Platinum Resistant Ovarian Cancer – Therapeutics Landscape

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Ovarian cancer is the leading cause of gynecological cancer mortality worldwide. While the median survival rate is estimated at five years post-onset, ovarian cancer is undetectable and often presents as an advanced disease. Platinum-based agents are widely used as either first-line, combination, or adjuvant therapies, however 80-90% of women diagnosed with advanced disease will develop platinum resistance.[1] Traditional chemotherapy is limited due to poor tumor localization, devastating side effects, and inconsistent efficacy.

Platinum Agents as Standard of Care

Platinum-based agents are used as a standard-of-care in cancer treatment for several tumor indications. Currently cisplatin, carboplatin and oxaliplatin are the only platinum agents approved for clinical use. Although they are curative against testicular cancer, their clinical utility remains limited in ovarian cancer, colon cancer, and non-small cell lung cancer, reflected in low 5-year survival rates between 5- 65%.[2]

Limitations of Platinum Agents

Despite clinical success with the use of cisplatin, carboplatin, and oxaliplatin, treatment with these compounds causes well-known toxic side effects that substantially affect patient quality of life.

Cancer response to platinum treatment is defined either as platinum-sensitive or platinum-resistant based on the time period from end of treatment to relapse, which is the platinum free interval. Treatment resistance may be inherent or develop over time. This is particularly challenging in ovarian cancer. Women with platinum resistant disease have a median survival of 9-12 months, while less than 15% respond to subsequent chemotherapy.[3]

One of the mechanisms of resistance involves dysfunction of the tumor suppressor p53 gene. The inability to overcome p53 dysfunction in combination with the dose limiting toxicities and poor tumor- specific drug delivery results in a clinical limitation to the current standard of care. This is particularly true in ovarian cancer.

Additionally, cancer cells continue to outsmart treatments, with drug resistance recognized as a significant issue resulting in disease progression. Drug resistance is responsible for up to 90% of cancer related deaths.[4] Patients can experience primary, or intrinsic resistance, meaning they do

[1] Lisio, M.-A., Fu, L., Goyeneche, A., Gao, Z. & Telleria, C. High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. International Journal of Molecular Sciences 20, (2019).
[2] Siddik, Z. H. Drug Resistance and the Tumor Suppressor p53: The Paradox of Wild-Type Genotype in Chemorefractory Cancers. in Drug Resistance in Cancer Cells (eds. Siddik, Z. H. & Mehta, K.) 209–231 (Springer, 2009).
[3] Vergote, I. et al. Treatment algorithm in patients with ovarian cancer. Facts Views Vis Obgyn 12, 227–239 (2020).
[4] Wang, X., Zhang, H. & Chen, X. Drug resistance and combating drug resistance in cancer. Cancer Drug Resist 2, 141–160 (2019).

not respond to initial therapy. Others may experience acquired resistance in which the cancer cells adopt new mechanisms over time to resist treatment. Ongoing research continues to explore these mechanisms.

Platinum Resistant Ovarian Cancer Therapeutics

The current treatment options for platinum-resistant disease consist of chemotherapy agents developed in the 1980s and 1990s. These older drugs have demonstrated limited response rates between 20 –30%. None of these agents have demonstrated a survival advantage over other treatment approaches, including palliation. Branded targeted therapies have demonstrated efficacy in both platinum-sensitive and platinum-resistant disease. These include bevacizumab (VEGF), olaparib (PARP), and rucaparib (PARP). However, response rates continue to hover in the 20 –30% range. In addition, only combination therapies - bevacizumab + chemotherapy and pazopanib + paclitaxel - have demonstrated a survival advantage in the clinical setting.[5]

Agents in development for platinum resistant ovarian cancer span four different mechanisms of action. These include:

- Anti-angiogenic therapies:
    - VEGF inhibitors (e.g., bevacizumab)
    - VEGF receptor inhibitors (e.g., cediranib, pazopanib, and nintedanib)
- PARP inhibitors for patients with BRCA mutations or defects in homologous recombination:
    - Approved and marketed: Olaparib, niraparib, and rucaparib
    - In development: veliparib and talazoparib
- Folate receptor targeting:
    - Inhibitors: farletuzumab
- Immunotherapies:
    - Checkpoint inhibitors, immune modulators[6]
    - Therapeutic vaccines

None of the above approaches have shown to be curative, while some may be even less effective than current chemotherapy when used alone (immunotherapy demonstrates objective response rates of 15–25% with few durable responses).[7] Combination therapy may lead to improved options. However, to-date, combination therapy is not preferred over single agent therapy in platinum resistant ovarian cancer patients.[3]

This highlights the need for improved cancer treatments across all types of solid tumors. InnovoTEX Inc. is a biopharmaceutical company developing a portfolio of novel therapeutics

[5] Thiabaud, G. et al. Oxaliplatin Pt(IV) prodrugs conjugated to gadolinium-texaphyrin as potential antitumor agents. Proceedings of the National Academy of Sciences 117, 7021–7029 (2020).
[6] Karoscik, K. Immunomodulators and Cancer Research. Applied Clinical Trials-08-01-2020, Volume 29, Issue 7/8 (2020).
[7] Ventola, C. L. Cancer Immunotherapy, Part 2: Efficacy, Safety, and Other Clinical Considerations. P T 42, 452–463 (2017).

capable of targeting multiple solid tumor indications. Our mission is to develop the next generation of therapeutic innovation.

To accomplish this mission, InnovoTEX is developing its proprietary TEX Core platform, which utilizes the tumor localizing and well-tolerated small molecule, texaphyrin, as the basis for a series of conjugates designed to treat both drug-sensitive and drug-resistant solid tumors. Within this platform, InnovoTEX currently has several drug candidates across four development programs. Each of the drug candidates is in different stages of development for the treatment of multiple solid tumor indications. From the TEX Core platform, OxaliTEX is the lead candidate currently in preclinical development for the treatment of platinum-resistant ovarian cancer.

Market Overview

The global oncology therapeutics market, specifically the ovarian cancer and platinum-resistant ovarian cancer markets, projects sizable expansions from 2022 to 2030 to address an urgent unmet clinical need in therapeutic development. The market will increase over 12-fold in value over the 9-year period 2021-30. Global market revenues are forecast to reach a peak of $19.92 billion USD with a CAGR of 23.8%.[8] InnovoTEX is managing several patent families that extend jurisdictions into these global markets.

There is significant, long-term market value in novel therapeutic development for platinum resistant tumors as standard of care combinations have shown limited efficacy to date. Therefore, InnovoTEX envisions multiple opportunities for commercialization.

[8] https://www.globenewswire.com/news-release/2022/05/30/2452740/0/en/Ovarian-Cancer-Market-to-reach-a-market-size-of-USD-19-92-Billion-by-2030-growing-at-a-CAGR-of-23-8-Straits-Research.html