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Role of Biomarkers in Germ Cell Tumors: Focus on microRNA371a-3p

Raul Vera Gimon

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ABSTRACT

Germ cell tumors (GCTs) are classified into seminomatous and non-seminomatous subtypes and are associated with distinct biomarkers that aid in diagnosis, risk stratification, and monitoring. While traditional serum markers such as AFP, HCG, and LDH have been mainstays in clinical practice, their limitations in sensitivity, especially in small-volume disease, have led to exploration of novel diagnostic tools. Immunohistochemical and molecular markers, including PLAP, OCT3/4, SOX17, SOX2, CD30, GPC3, SALL4, KIT mutations, and I 12p, support histological classification and prognosis. Among emerging biomarkers, microRNA-371a-3p stands out for its superior sensitivity and specificity, rapid serum clearance, and potential to detect minimal residual disease. Although it lacks utility in identifying teratomas, miR371a-3p shows promise in surveillance and early relapse detection, potentially reducing reliance on imaging. Ongoing trials are evaluating its clinical applicability. This review synthesizes current data on established and emerging biomarkers in GCTs, emphasizing the transformative potential of miR-371a-3p in disease management.

Introduction

Germ cell tumors are broadly classified into seminomatous and non-seminomatous subtypes. Each group has distinct histological, molecular, and clinical characteristics, needing the use of specific biomarkers for diagnosis, classification, prognosis, and treatment monitoring. Traditional biomarkers have long served as the cornerstone of GCT management, but recent advances particularly the emergence of microRNA-371a-3p miR-371a-3p have improved diagnostic accuracy and clinical decision-making. It is elevated in serum and plasma of patients with non seminomatous and seminomatous GCTs but not in teratomas or benign lesions. It has a superior sensitivity of 90% and specificity 94% compared to traditional markers like AFP, B-HCG and LDH, levels fall rapidly after orchiectomy or chemotherapy correlating with tumor burden. May detect relapses earlier than imaging or serum tumor markers.

This marker has rapid clearance from circulation with half life < less than 24 hours allowing real time treatment monitoring. It is noninvasive, requires only a blood sample and has broad applicability across seminomas and non seminomatous except for teratoma.

Traditional Biomarkers

Immunohistochemical Markers

Placental alkaline phosphatase PLAP: Typically expressed in seminomas and some non-seminomatous GCTs[1,2].OCT3/4: Highly expressed in seminomas and embryonal carcinoma; negative in yolk sac tumors and teratomas[3].SOX2 and SOX17: SOX2 is expressed in embryonal carcinoma, while SOX17 is specific for seminomas. These markers aid in distinguishing seminoma from embryonal carcinoma[4]. Glypican-3 (GPC3): Found in yolk sac tumors and some embryonal carcinomas, but not in seminomas[5]. CD30: A marker for embryonal carcinoma; not expressed in seminomas[6]. SALL4: A general marker for both seminomatous and non-seminomatous GCTs[7,8].

Molecular Markers

KIT Mutations: Occur predominantly in seminomas, often associated with PLAP positivity[9]. Isochromosome 12p: A pathognomonic cytogenetic feature found in both seminomas and non-seminomatous GCTs[10].

Serum Tumor Markers

Alpha-fetoprotein (AFP): Elevated in non-seminomatous tumors, particularly yolk sac tumors and embryonal carcinoma; not elevated in pure seminomas or choriocarcinomas. AFP has a half-life of 5–7 days, with normalization over 25–30 days after effective therapy[11–13]. Mild AFP elevations <30 ng/mL may occur and are not necessarily indicative of active disease[14]. Beta-human chorionic gonadotropin: Elevated in choriocarcinoma and some embryonal carcinomas; can also be increased in 15–20% of seminomas. Its half-life is 1.5–3 days[13]. Lactate dehydrogenase (LDH): A non-specific marker often elevated in advanced GCTs; correlates with tumor burden[13].

Limitations of Traditional Markers

While traditional markers are valuable, they lack sensitivity in small-volume diseases and in certain histologic subtypes such as teratoma. Imaging and histopathology are often needed to complement serum marker results[13].

miR-371a-3p: A New Diagnostic tool

Biological Characteristics miR-371a-3p is a small, non-coding RNA highly expressed in active germ cell malignancies, including both seminomas and non-seminomas. It is detectable by real-time PCR in serum or plasma and has a rapid decay, with a half-life of less than 5 hours[15,16].

Diagnostic Utility: miR-371a-3p is detectable in 44% of GCTs smaller than 1 cm and is particularly useful when traditional markers are within normal ranges. Healthy control subjects and patients with nonmalignant scrotal disease, as well as those with non-GCT of the testis (LCT), did not express the marker[18]. In a prospective, multicentric study,

serum samples of 616 patients with testicular GCTs and 258 male controls were examined for serum levels of miRNA-371a-3p by quantitative polymerase chain reaction. The GCT population encompassed 359 patients with seminoma and 257 with non-seminoma; 371 had clinical stage I disease, 201 had systemic disease, and 46 had relapses. Paired measurements before and after orchiectomy were performed in 424 patients; 118 with systemic disease had serial measurements during treatment. For the primary diagnosis of GCT, the M371a-3p test showed a sensitivity of 90.1%, a specificity of 94.0%, an area under the curve of 0.966 upon receiver operating characteristic analysis, and a positive predictive value of 97.2%. α-Fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase had sensitivities of less than 50% in seminoma and slightly higher sensitivities in non-seminomas. miR371a-3p levels were significantly associated with clinical stage, primary tumor size, and response to treatment. Relapses had elevated miR371-a levels that subsequently dropped to normal upon remission. Teratoma did not express miR371a-3p.[19].

Comparison with Traditional Markers: miR-371a-3p is more sensitive than AFP and beta hCG and can detect microscopic or minimal residual disease.[20] It is not effective in detecting pure teratomas [21–23], which remains a limitation. The combined use of miR-375 and miR-371a-3p is under investigation for this purpose[24].

Surveillance and Relapse Detection: Normalization of miR-371a-3p levels post-orchiectomy correlates with the absence of residual tumor[17]. While post-operative levels may not predict relapses in clinical stage I[25,26], serial monitoring enables early detection of recurrence. Measurement of miR371 during follow up may allow saving several of the imaging procedures, thus saving costs and energy consumption. Due to its noticeably short half-life, the test could rapidly uncover patients not-responding to chemotherapy, thus aiding early change in therapeutic regimens; Positive levels may precede clinical relapses by a median of 3 months[27].

A meta-analysis highlights the potential of serum microRNAs in predicting RPLND pathology, particularly in distinguishing between viable germ cell tumors and benign conditions, including necrosis and teratomas, using microRNA-371a-3p. However, the data available for differentiating teratomas from necrosis is limited[28].

One promising approach was described by Ozgun et al.[31], who developed a machine learning model combining CT-based radiomic features with circulating levels of miR-371 and miR-375 to predict teratoma histology in post chemotherapy residual lesions of NSTC. In their retrospective analysis of 105 lesions across 52 patients, the best-performing Cat Boost model achieved an AUC of 0.83 in the test set, with a sensitivity of 0.71 and specificity of 0.76 for identifying teratoma. This multi-modal strategy, integrating imaging and liquid biopsy data, may help refine the identification of residual teratoma and reduce unnecessary surgical resections in patients with fibrosis or necrosis.

Standardization Challenges

There is a need for consensus on assay methodology, sample type, normalization, and cut-off thresholds to allow for broader clinical adoption[29].

Role in Cisplatin Resistance

miR-371a-3p expression is elevated in cisplatin-resistant cell lines. Inhibition of miR-371a-3p restores sensitivity, suggesting its role in chemoresistance mechanisms[30].

Clinical Trials Validation studies are ongoing, including SWOG-S1823 (NCT04435756), AGCT1531 (NCT03067181), and CLIMATE ANZUP1906. These trials aim to establish the utility of miR-371a-3p in both adult and pediatric populations.

Conclusion

miR-371a-3p represents a breakthrough in the biomarker landscape for germ cell tumors. It offers superior diagnostic performance, early relapse detection, and potential to reduce reliance on

imaging in surveillance strategies. While it is not yet incorporated into standard guidelines and has limited utility in teratomas, miR-371a-3p is poised to transform GCT management pending further validation and standardization.

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