Biomarkers for Diagnosis and Prognosis of Testicular Cancer

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Introduction

Testicular cancer/Testicular germ cell tumor (TGCT) is a solid neoplasm which is a type of germ cell tumors that occur in testicles (testes). It is a less common malignancy in males between the ages of 15 and 35 that is often manageable due to its well response towards chemotherapy and radiotherapy with highest survival rates. The general five-year survival rate for men with testicular cancer is 95%. Testicular cancer occurs as seminomas and nonseminomas types based on histology. Nonseminomatous type of germ cell tumors (embryonal cell carcinoma, yolk sac tumor, choriocarcinoma, and teratoma) secrete most tumor markers in testicular cancer. Treatment prognosis also depends on the histology of the GCTs. Seminomas responds well to chemo and radio therapy whereas nonseminomas are susceptible to platinum combination chemotherapy than radiation except teratomas which are resistant to platinum-based treatments. Novel markers like OCT3/4, SOX2, SOX17, HMGA1, HMGA2, PATZ1, GPR30, Aurora B and estrogen receptor β helps to distinguish between the histology types of testicular cancer [1].

Clinical evaluation and early diagnosis are critical for the prognosis and treatment of testicular cancer. Cryptorchidism (undescended testicle) is often a risk factor associated with it. Current review focuses on recent developments for the identification of novel biomarkers and their emerging clinical applications in the management of the disease. Sensitive and reliable clinical biomarkers could offer insights in to patient risk-stratification, guide surgical decisions and precise treatment optimization for cisplatin combination-resistant patients and post-treatment early detection of recurrence. Significant changes associated with clinical markers following chemotherapy are an important prognostic indicator for progression-free survival (PFS) [2].

Testicular Serum Tumor Markers

The International Germ Cell Cancer Collaborative Group (IGCCCG) established the following serum biomarkers in testicular germ cell tumors (GCTs) which include α-fetoprotein (AFP), β-human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH) for risk stratification, staging, and disease monitoring response to therapy. They were detected in approximately 60% of men with testicular cancer. The elevated levels during diagnosis can guide the oncologists with their follow-up levels resulting from the response to the treatment and rising levels are also an accurate indicator of recurrence. The major limitations with them however are due to low accuracy and specificity as there were several other conditions with elevations in these tumor markers.

Hypogonadism causes a compensatory increase in the pituitary production of bHCG and LH and cause false-positive results [3].

Among the three serum markers for GCTs, LDH has relatively limited specificity due to its isoforms and inconsistent variations based on the assay whereas AFP or bHCG elevation is directly proportional to tumor burden.

American Society of Clinical Oncology (ASCO) recommendations for the Interpretation of serum markers (AFP, bHCG, LDH) levels draws the following conclusions

a. Decisions regarding proceeding for orchiectomy (surgery to remove one or both testicles) and treatment should not be relied up on screening of AFP and bHCG
b. If levels the levels of AFP, bHCG and LDH are high before orchiectomy, they should be rechecked after orchiectomy to identify if they are resumed to normal levels.
c. To determine the stage and prognosis of a non-seminoma AFP, bHCG and LDH levels should be measured after orchiectomy and before the commencement of chemotherapy.
d. Levels of AFP and bHCG should be measured before retroperitoneal lymph node dissection (RPLND) and before each cycle of chemotherapy.
e. Testicular seminoma that metastasis to other body parts (stage II or III disease) bHCG and AFP should be measured intermittently after the treatment ends to help monitor the recurrence of cancer.
f. Tumor serum markers should not be used for treatment decision changes and recurrence of stage I seminoma.

Having thoroughly identified the limitations of conventional serum tumor markers, there is a need for a novel specific and sensitive marker to analyse its implications for potential applications in clinical settings. Placental-like alkaline phosphatase (PLAP), Neuron-specific enolase (NSE), Lectin-reactive AFP (AFP-L3), TRA-1-60 and Cell-free circulating DNA are investigational markers explored but significant findings for their specific role in testicular cancer is yet to be established [4].

DNA analysis of tumor samples from testicular cancer patients observed specific genes associated with risk of testicular cancer and possible inherited genetic factors leading to cryptorchidism. Genomic studies also identified three mutations on genes KIT, KRAS, and NRAS.DNA repair enzyme poly (ADP-ribose) polymerase (PARP) higher expression was reported in GCT tissue compared to normal testicular tissues.

Immune Biomarkers

Programmed-death receptor and its ligand (PD-1 and PD-L1) signalling and expression was found in both seminomas and non-seminoma GCT [5]. Higher PD-L1 expression on tumor infiltrating lymphocytes (TIL) had found to have better prognosis compared with patients with lower PD-L1 TIL. Anti-PD1 agents like pembrolizumab and avelumab were studied for refractory GCT. PD-1/PD-L1 expression found in other types of cancer could mean lacking in specificity. Pro-inflammatory micro environment parameters like systemic-immune infiltration index (SII) and cytokines, such as IFN-α2, IL-2Rα, or IL-16 signalling were elevated to counteract the

progressing tumor growth. β-1,4- galactosyltransferase-I (B4GALT1) in peripheral T-lymphocytes is a marker of relapse in GCT patients treated with salvage high-dose chemotherapy [6-10].

Epigenetic Biomarkers

MicroRNAs (miRNAs) are non-coding RNAs which are novel biomarkers that regulate the level of gene expression on a post-transcriptional level that can be detected through RT-PCR. They are post-transcriptional regulators that have a role in carcinogenesis. miRNAs are specific and intervene with the translation of a given mRNA to a protein and acts a tumor-suppressor genes or oncogenes. miRNAs had a significant role in cell differentiation, proliferation and apoptosis, and imbalance in their expression leads to oncogenesis.

Epigenetic mechanisms like hypermethylation of dynamine 3 (DNM3) at chromosome 1q24.3 leads to down-regulation of miR-199 [11-13]. Podocalyxin-like protein 1 (PODXL) is an anti-adhesion transmembrane protein targeted by miR-199a. It has greater expression in the testicular cancer that could be co-related for the assessment of hypermethylation with miR-199a [14,15].

Serum miRNA test (TSmiR) for the identification of miR371-373 is also a specific epigenetic marker with better sensitivity compared to the conventional markers **Table 1**.

Conclusion

Accurate diagnosis and prognosis through biomarkers are pivotal for the precise antineoplastic strategies to deal with the testicular cancer and the disease management with regular assessment of recurrence following the therapy is also critical to reduce the burden of adverse events associated with the chemotherapy. Novel biomarkers with specific affinity towards the GCTs need to be established for monitoring the disease. Recent advancements with microRNA markers can helps with the treatment optimization for prevention of long-term toxicities and improve the quality of life of patients.