Analysis of Chromosome 12 Abnormalities in Male Germ Cell Cancers


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Introduction

A specific cytogenetic abnormality, an isochromosome 12p, i(12p), has been described in male germ cell cancers (Atkin and Baker 1982, 1983). The incidence of this abnormality has been stated to be as high as 90% (Heim and Mitelman 1987), occurring in tumors histopathologically diagnosed as seminoma, nonseminoma, and teratoma (Castedo et al. 1989a,b,c; Bosl et al. 1989; Samaniego et al. 1990). Our investigations of i(12p) in human germ cell cancer provide further support for the diagnostic importance of this cytogenetic marker. This review presents the molecular and cytogenetic studies from the Memorial Sloan-Kettering Cancer Center principally concerning chromosome 12 in primary and metastatic germ cell tumors and in established germ cell cancer cell lines.

Cytogenetic Abnormalities

A comprehensive cytogenetic analysis was performed by Chaganti and colleagues on primary gonadal, extragonadal, and metastatic germ cell tumors as well as on a number of established germ cell cancer cell lines (Chaganti et al. 1989; Ladanyi et al. 1990; Samaniego et al. 1990; Murty et al. 1990). An i(12p) was identified in all histologic subtypes (including choriocarcinoma and mature teratoma) and in tumors obtained from both gonadal and extragonadal primary sites (Bosl et al. 1989; Samaniego et al. 1990). In 29 tumor specimens obtained from 24 male germ cell tumors, an i(12p) was found in 20 specimens from 16 patients, representing an identification in 69% of all our examined specimens. Two specimens had a del (12q) in addition to the i(12p) and eight had a normal karyotype (46, XY), suggesting outgrowth of the nonmalignant elements within the tumors. One patient's tumor was a cytogenetic failure. Other cytogenetic alterations included the near-triploid
karyotypes in 15/16 (94%) patients, homogeneous-staining regions (HSRs) in 3/16 (19%) patients, and double minute chromosomes in 2/16 (13%) patients. Chromosomes 1, 7, 9, 12, 17, 21, 22, and X were nonrandomly gained in these tumors and a del(12) (q13–q22) was observed in 44% of nonseminomatous and mixed germ cell tumors (Samaniego et al. 1990). Taken together, these data along with those from the published literature provide evidence for the specificity of this cytogenetic change in germ cell tumors and raise the prospect of the importance of i(12p) in the transformation of normal human germ cells. Diagnostically, the examination of tumors of unclear histogenesis such as in the “unrecognized germ cell tumor syndrome” (Greco et al. 1986) for the presence of i(12p) might aid in their clinical management since tumors with an i(12p) may respond to germ cell tumor treatments.

One patient among these 24 presented with a mediastinal primary germ cell cancer. He was treated with a combination chemotherapy regimen, but relapsed with both progressive mediastinal disease and an acute myelomonocytic leukemia 11 months after the germ cell tumor diagnosis (Chaganti et al. 1989). Isochromosome (12p) was identified in the original mediastinal tumor specimen and in the acute leukemia, suggesting that the clonal origin of the acute leukemia cell and the germ cell tumor were the same. The germ cell origin of a subset of leukemias arising in patients with mediastinal germ cell tumors was confirmed on the basis of the presence of the i(12p) and/or common immunohistochemical markers (Ladanyi et al. 1990). These studies highlight the potential for differentiation which germ cell tumors can exhibit and the value of the i(12p) as a marker in germ cell derived tumors.

Since nearly all patients were entered onto ongoing germ cell tumor treatment protocols, studies of the correlation between 12p copy number and treatment outcome were undertaken. The presence of three or more additional copies of 12p was associated with a statistically greater likelihood of a clinical treatment failure (Bosl et al. 1989). This is analogous to the experience in chronic myelogenous leukemia in which the appearance of two copies of the Philadelphia chromosome is a harbinger of a more aggressive clinical phase (Watmore et al. 1985). In contrast, patients whose tumors had a normal karyotype or had two or less additional copies of 12p had a more favorable treatment outcome (Bosl et al. 1989). These data suggest that cytogenetics may provide important prognostic information, in addition to clinical features (Bosl et al. 1983) such as sites of metastases, lactate dehydrogenase (LDH) levels, and human chorionic gonadotropin (HCG) values which are known to be important in this malignancy.

In order to investigate chromosome 12 abnormalities in greater detail, cytogenetic studies of established human germ cell cancer cell lines were undertaken. An i(12p) marker was present in seven out of seven male germ cell cancer cell lines, but not in a single female teratocarcinoma cell line (Dmitrovsky et al. 1990). Other nonrandom chromosome 12 abnormalities contained within these male germ cell cancer cell lines included a del(12q14)