer, testicular germ cells tumors.

Correspondence: P. Chieffi, Dipartimento di Psicologia, Via Vivaldi, 43 81132 Caserta, Italy.
E-mail: Paolo.Chieffi@unina2.it
Accepted October 10, 2012.
First published online November 12, 2012.
Thus, despite the general success of post-pubertal TGCT treatment, 10-20% of patients diagnosed with metastatic disease will not achieve a durable complete remission after initial treatment, either due to incomplete response or a tumors relapse. The present review will describe the molecular alterations identified in post-pubertal TGCT and on novel targeted anti-neoplastic strategies to cure chemotherapy-resistant TGCT.

HISTOPATHOLOGY OF TGCT

The origin and biology of TGCT are currently distinct on whether they occur in pre- and post-pubertal age. Pure teratomas and YST with a substantially benign prognosis are the most common histotypes of pre-pubertal testis and SEM, while pure NSEM tumors and mixed germ cell tumors (MGCT) with a relative more aggressive behavior are typical of adult testis (1, 2). It has been suggested that the initiating event in the pathogenesis of TGCT occurs during embryonal development (3, 4). The most widely accepted model of post-pubertal TGCT development proposes an initial tumorigenic event in utero and the development of a precursor lesion known as intratubular germ cell neoplasia, undifferentiated (ITGCNU), also known as CIS (11). This is followed by a period of dormancy until after puberty when post-pubertal TGCT emerge. The pre-pubertal dormancy suggests that the TGCT development is hormone dependent. Recently, it has been proposed that tumors originate from neoplastic cells that retain stem cell properties such as self-renewal (12), and this novel hypothesis has fundamental implications for the pathogenesis of TGCT. According to the stem cells hypothesis, tumors originate from tissue stem cells or from their immediate progeny. This cellular subcomponent drives tumorigenesis and aberrant differentiation, contributing to cellular heterogeneity of the tumor and also to the resistance to antineoplastic treatments (12).

ITGCNU cells are generally accepted as the common pre-invasive precursor cells that give rise to post-pubertal TGCT (1-6). ITGCNU almost found invariably in the periphery of overt post-pubertal TGCT and is estimated that it is present in approximately 5% of the contralateral tests of patients with post-pubertal TGCT (13). Pre-invasive ITGCNU cells are supposed to be able to develop in different germinal and somatic tissues and are regarded as pluripotent or totipotent cells and, therefore, can be considered as TGCT stem cells. ITGCNU cells share morphological similarities with gonocytes and it has been proposed that ITGCNU cells could be remnants of undifferentiated embryonic/fetal cells (14). This hypothesis is further supported by immunohistochemical studies in ITGCNU, also shown to be present in PGC and gonocytes. The identification of ITGCNU cells in pre-pubertal patients, who later developed TGCT, indicated that the cells had originated prior to puberty. Therefore, ITGCNU cell represents an interesting variant of cancer stem cell since it originates before the tissue that it propagates in is fully differentiated and functional. The observation that two transcription factors, POU5F1 (OCT3/4) and NANOG, known to be associated with pluripotency in embryonic stem (ES) cells are expressed in ITGCNU has further contributed to assess the embryonic origin of these cells. A link between ITGCNU cells and embryonic cells has been further supported by a substantial overlap between each gene expression profiles, as shown by Almstrup et al. (15). All histotypes could be present in post-pubertal TGCT, because of its totipotent profile, even SEM can switch to NSE histotype through reprogramming phenomenon (Fig. 1) (16). The role of these