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Current Status and Future Prospects of CAR-T Cell Therapy in Ovarian Cancer

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Abstract. Ovarian cancer is one of the most deadly gynecologic cancers and is often detected at an advanced stage when the disease is disseminated. Initial disease control can be achieved with cytoreductive surgery and platinum-based chemotherapy, but recurrence is very common. Fluctuation of the CAR-T therapy in some types of hematologic malignancy has sparked interest in perhaps expanding this therapy to ovarian cancer; this is still to be seen. This review assesses the available clinical evidence without making the assumption that findings in blood cancers can be directly extrapolated to a solid tumor. Based on the level of evidence supporting each target, mesothelin, FRα, MUC16/CA125 and B7-H3 are considered. The results have been variable; and stable disease has been seen often, while significant regression and complete remissions are rare. Combination strategies, fertility issues and practical limitations that still remain in the use of CAR-T therapy in ovarian cancer are also discussed.

Keywords: Ovarian cancer, CAR-T cell therapy, current status, future prospects

1. Introduction

Epithelial ovarian cancer is the fifth leading cause of cancer-related death in women and for advanced disease the five-year survival rate is ~30% [1]. Diagnosis is still a big challenge. However, problems of bloating, pelvic pain and early satiety are common but not very specific to ovarian cancer; routine screening has not helped overcome this. As a result, many patients present with advanced disease (FIGO stage III or IV) and frequently with peritoneal cavity involvement [2]. Treatment may be available, but has significant limitations. Cytoreductive surgery is performed to remove visible disease where possible, and chemotherapy with platinum and taxanes is used to treat remaining disease.

There may be microscopic disease remaining after surgery and there are side effects of myelosuppression, neuropathy and hair loss with treatment and it is very common to recur within 2 years [3]. When platinum resistance occurs, future therapeutic options are even fewer. This is what has spurred the interest in CAR-T therapy. CAR-T therapy differs from chemotherapy, which relies on the effect of the drugs, as it modifies the patient's T cells to target a specific tumor antigen. Cells are harvested, genetically engineered, grown and returned. CAR mediated recognition is not limited to HLA, which makes this approach an alternative method to direct immune activity against tumor

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cells [4]. It has already proven to be effective in B-cell malignancies. The question is whether such an effect on the biology of ovarian cancer would be clinically meaningful. The following sections discuss this question in the context of mechanism, target selection, clinical outcomes, safety, fertility and the major unanswered questions.

2. A description of how the process works and why it works

2.1. The construction of CAR-T cells and their function

The manufacture process of CAR-Ts starts with the collection of T cells using a leukapheresis process. The cells are subsequently activated ex vivo and genetically engineered, typically by a viral vector containing the CAR sequence. Each receptor has a modular structure. Extracellular domain, usually a single-chain variable fragment (scFv), mediates target binding. The receptor has a transmembrane region which anchors the receptor in the cell membrane and intracellular domains which transmit the activation signal. The CD3ζ is always fused into the signaling module with either 4-1BB or CD28, in most second generation CARs. Patients are usually treated with lymphodepleting chemotherapy prior to infusion. Once the CAR has bound to its target, the T-cells are able to kill the target cell via perforin, granzyme, and Fas/FasL signaling [4]. While the mechanism is well understood, the biggest clinical challenge of ovarian cancers is once these cells are exposed to the solid-tumor environment.

2.2. Theoretical benefits vs. clinical benefits

There are a number of theoretical benefits of CAR-T therapy. Antigen recognition does not require HLA presentation, infused cells can expand following infusion and in some situations can give rise to durable responses. The benefits have been well documented in certain hematologic cancers but much less impressive in ovarian cancer. In the few small studies that have been conducted to date, the rate of disease stabilization has generally exceeded the rate of significant tumor shrinkage, as has the duration of persistence of transferred cells. This distinction is clinically relevant because sometimes there is no correlation between technical feasibility and therapeutic effectiveness. The existing ovarian cancer data are interesting, but it is not possible to extrapolate the magnitude or durability of responses from the blood cancer to the solid tumor setting [5, 6].

2.3. Why it is a suitable target: ovarian cancer

Yet, for two main reasons, ovarian cancer is of interest. The first is the differential expression of several tumor associated surface antigens. They are more abundant on ovarian cancer cells than in most normal cells, potentially allowing targeted therapy. Second, there may be a significant amount of disease within the abdominal cavity. Intraperitoneal delivery allows for the administration and could result in greater local CAR-T cell levels around tumor deposits than intravenous infusion alone [2]. While neither of these properties is sufficient to demonstrate efficacy, both properties offer a good dogma for considering this approach in ovarian cancer.

3. Target antigens, clinical evidence

The evidence to support the individual targets is very wide-ranging. Mesothelin has the most clinical experience, while FRα and MUC16 have been assessed in less number of patients. B7-H3 and HER2 are still in early stages of development. This discussion is then structured to present these

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targets in the order of the maturity of the evidence available rather than providing a list of equally established targets.

3.1. Mesothelin (MSLN)

Many epithelial ovarian cancers, especially serous tumors, express mesothelin while expression of mesothelin in normal tissues is limited to mesothelial. This differential expression led to mesothelin becoming an early and sustained target for CAR-T research. Now with accumulated clinical experience, it gives insight on the strengths as well as the weaknesses of this field.

Prominent safety data from clinical trials in mesothelin have been reported. Repeated administration of mRNA-transfected mesothelin CAR-T cells resulted in anaphylaxis and cardiac arrest in 2013 in the report from Maus et al., the CAR of which was based on a mouse-derived antibody fragment [7]. The following studies employed modified platforms and provided more informative efficacy results.

Clinical cohorts were still small. Haas et al. tackled 15 patients with advanced solid tumors in 2019, among them five patients with ovarian cancer. Stable disease was observed in 11, but the engineered cells were undetectable after 28 days [8]. Tanyi et al. (NCT02159716) gave CART-meso to six patients with recurrent serous ovarian cancer in their Phase I study. At one month, all were stable and malignant cells were no longer seen in one patient's pleural effusion while CRS was not a problem [9]. Of the three cases of ovarian cancer described later on by Chen et al. two had stable disease; the corresponding PFS durations were 5.8 and 4.6 months [10]. Xia et al. tested for αPD-1-mesoCAR-T that secretes PD-1 blocking nanobodies. All seven patients with advanced gynecologic cancers achieved disease control with no grade 3 or greater adverse events reported. PFS durations in the two patients whose lesions decreased were 5.3 and 4.1 months [6]. The logic-gated product A2B694 was added to the preliminary 2025 EVEREST-2 data. Five patients were treated including three ovarian cancer patients without dose limiting toxicities, CRS or neurotoxicity [11]. In general, these studies have consistently demonstrated disease stabilization and promising safety but not persistent tumor regression.

3.2. Folate receptor α (FRα)

FRα is a GPI (glycosylphosphatidylinositol)-anchored glycoprotein, and the FOLR1 gene encodes FRα. Around 80% of the epithelial ovarian cancers express FRα, while expression in normal tissues is very low [12]. One of the first ovarian cancer CAR-T trials was published in 2006 by Kershaw et al. Fourteen patients were given gene modified T cells, with no objective tumor shrinkage. Cell persistence was observed only for days to weeks and serum factors that suppressed T-cell function were observed in some patients [13]. Nevertheless, FRα is still to be studied. Newer constructs directed towards FRα are being tested with improved co-stimulatory domains in ongoing studies.

3.3. MUC16 / CA125

CA125, otherwise called mucin 16 (MUC16), is the serum marker that is most commonly used for monitoring ovarian cancer. It is a heavily glycosylated mucin which is expressed on most ovarian cancer cells. CAR-T cells target the extracellular portion, which is retained and known as MUC16ecto. Chekmashova et al. reported on some promising preclinical results in 2010. CD19-directed CAR-T cells were able to eradicate well-established ovarian tumors in the peritoneal cavity of SCID-beige mice and therefore could be used for clinical translation [14]. In 2015, Koneru et al.

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designed a Phase I trial that involved cells which targeted MUC16ecto, secreted IL-12 and contained a safety elimination gene. The eligible participant has recurrent ovarian cancer that is platinum resistant [15].

3.4. B7-H3 and other new targets

B7-H3 (CD276) is highly expressed in various solid tumors, including ovarian cancer, and high expression is associated with recurrence. The first clinical testing of B7-H3-targeted CAR-T products is currently being carried out [3]. CAR-T therapy targeting the HER2 has also been evaluated in gynecologic cancers [16]. But efficacy data for both targets are too early to evaluate for the therapeutic use of ovarian cancer.

4. Clinically and safety

4.1. A trial landscape and developmental timeline are provided to assist with the planning process

The length of the research activity could overestimate the maturity of the field. The CAR-T research in ovarian cancer now spans over about 20 years. The early FRα trial was published by Kershaw et al. in 2006, the mesothelin-directed programs appeared in the next decade and the Phase I efficacy indings were published in 2019 and 2020 [7-9,13]. By 2015, there had also been a process of development that was MUC16-directed [15]. Logic-gated agents are more recent and have progressed to clinical studies. One such example is A2B694, the initial EVEREST-2 results are expected in 2025 [11]. However, the majority of programs are still at Phase I or is in the early stages of Phase II. Thus, these trials give much more data on feasibility, dose, and toxicity than on definitive clinical benefits. Interestingly, no CAR-T product is approved for ovarian cancer, which is particularly relevant to the size of the cohorts of these studies [3].

4.2. Safety profile CAR-T trials in ovarian cancer

Generally, toxicity in the ovarian cancer trials has been less pronounced than for some CAR-T therapies for hematologic cancers. The most common adverse events include fever, fatigue, nausea and abdominal pain, and CRS, if present, has typically been mild. In ovarian cancer specific studies, no deaths have been reported due to treatment [3]. It is, however, important to remember that there are safety issues to be considered. Because of the presence of mesothelin and FRα in normal tissues, on-target, off-tumor toxicity is possible. Immunogenicity is also an issue, especially for CARs with mouse antibody sequences. Maus et al. provide a clear example of this in an anaphylactic reaction [7]. Humanized binding domains and logic gated designs are partly being developed to counter these problems in addition to enhancing potency.

4.3. Combination & next generation strategies

Modification of the CAR construct alone might not be enough to combat the tumor microenvironment. Ovarian tumors can inhibit the T-cell functionality after infiltrating, so investigators are now testing CAR-T in combination with other therapies and are adding other functions to the engineered cells. Commonly evaluated partner drugs are checkpoint inhibitors and chemotherapy. Xia et al. aimed to achieve local immunomodulation by employing αPD-1-mesoCAR-T cells to secrete PD-1-blocking nanobodies at the tumor site [6]. EVEREST-2 is based

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on another limitation. The A2B694 Tmod platform is a dual receptor platform which comprises a receptor that activates mesothelin and a second receptor that inhibits activation in the presence of HLA-A*02. Some tumor cells may lose HLA expression, so this system is designed to identify antigen-positive normal cells as opposed to the antigen-negative malignant tissue [11]. So, the two methods attack different tumor failure mechanisms: shutting down of an immunosuppressive tumour and injury to the normal tissue. This distinction is applicable if there is a second trial.

5. Fertility considerations

Fertility is not a focus of most of the CAR-T trials but is clinically relevant to premenopausal patients. Some platinum-containing chemotherapy can damage the ovary and lead to early ovarian failure or infertility. CAR-T cells do not require the use of alkylating agents and therefore may have less direct gonadal toxicity; however, lymphodepleting chemotherapy is typically used prior to CAR-T cell infusion and may lead to decreased ovarian reserve. This should therefore be considered with younger patients prior to treatment as a means to preserve fertility. Cryopreservation is possible for any of the following: oocytes, embryos, and ovarian tissue [17]. Fertility has less relevance for postmenopausal patients, nonetheless, for younger patients, it's important to integrate fertility into the oncologic plan prior to therapy.

6. Obstacles and prospects for the future

The limited effectiveness seen so far can be attributed to multiple factors. Limitations are found at many points, starting with the quality of the evidence to the ability of the CAR-T cells to reach, recognise and be effective against the tumour.

The first main limitation is the small amount of evidence available from clinical studies. Most of the published studies included only three to 15 patients and many of these patients had undergone several lines of therapy. In cohorts of this size, an apparent response might be impressive but not reproducible and the absence of response might be due to the stage of the disease or to prior therapy rather than to the CAR-T product. More extensive studies need to be conducted, and studies earlier in the disease course might help untangle these influences.

The tumour microenvironment presents an extra barrier once the cells have arrived at the tumour. Immunosuppressive cells and cytokines in this environment such as regulatory T cells, tumor-associated macrophages and immunosuppressive cytokines may contribute to CAR-T exhaustion [18]. Strategies being considered include the use of armored CAR-T cells that secrete cytokines such as IL-7 or IL-12, local checkpoint blockade, and systemic checkpoint blockade in combination with other therapies. Despite the differences in design, the underlying principle of each of these strategies is to maintain the activity of engineered T cells once they come into contact with an immunosuppressive tumor milieu in vivo.

Antigen recognition can also decay with time since tumors do not necessarily need to be antigenically stable. A clone that decreases or loses expression of a CAR target will be less easily recognized and will lead to recurrence. Dual-target and multi-target constructs are designed to minimize the chance of immune escape.

The access to the tumor is a challenge different from target recognition. Solid tumors with extensive stromal and extracellular matrix may hinder the infiltration of CAR-T cells into the tumor core [1]. Ovarian cancer may be practically a better example in this regard as most of the disease is intraperitoneal. Intraperitoneal administration might enhance CAR-T-cell delivery to a tumor close by the tumor deposit, but efficacy has not been proven.

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Potency is important only if specificity is maintained. Logic-gated platforms aim to activate against tumour cells, but not against normal tissue, such as Tmod. This idea is tackling a known issue of CAR-T therapy in solid tumors, and at this time, there is not enough evidence to know if this increased specificity will yield a lasting clinical impact.

7. Conclusion

The evidence regarding CAR-T for ovarian cancer is encouraging but is also quite limited. Though the most extensive clinical experience is with Mesothelin, small Phase I studies have uniformly had higher rates of disease stabilization than significant or sustained disease regression. None of the groups have seen a complete response rate, and there is ongoing concern about limited cell persistence. Previously, FRα results were not as promising, as none of 14 patients in the 2006 Kershaw study had an objective tumor reduction. Unlike B7-H3 and HER2, which are at earlier stages of development, MUC16/CA125 has stronger preclinical evidence and has reached the Phase I evaluation. So the evidence only allows for a cautious conclusion. Clinical feasibility has been proven and toxicity has been generally controlled in ovarian cancer trials, with mostly mild CRS and no treatment-related deaths. However, efficacy is still much less clear, and studies are done in small patient cohorts, with unresolved issues including the immunosuppressive microenvironment, antigen escape, inadequate penetration of solid tumor tissues and off-tumor effects. Multi-target constructs, logic-gated receptors, armored cells, and combination therapy each target a part of these limitations. Fertility counseling also continues to be important for younger patients with the progression of clinical development. The role of CAR-T in ovarian cancer treatment is not yet defined but is a possibility for the future.

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