Editorial

Mediastinal germ cell tumors: new therapeutic insights

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Extragonadal germ cell tumours are rare and comprise a heterogeneous group of neoplasms with distinct natural history and responses to different treatment modalities. The most frequent site of extragonadal germ cell tumours is the anterior mediastinum (1). Histologically, primary mediastinal germ cell tumours (MGCTs) classification includes seminomatous and non-seminomatous type. The latter consists of a single histologic variant or is mixed with a seminomatous component. Germ cell tumours are generally chemosensitive, but their response is linked to the histological type (2). In general, seminomatous MGCTs have an almost 90% rate of survival, whereas non-seminomatous variants have an overall survival less than half than that of the seminomatous counterpart (3). A chemioterapic combination of cisplatin and etoposide is curative in more than 80% of germ cell tumour patients with metastatic disease (2,3). Unfortunately, approximately 10% of patients with metastatic germ cell tumours die, mostly because of chemoresistant nature of the neoplastic disease (3). Some studies report that the outcome of extragonadal germ cell tumors remains inferior to those of testicular tumors GGCTs (4). Difficulties and controversial in the diagnosis and cure of MGCTs derive in part from the evidence that, despite the similar morphologic and microscopic appearance, carcinogenetic events may be distinct from the gonadal counterparts, with a lower overall survival (2,3). Non-seminomatous tumors display an overexpression of p53, MIB-1, and COX-2 compared with matched cohorts of patients with seminomatous extragonadal germ cell tumors, highlighting biologic differences and a different response to the stimulation (5). It is worth of noting that the same regulating peptides and genes documented in carcinogenetic pathways of germ cell tumors also influence differentiation, function and proliferative behavior of adult cells (6-10). *In vitro* studies often reveal potential therapeutic targeting. Stable overexpression of cyclin L2 in P19 embryonic carcinoma cell gene reduced growth rate and induce down-regulation of anti-apoptotic Bcl-2 protein (11). In addition, real-time PCR analysis revealed that expression of Wnt, beta-catenin was suppressed, and GSK3beta was induced in the cyclin L2-overexpressing P19 cells, suggesting that overexpression of cyclin L2 inhibits proliferation and differentiation of mouse embryonic carcinoma P19 cells and induces them to undergo apoptosis (11).

Recently, investigation of whole-exome and transcriptome sequencing of both human primary and metastatic gonadal and MGCTs revealed that the primary somatic feature of germ cell tumours are recurrent chromosome arm level amplifications and reciprocal deletions, and those variations are increased in germ cell tumours compared to many other cancer types (12). Moreover, *KRAS* mutations seem to concur to germ cell tumour carcinogenesis during the carcinogenetic development from precursor to primary disease (12). Phylogenetic analysis of tumours with chemotherapy resistance revealed additional reciprocal loss of heterozygosity associated with loss of pluripotency markers

NANOG and *POU5F* in chemoresistant teratomas or transformed carcinomas (13). Altogether, those results strongly support that biological aggressiveness in germ cell tumours associates with the progressive gain of a distinct multifactorial genomic profile leading to the progression to chemoresistance (12). More in detail, chemosensitivity in germ cell tumours may be the result of high mitochondrial priming properties. Consequently, additional screening per expression pro-apoptotic and pro-apoptotic genes determining chemotherapy-induced apoptosis in tumor tissue may be extremely helpful to address a more personalized therapy. Some studies also report the treatment of MGCTs patients with relapse with a high-dose chemotherapy with stem cell support, although prospective, randomized data are lacking (14). Although potentially beneficial, the enrichment with stem cells must be carefully evaluated, since stem cells produce autocrine growth factors that potentially influence tumour cell growth (15).

Recently, Tanaka *et al.* (16) reported a study of patients with MGCTs treated using multimodal therapy. Three patients received a variable post-surgical chemotherapy with bleomycin, etoposide and cisplatin (BEP), or etoposide and cisplatin (EP). One of these three patients developed metastasis 17 months after surgery and received an additional treatment with vinblastine, fosfamide and cisplatin, followed from complete remission of the disease. Other three patients with MGCTs received initial BEP and EP chemotherapy, and two of these presented lung and supraclavicular lymph node metastasis and surgical treatment was performed to remove residual tumor after treatment, with complete remission. The Authors conclude that multimodal treatment is required for patients with MGCTs (16). Although clinical results are quite promising, a longer follow-up is required to confirm the remission of the disease. Moreover, it appears also evident that the choice of the initial therapy depends on many factors, including tumor size, microscopic examination, post-surgical staging and clinical information. For this reason, additional cases will be greatly useful to standardize the treatment of MGCTs, with progressive greater involvement of a multidisciplinary medical team. Additional studies will also elucidate whether a more intensive chemotherapy or a targeted drug selection can improve outcomes in patients with MGCTs.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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