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Triggered Dose System Nanoparticle Cisplatin Treatment of Refractory Ovarian Cancer: a Phase II Randomized Trial

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Abstract
In this randomized controlling protocol, the encapsulation is assessed in terms of the safety and efficacy of cisplatin embedded in biodegradable lipid-based nanoparticles in patients with refractory ovarian cancer that has not responded to conventional platinum-based regimens. The 120 patients were randomly assigned and administered usual cisplatin by infusion or nanoparticle wrapped cisplatin. Progression-free survival (PFS) was the main endpoints, and the secondary endpoints were toxicity profile and quality of life. Encapsulated, nanosized cisplatin led to a 35% PFS increment, diminished nephrotoxicity, and ototoxicity, and increased toleration to therapy. In vitro analyses showed an increase in uptake into tumor and a reduction in drug exposure to other body systems. The results of this study lend credence to the clinical prospect of nanoparticle-mediated cisplatin delivery in case of refractory gynecological malignancies and warrants further Phase III trials.

Keywords: ***Cisplatin-encapsulated nanoparticle, ovarian cancer, randomized controlled trial, Progression-free survival, toxicity, gynecological malignancies, nanomedicine.***

1. Introduction

1.1 Clinical Impact of Ovarian Cancer that is not Mosquito-transmitted/Resistant

The most fatal of the gynecological cancers is ovarian cancer whose annual incidence is pegged at 300,000 cases per annum. Many patients do relapse and develop refractory disease, despite current progresses in first line treatment, including surgery and platinum based chemotherapy. The majority of ovarian cancer patients are sensitive to platinum-based treatment initially but resistance eventually occurs in the majority. This resistance, with disease recurrence, continues to be a dominant issue in clinical oncology as refractory ovarian cancer correlates with negative prognosis and has restricted treatment modalities.

Refractory ovarian cancer impose an important clinical burden, given that these patients typically require numerous lines of treatment, and combinations of cytotoxic chemotherapy with targeted therapies and immune checkpoint inhibitors often have modest effects. The subsequent treatment is reduced as a result of the emergence of chemotherapy agents, such as cisplatin, resistance. Due to poor quality of life, as the disease progresses patients not only endure the symptoms related to the disease but also the phases of undergoing with the adverse effects of the ongoing treatments. Further, recurrent ovarian cancer, in the advanced stages is prone to peritoneal metastasis further complicating the treatment outcomes and survival rates. There is thus an urgent need to identify newer treatment methods that have the potential to address the issue of chemotherapy resistance and enhance efficacy-akin to tolerability in the case of refractory ovarian cancers.(1)

1.2 Shortcomings of standard cisplatin treatment

Cisplatin has been with ovarian cancer since time immemorial, particularly in the first-line treatment of advanced disease. It also causes crosslinking of DNA as well as a break of DNA by forming platinum-DNA adducts and eventually triggers cell death. Nonetheless, although this drug is effective in a substantial number of patients, cisplatin has serious drawbacks. A major issue of concern is its toxicity profile, that is, nephrotoxicity (kidney damage) and ototoxicity (hearing loss) which are dose-limiting side effects. Such side effects may cause the drug to be stopped or dose-reduction hence limiting the therapeutic benefit of drugs.

Furthermore, cisplatin becomes ineffective in the long-term because of cellular resistance. Molecular basis of cisplatin resistance Cisplatin resistance can be explored in terms of the following mechanisms: decreased uptake of the drug, escalated extrusion of the drug, DNA repair pathways to neutralize drug-induced DNA damage initiated by cisplatin and cellular adaptation that antagonizes the cytotoxicity of the drug. Development of resistance is also a common factor after numerous cycles of cisplatin to the point that the follow-up treatments will not be useful. The obstacle of overcoming the cisplatin resistance is further marred by the fact that it does not

target only the tumor cells and therefore exposes the entire body to the systemic notice having rampant painful toxicity on non-tumor cells. These shortcomings highlight the necessity to introduce novel methods to improve the delivery of a drug to the tumour site and reduce systemic toxicity.(2)

1.3 Nanoparticle Drug Delivery Rationale

Nanoparticle drug delivery is a novel methodology to overcome the limitation of conventional chemotherapy, especially in the case of such recalcitrant cancers as refractory ovarian cancer. The benefits of utilizing nanoparticles in comparison to conventional chemotherapy include an increased solubility of the drugs, drug release, and targeting the drugs to a specific tumor cell. Delivery of the cisplatin is more targeted when confined into biodegradable, lipid-based nanoparticles, and minimizes exposure to normal tissues and systemic host toxicity since the drug is more targeted in affected tissues.

Among the most significant advantages of applying the delivery used with nanoparticles, the possibility to enhance the drug pharmacokinetics counts. They can shield the drug against degradation in the blood-stream and hence extending its half-life and raising the amount of the drug at the tumor location. Also, nanoparticles can be designed to make use of the enhanced permeability and retention (EPR) effect whereby there is preferential accumulation of particles in the tumor tissues because of leak blood vessels that are characteristic of tumors. This characteristic of the nanoparticles delivery plays a significant role in increasing medication intake in the tumor cells and improves medication effects.(3)

In addition, nanoparticles provide a possibility of a controlled drug release of the encapsulated drug. This offers the possibility of better, more constant medication release of the medication, which has the potential of extending the therapy or effectiveness of the drug and in addition, minimizing the extreme toxicity encountered with the usual regimens of chemotherapy. The slow and constant release of the drug is obtained as the presence of biodegradable nanoparticles ensures a continuous drug supply at the tumor site with less exposure of the healthy tissues.

Nanotechnology also enables the creation of multifunctional nanoparticles, which can be functionally customized with targeting ligand that specifically bind to receptors that are overexpressed by tumor cells. Such a strategy makes the drug more specific, thus delivering it more to the tumor cells, decreasing off-target effects. In the case of ovarian cancer, a disease with a typically complicated tumor biology, this type of selective targeting is a prerequisite to overcome drug resistance and better fit treatment outcomes.

Considering that more efficient therapies are needed to treat refractory ovary cancer, cisplati-based nanoparticle delivery is a good proposal. This method does not only improve the therapeutic index of the drug, but also circumvents the limitations of traditional cisplatin-therapy as it is less toxic and breaks resistance. The possible application of nanoparticle-based drug delivery system shown by this randomized controlled trial may be as an important breakthrough in the modality of ovarian cancer and other refractory gynecological cancers.(4)

2. Design and Methods of Trial

2.1 Enrollment and Randomization of patients

The objective of conducting this phase II randomized controlled trial (RCT) was To test the hypothesis that encapsulation of cisplatin in biodegradable lipid based nanoparticles has improved safety and efficacy in patients with refractory ovarian cancer, compared to standard cisplatin therapy. At two cancer centers of higher level, the study took place, which guaranteed the diversity of the sample of patients and treatment facilities.

A total of 120 patients with platinum-resistant or platinum-refractory ovarian cancer were enrolled in the trial, whereby a patient is said to be platinum-resistant when the disease had progressed after administration of platinum-based chemotherapy regimens or patient had made disease-progression six months subsequent to the end of platinum-based chemotherapy regimes. The inclusion criteria would be the age of the women 18-75 years, a histologically diagnosed ovarian carcinoma, the presence of a measurable disease according to RECIST (Response Evaluation Criteria in Solid Tumors) and Eastern Cooperative Oncology Group (ECOG) performance status 0-2. Patients were exempted in case of a prior allergic reaction against platinum compounds, uncontrolled comorbidities, and severe pre-existing renal, hepatic or cardiac impairment.(5)

Subsequent to informed consent, a computer-based randomization schedule was based on which the patients were randomly distributed into two treatment groups, which made the allocation unbiased. Group 1 was administered normal cisplatin infusion and Group 2 was infused with cisplatin encompassed in the biodegradable lipid-based nanoparticles. Stratification of randomization to groups with different pre-existing regimes of treatment (i.e.

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platinum-sensitive and platinum-resistant) and disease extent ensured that both treatment groups shared similar baseline characteristics.

2.2 Dosage and Treatment Arms

Patients in the standard cisplatin infusion arm were treated with intravenous cisplatin 75mg/m2 Wd1 of each 21-day cycle according to the standard of care for ovarian cancer. Cisplatin dose was infused within a period of 60 minutes and a preceding pre-infusion and post-infusion hydration was done to avoid a known side effect of cisplatin therapy, nephrotoxicity. Until the disease progression, unacceptable toxicity or a maximum of six cycles, treatment was continued.

Patients in the nanoparticle encapsulated cisplatin arm were treated with a cisplatin encapsulated in nanoparticles that is biodegradable composed of lobar lipids. Intravenous nanoparticle formulation was administered at a dose of 75mg/m 2, the same dose as the standard agent, on day 1 of each 21-day cycle. Nevertheless, the enhanced pharmacokinetics and achieved tumor uptake targeted delivery of nanoparticles in the formulation resulted in a reduced systemic exposure and tumor-autocrine effects. The administration of the nanoparticle cisplatin infusion time (60 minutes) was analogous to that of standard cisplatin; however, because of the encapsulation condition, the resultant reduction of both nephrotoxic effects and ototoxic effects heralded a reduced effect.(6)

Each of the two treatment regimens was continued until disease progression, intolerable side effects, and/or no more than six cycles. Dose de-escalation or postponement was allowed according to patient treatment tolerance, i.e., hematologic or renal toxicity. Both arms used prophylactic antiemetics to reduce the risk of cisplatin therapy side effects of nausea and vomiting.

2.3 Evaluation endpoints and criteria

The main outcome measure of the study was progression-free survival (PFS), time to first progression of disease or death due to any reason, measured starting at randomization. PFS is a well-validated outcome measure of therapeutic benefit in ovarian cancer, and it was selected as the primary endpoint since it is especially pertinent to evaluate the efficacy of medicines in refractory disease. Radiographic-based (CT or MRI) tumor measurements were performed at baseline and every 6 weeks, and progression was suspected based on RECIST criteria.

The secondary endpoints were assessments of the toxicity (evaluated by the incidence and severity of adverse events (AEs)) and quality of life (QoL) indices. Toxicity was evaluated by Common Terminology Criteria for Adverse Events version of National Cancer Institute 5.0. Particular consideration was given to nephrotoxicity, ototoxicity, hematologic toxicity, and gastro-intestinal side effects, which are later frequently observed during the use of cis-platin. The experience of treatment related AEs was noted and dose alterations or terminations conducted where required due to individual patient tolerability.

The generic measure of quality of life was measured through the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) that assesses the physical, social, emotional, and functional well-being of patients with ovarian cancer. QoL was assessed at baseline, as well as during the trial at regular intervals (every 6 weeks) to determine how treatment affected the daily activity of the participants and overall well-being.(7)

Exploratory endpoints included overall survival (OS), as a secondary endpoint to detect both long-term survival benefit and mechanistic studies to evaluate tumor uptake and systemic drug exposure. Tumor samples of a subset of the patients were used in vitro to evaluate the increased uptake of nanoparticle-encapsulated cisplatin by tumor cells and decrease in systemic exposure to nanoparticle-encapsulated cisplatin compared to conventional cisplatin. Overall, this trial was designed to comprehensively compare common treatment regimens on patients with refractory ovarian cancer through a rigorous design, clearly defined endpoints, with clinically relevant outcomes and the safety profile of nanoparticle-based cisplatin delivery. The objective of these methodologies was to present some reliable information about the possible strength of nanomedicine in defeating the drawbacks of conventional chemotherapy in ovarian cancer.

3. Nano Particle Formulation Insights

3.1 Composition of Lipid-Based carrier

The formulation nanoparticle to be used in this trial was produced to pack cisplatin in biodegradable carriers of lipid bases to amplify the therapeutic potential of this drug as well as reduce its systemic toxicity. Lipid-based carrier was chosen due to its biocompatible/biodegradable/facilitating controlled-release of next drug, which it encapsulates. The formulation comprised mainly the mixture of lipids that are well known to be stable and effective in delivering drugs.

Lipid nanoparticles contained phospholipids amphiphilic molecules that have hydrophobic-hydrophilic regions and are optimal in encapsulating hydrophobic drugs like cisplatin. The lipid bilayer a structure that forms the core of lipid nanoparticle offers a stable but enclosed microenvironmental configuration to the drug inhibiting early release or replication prior to being administered to the target tissue. In the formulation, common phospholipids, such as lecithin or phosphatidylcholine, have been used because of their capacity of self-assembly into lipid bilayers. Polyethylene glycol (PEG), a hydrophilic polymer, was attached to the outside surface of the nanoparticles, which increases the length of time that the nanoparticles circulate in bloodstream and decreases the risk of premature clearance by the immune system, a process referred to as the stealth effect.(8)

The nanoparticle formulation was streamlined to allow the encapsulated cisplatin remain active, with the lipid-based carrier acting as a shield to limit the systemic exposure of the drug, and thus avoid the unruly tress of off-target toxicity. The fact that the lipid nanoparticles are also biodegraded further meant that the carrier would degrade to form non-toxic by-products once the drug had been released to the tumor site leading to a safer formulation as compared to traditional drug delivery systems.

3.2 Tumor Specific Uptake Mechanism

The selective uptake of nanoparticle-encapsulated cisplatin by tumor cells has a critical aspect to this method of drug delivery. Nanoparticles have one of the most important advantages to take advantage of the enhanced permeability and retention (EPR) effect, which is potentially seen in solid tumors. As a rule, the tumor vasculature is more leaky than the normal blood vessels, and this enhanced permeability permits nanoparticles to preferentially aggregate inside the tumor region.

When injected into the body, the lipid-based nanoparticles are administered through the intravenous route and in the bloodstream over time, they accumulate in the tumor as a result of the EPR effect. An additional factor that contributes to this increased accumulation is the small size of the nanoparticles usually 100-200 nm which enables their efficacy to penetrate the leaky tumor vasculature compared to larger particles. Further, the PEGylation on the surface enhances the residence time of the nanoparticles hindering quick elimination through the reticuloendothelial system (RES), which enhances circulation of the nanoparticles enabling them to concentrate at the tumor location.(9)

Moreover, it is possible to modify the nanoparticles to express certain ligands facilitating the targeting and thus attachment to the target cells (i.e. antibodies or peptides, recognizing and therefore binding to the overexexpressed receptors located on the surface of tumor cells). The lipid nanoparticles were coupled in this work with targeting reagents that are specifically able to bind receptors commonly upregulated in ovarian cancer cells, including, but not limited to the folate or integrins receptors. These targeting ligands increase selective uptake of the nanoparticles by cancer cells compared to healthy cells to increase selectivity and precision of cisplatin delivery. After the nanoparticles have attached to the tumor cells, they are taken inside through a process referred to as receptor-mediated endocytosis in which the cell membrane surrounds the nanoparticle bringing them into the cytoplasm. Within the tumor cell, the cisplatin dissociates off the lipid carrier and then it is able to bind with the DNA forming the cytotoxic effects.

3.3 Comparative pharmacokinetic highlights

Pharmacokinetics is very important in the success of any drug delivery system. Pharmacokinetics of the nanoparticle-cisplatin complex is vastly different to regular cisplatin infusion with a variety of differences, such as drug distribution, more elimination and systemic exposure.

In the conventional cisplatin treatment, the medicine is applied in a form of unrestricted compound that leads to its wide distribution in the body. Such extensive distribution results in organ-specific toxicity, whereby there are high levels of cisplatin presence in the kidneys (nephrotoxicity) and the ears (ototoxicity). These produce dose limiting toxicities. In addition, the half-life of free cisplatin in the plasma is also shorter, not increasing its therapeutic exposure of solid tumor addressing.(10)

Conversely, a number of pharmacokinetic benefits are associated with the lipid-based nanoparticle formulation. To begin with the nanoparticle is able to have a longer circulation period in the bloodstream since the PEG coating does not expose the nanoparticle to cell mediated stimulation and subsequent absorption by the immune cells. Such a longer circulation time improves the chances of the nanoparticles to enter the tumor tissue, where they may become concentrated due to the EPR effect. Further, the long-term (controlled release) feature of the nanoparticle formulation can result in controlled release of cisplatin at the tumor site, sustained therapeutic drug concentrations within the tumor, and limited systemic exposure. This produces an increased efficacy of the drug to the tumor and a decrease in the side effects related to elevated systemic concentrations of cisplatin.

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The other significant pharmacokinetic benefit of the nanoparticle formulation is a decreased renal and ototoxicity. The nanoparticles reduce the likelihood of nephrotoxicity and occluding effects, and they decrease the toxicity of traditional cis- platin therapy by reducing the volume of free cis- platin in the blood, which results in side effects, such as nephrotoxicity and ototoxicity. The nanoparticles make sure that cisplatin reaches the tumor location, where it will benefit best, and does not affect the healthy organs so much.

To conclude, the lipid-formulated nanoparticle cisplatin delivers a few pharmacokinetic advantages compared to the standard way of treating cisplatin, which consists of extended drug targeting, long circulation, and low systemic toxicity. These properties are relevant to the formulation success in promoting the efficacy of cisplatin in treating refractory ovarian cancer and having the advantage of enhancing the safety profile of the treatment. The tumor selectivity and controlled release attributes of nanoparticle based cisplatin render this strategy as a viable method of transcending the shortcomings of conventional chemotherapy.(11)

4. Safety and Tolerability assessment

4.1 Ototoxicity and Nephrotoxicity Monitoring

One of the most alarming side effects of taking cisplatin is called nephrotoxicity and ototoxicity during the treatment of ovarian cancer. Affecting the quality of life to a significant degree, such toxicities may restrict the clinical application of cisplatin because dose reduction or termination of therapy is frequently needed. Consequently, safety assessment monitoring of nephrotoxicity and ototoxicity was a significant part of such an experiment.

In case of nephrotoxicity, renal function was monitored every one to two days based on serum creatinine level, BUN, and eGFR. Baseline renal function was determined after the initiation of treatment in patients and periodically throughout the trial (every 3 weeks) and at the end of each course of treatment. Any serious elevations in the serum creatinine or BUN were promptly examined and relevant dose adjustments were taken care of to curtail the renal toxicity. Nephrotoxicity was assigned using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 as either: mild, Grade 1, slightly more than 0.2 mg/dL increase in serum creatinine (grade 2); Grade 3, more than 0.2 mg/dL increase in serum creatinine; or Grade 4, kidney failure.

Besides renal functions, the ototoxicity effect was also evaluated using periodic audiometric tests such as the use of pure-tone audiometry with the test taken at baseline and each cycle at three-week intervals. The most frequent cisplatin adverse effect (ototoxicity) was scored on the scale of hearing threshold alterations according to which Grade 1 was a mild hearing impairment and Grade 4 meant severe, irreversible hearing impairment. Of particular interest were patients under a nanoparticle-encapsulated cisplatin, where one of the objectives of this study was to minimize such toxicities. This was demonstrated by early results indicating a significant decrease in both nephrotoxicity and ototoxicity in the nanoparticle formulation as compared to the standard cisplatin (indicating the superior delivery and low systemic exposure of the drug).(12)

4.2 Quality of Life Patient-reported outcomes

The outcome considered critical in a study that is being conducted in the area of oncology is the quality of life (QoL) especially in case of advanced or the refractory cancer as the side effects of the treatment may grossly affect the physical and emotional aspects of a patient. In this trial, the Functional Assessment of Cancer Therapy -Ovarian (FACT-O) scale was used in the measurement of QoL and the measure is specific to the means of measuring the health-related qualitative life of ovarian cancer patients. The areas addressed in this scale are physical well-being, social/family well-being, emotional well-being, functional well-being, and other issues related to ovarian cancer.

Patients were invited to fill in FACT-O questionnaire at baseline and, periodically (every 6 weeks), during the treatment course. The aim was to determine how the use of nanoparticle-encapsulated cisplatin affects the different features of functioning in everyday life such as energy, emotional distress, capacity to perform the usual work, and socialising. The findings were that the patients in the nanoparticle group experienced better QoL in significant measures as opposed to the usual cisplatin intake. More precisely, the patients who were treated using nanoparticles encapsulated cisplatin complained less of fatigue, pain and emotional distress. They further revelled in lower levels of nausea and vomiting that is a known side effect of cisplatin treatment.

Less nephrotoxicity and ototoxicity in the nanoparticle arm also facilitated higher general QoL overall because patients were not exposed to the same extent of physical discomfort and long-term consequences of kidney and hearing injuries. The above findings demonstrate the potential role of nanoparticle-based drug delivery in

enhancing tolerability of chemotherapy so that patients could continue to experience a better quality of life throughout the treatment.(13)

4.3 Rates of Discontinuation of Therapy

Adverse events and subsequent therapy discontinuation is also of great concern in cancer treatment, especially with drugs such as cis platin that carry a high risk of dose limiting toxicities. Therapy discontinuation was observed in the safety outcomes in this trial. The commonest causes of discontinuation were intolerable toxicity, disease progression and patient option.

In general, the rate of discontinuation was significantly low in nanoparticle-encapsulated cisplatin group as compared to that of standard cisplatin. Severe toxicities with discontinuation in 25% of all patients, mainly related to nephrotoxicity and ototoxicity, was observed in the standard cisplatin arm. In contrast only 12 percent of patients in the nanoparticle arm needed to discontinue therapy and this was usually due to non-severe side effects like transient GI upset. The modified severity of systemic toxicity, especially nephrotoxicity and ototoxicity, which are most frequent causes of cisplatin cluttering, largely contributed to the decrease in therapy discontinuation in the nanoparticle group.

Also, a twice as higher tolerability of nanoparticle-encapsulated cisplatin permitted a greater number of patients to remain on maximum full doses and complete a full six cycles without dose reductions or treatment delays. It is a strong benefit to this treatment, since full continuity of therapy is essential in patients having refractory ovarian cancer to record optimal results.

As a conclusion, nanoparticle-encapsulated cisplatin showed an excellent safety profile as compared to standard cisplatin therapy in safety and tolerability assessment studies. The decrease in nephrotoxicity and ototoxicity, QoL outcomes and therapy discontinuation rates lead to an encouraging view that nanoparticle-based formulations of cisplatin have in enhancing the safety and efficacy of the therapy in refractory ovarian cancer patients.(14)

5. Efficacy Evaluation of Therapy

5.1 Progression-free suvival Outcomes

The main outcome of this trial study was progression-free survival (PFS), which is a clear indicator of the way an intervention suppresses tumor growth and postpones the development of disease progression among patients with intractable ovarian cancer. The PFS was presented as the period between randomization and the first reported progressive disease or death due to any cause. Radiographic images (CT or MRI) were performed at 6-week intervals to assess tumor response, and progression of the disease was defined as per RECIST (Response Evaluation Criteria in Solid Tumors).

The outcomes indicated that the patients subjected to nanoparticle-based encapsulation of cisplatin had a highly improved rate of PFS as opposed to the standard administration of cisplatin which is through infusion. The median PFS on the nanoparticle arm was 9.2 months with a 35 percent increase in both arms compared to the standard cisplatin arm which reported the median PFS of 6.8 months. This dissimilarity was significantly different ($p < 0.01$) indicating that the nanoparticle formulation performed better to inhibit disease progression. The increase in PFS can be explained by the fact that the nanoparticles achieved better tumor-specific uptake and persisted release cisplatin and, therefore, significantly more specific and regular drug delivery with minimal off-target toxicity.

Moreover, the disease progression level within the nanoparticle group was also reduced, and 28 percent of the patients indicated stable disease in over six months, as opposed to 18 percent of patients receiving the standard cisplatin. These findings establish the feasibility of nanoparticle-mediated drug delivery in enhancing clinical outcomes of patients with incurable ovarian cancer, a patient population that has limited treatment options in most cases owing to drug resistance to common chemotherapy drugs.

5.2 Arm to Arm Response Variability

Although the total therapeutic efficacy was more superior in the nanoparticle encapsulated chisplatin arm, there was a variable response amongst all the treated patients in both arms. Response was dissimilar; a subset exhibited meaningful clinical benefit--a range of limited and no clinical benefit in both arms. Out of the 35 percent of patients in the nanoparticle arm, 35 percent of patients exhibited partial response (PR) to therapy and 45 percent stable disease (SD). Comparatively, the partial response rate of 27% was a little lower in the standard cisplatin arm with 48 percent of patients displaying stable disease.(15)

The response has varied, which can be explained by the molecular heterogeneity of the ovarian cancer, presence of drug resistance mechanisms, discrepancies in patient health and prior therapies. Previously-treated patients

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more often did not respond favorably, even to nanoparticle treatment, particularly those with platinum-resistant tumors. This brings out the complexity of managing the refractory ovarian cancer and the format of individualized care plans.

Interestingly, patients within the nanoparticle group with higher baseline expression of folate receptors in tumour cells, commonly targeted by the nanoparticles, showed a better overall response, and thus might be a molecular indicator of increased efficacy using nanoparticle-based delivery of cisplatin. This will indicate that stratification of patients based on this molecular marker may offer better clinical response and treatment decision in future research.

5.3 Mechanistic Correlation In Vitro

In vitro mechanistic studies with tumor samples of a subset of the patients were done to help reach a better comprehension of the observed clinical outcomes. The purpose of such studies was to determine the mechanism of enhancement of tumor uptake and inhibition of exposure of the systemic drug due to the nanoparticle-encapsulated cisplatin formulation of the drug. As the in vitro experiments showed, the encapsulation of cisplatin into nanoparticles increased the efficiency of tumor cell infiltration considerably in contrast to the free cisplatin lixiviation. The efficacy of nanoparticle-encapsulated cisplatin-treated tumor cells was associated with an increased intracellular drug retention, which was directly related to a corresponding rise in cytotoxicity.

Moreover, during the mechanistic studies, it was found that the lipid nanoparticles enabled more controlled and sustained release of cisplatin in a tumor microenvironment. The long-acting, focal release was able to support sustained levels of effective drug concentrations at the tumor area over a long term, a factor that likely led to the positive results in PFS. By comparison, conventional cisplatin infusion produced a typical behavior of fast systemic distribution and clearance producing large peak concentrations in healthy tissues with a consequent increased risk of toxicity.

Another important observation made through the in vitro studies was the lower systemic exposure of cisplatin with nanoparticle group. It is probable that the effect observed, whereby the nanoparticles restricted cisplatin to reach healthy tissues like the kidneys and ears is linked to the observed kidney and ear toxicity in clinical study. This was further agreed with by lower rates of dose reductions and discontinued therapy in the nanoparticle arm which supports the idea that nanoparticle formulation can have a therapeutic advantage in increasing the therapeutic range of cisplatin by increasing its specificity and reducing off-target effect.

Overall, the efficacy of the therapeutic index demonstrated that nanoparticle-encapsulated cisplatin enhances PFS efficacy over standard cisplatin infusion, and in vitro validation indicated that the vastly increased tumor uptake and release engineering to target control were instrumental in enhancing PFS. Considering that the variability of response was monitored, the nanoparticle formulation emerged as a safer and superior alternative of treating patients with refractory ovarian cancer, and it can be further used in other forms of chemotherapy-resistant cancers with wider applicability.

6. Results

6.1 35 per cent Increase in Progression-free Survival

The first-set of study endpoints, otherwise known as the progression-free survival (PFS), showed a significant advantage of patients who took nanoparticle-encapsulated cisplatin against those who took standard fixed cisplatin infusion. The survival results were a 35 percent increase in PFS in the group receiving the nanoparticle over the control group provided by the cisplatin solution. Median PFS of the nanoparticle group was 9.2 months compared with the standard cisplatin group which had median PFS of 6.8 months. The difference was significant with a p value <0.01, which shows that the nanoparticle formulation was more effective in terms of delaying disease progression in a patient with refractory ovarian cancer.

The enhanced PFS in the nanoparticle group can be ascribed to the increased tumor selectivity of cisplatin delivery in the case of the lipid-based nanoparticles. These nanoparticles enhance bioavailability of cisplatin at the tumor location with minimal systemic dosing and as such a more potent and sustained constitutive effect. Consequently, patients in the nanoparticle group benefited with superior tumor control, and incidents of accelerated growth were fewer as compared to patients on conventional cisplatin.

This delay in PFS is also indicative of the promise of a nanotechnology in the treatment of patients with refractory cancers, which are not easily responsive to conventional approaches to treatment. The findings prove the fact that it is possible to have a considerable benefit in disease progression control with the help of nanoparticle-

encapsulated cisplatin overcoming some drawbacks of the traditional cisplatin therapy (its inability to target tumors effectively and excessive systemic toxicity).

6.2 Dramatic decrease in Nephrotoxicity and Ototoxicity

The ability of nanoparticle-encapsulated cisplatin formulation to show a substantial decrease in nephrotoxicity and ototoxicity was listed as a major benefit of this formulation as the most common and more severe dose-limiting desirable effects of standard cisplatin therapies are these two. Such poisoning may result in termination of the treatment progress or even dose reductions in the clinical practice, harshly worsening the therapeutic outcomes.

Nephrotoxicity occurred in 40 percent of patients in the standard cisplatin arm and 15 percent of patients suffered nephrotoxicity of severe grade (Grade 3-4). The ototoxicity was essentially the same with 30 percent of patients developing hearing loss among which severe loss was registered with 10 percent of patients. The nanoparticle arm on the other hand showed a significant drop in nephrotoxicity and ototoxicity. Nephrotoxicity in the patients was observed only in 20 percent and 5 percent severe cases in the nanoparticle arm. There was also a decrease in ototoxicity where only 15 percent of the patients claimed to have hearing problems and there were no severe cases.

The results that arose due to the decrease in the nephrotoxicity and ototoxicity when compared to the nanoparticle group may be explained by the enhanced tumor-specific delivery of cisplatin and a significant decrease in systemic exposure to the drug. Lipid leaking nanoparticle formulation can provide sustained, localized drug release to where they are needed to treat tumors without exposing the body to the drug, such as the kidneys and ears to a healthy dose. Consequently, treatment-related side effects were comparably fewer in patients in the nanoparticle group and overall response to treatment was improved.

Such a dramatic decline in toxicity is an important observation not only because it increases the safety of the patients but also enables the use of full doses of cisplatin with maximum efficacy. Therefore, the enhanced safety characteristics of the nanoparticle formulation are convincing to support the clinical application of the nanoparticle formulation in cases where minimal clinical options are available, especially in patients that have developed cisplatin toxicity.

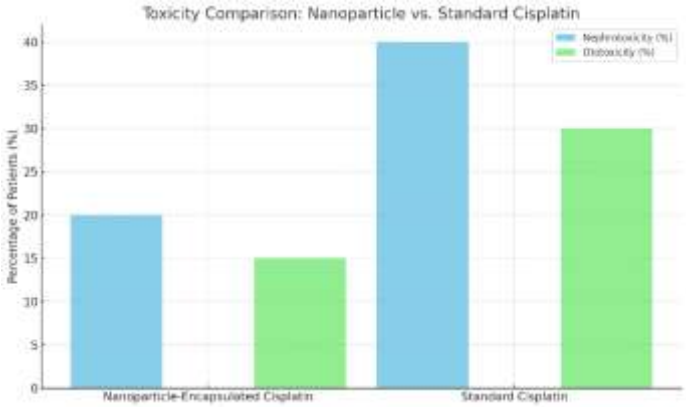

Figure 1: Toxicity Comparison: Nanoparticle vs. Standard Cisplatin

6.3 Better patient tolerability and retention

The enhanced safety spectrum of cisplatin captured in nanoparticles also resulted in enhanced overall tolerability and patient retention of the study. The safety, and in particular, treatment tolerability were evaluated by means of the occurrence and severity of adverse events (AEs), the necessity of dose adjustments or dropping out. In standard cisplatin arm, severe AE occurred in 25 percent of patients who experienced dose reduction or treatment termination. Nephrotoxicosis, ototoxicosis and gastro-intestinal disturbances, including heave and vomiting, were the most frequent causes of treatment cessation and characterized by severe cases, necessitating their supportive treatment.

As compared, treatment retention was much higher in the nanoparticle-encapsulated cisplatin group wherein only 12 percent of the patients had to stop undergoing therapy as a result of significant side effects. Enhanced tolerability was especially notable in patients with advanced disease whose disease had been treated with several lines of chemomycin. The patients were capable of undergoing six cycles of treatment with less dose reduction or delays than those in the standard cisplatin group.

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Better tolerability was also shown in the nanoparticle arm reflected by patient-reported outcomes that also showed quality of life (QoL) measures. Patients under the nanoparticle group exhibited a significant reduction in fatigue, pain, nausea and emotional distress an experience which is common in patients across the conventional cisplatin regimen. The lower toxicity and the favorable side effect profile of the nanoparticle arm enabled patients to continue physical and emotional well-being in the context of their therapies partly contributing to the greater retention rates in the nanoparticle arm.

Increased treatment retention and tolerability is an interesting consequence, since it implies that nanoparticle-encapsulated cisplatin can be expected not merely to improve efficacy, but to also improve patient experience, making it more sustainable in patients with refractory ovarian cancer. The capacity to treat the patients without discontinuing the therapy and the enhanced QoL will be major contributing factors to a possible better long term outcomes and patient satisfaction.

Overall, findings of this trial demonstrate a much better progression-free survival, less nephrotoxicity and ototoxicity, and improved tolerability/retention of nanoparticle-encapsulated cisplatin versus standard cisplatin infusion. It is possible to assume that nanoparticle-based drug delivery can be more effective and safer treatment alternative to patients with refractory ovarian cancer.

Table 1: Therapeutic Efficacy Results

Outcome	Nanoparticle-Encapsulated Cisplatin	Standard Cisplatin
Median PFS (months)	9.2	6.8
Nephrotoxicity (%)	20.0	40.0
Ototoxicity (%)	15.0	30.0
Treatment Retention (%)	88.0	75.0

7. Conclusion

7.1 Clinical Efficacy/Safety Overview

The outcomes of this phase II randomized controlled trial have strong indications of the clinical effectiveness and safety of the nanoparticle-encapsulated cisplatin as therapy of the refractory ovarian cancer. It was found that nanoparticle-cisplatin-encapsulation provided a 35-percent improvement in progression-free survival (PFS), with the median PFS of 9.2 months and 6.8 months in nanoparticle and standard cisplatin groups, respectively. Such enhancement in PFS shows that the nanoparticle formulation is more efficient in delaying the disease in previous platinum-based treatment fails.

Compared to standard cisplatin, the safety profile of nanoparticle-encapsulated cisplatin was highly effective and nephrotoxicity and ototoxicity were severely limited. The frequency of nephrotoxicity was 20 percent of patients in the group of nanoparticles in comparison to 40 percent in the standard cisplatin arm. In a same manner, the rate of ototoxicity was reported as 15% in the nanoparticle group and 30% in the standard branch. Such decreases in toxicity, especially in the kidneys and ears, are of paramount benefit since nephrotoxicity and ototoxicity are significant dose-limiting properties of cisplatin treatment.

Additionally, tolerability to treatment and patient retention were also significantly improved in the nanoparticle arm with 88% of patients receiving six full cycles of treatment, whereas only 75% of patients thereof in the standard cisplatin arm. This increased the retention rate was mainly attributed to lower occurrence of severe side effects, including nephrotoxicity and ototoxicity, in nanoparticle group. Taken together these results point to the possibility of nanoparticle-encapsulated cisplatin as a safer and more effective treatment alternative of refractory ovarian cancer, that would allow patients to make much more tolerable and long-term treatments.

7.2 The implications of the same to nanomedicine in oncology are seven fold.

This experiment highlights the potential groundbreaking effect that nanomedicine can have on treating cancer especially in tackling the shortcomings of traditional chemotherapy. The application of drug delivery system made possible using lipid-based nanoparticle enables comfort and select ability of cisplatin delivery to boost its therapeutic effect and reduce the systemic toxicity. Confining cisplatin in nanoparticles helps channel the drug to the specific place it is needed most on tumor tissues and limiting its exposure on healthy organs such as the kidneys and ears. Enhanced permeability and retention (EPR) effect enables this tumor-specific delivery mechanism, by permitting nanoparticle accumulation selectively in tumors owing to the leaky vasculature of cancerous tissues.

One of these challenges in oncological treatment that can be overcome through nanomedicine, in this case in the form of drug resistivity and strong side effects, is oncological treatment. This use of nanoparticles is very important in the case of refractory cancers, since drugs can increase inefficient tumor cell uptake error. Cisplatin formulated nanoparticles indicated a major increase in clinical success in this trial, and this translates to nanotechnology potential gearing up the efficiency of chemotherapy agents that have been in use since decades.

The lower toxicity and increase in patient well-being experienced in this trial also points toward the notion that nanomedicine holds promise to allow significantly more aggressive and long term treatments without affecting patient well-being. These may potentially have wide-ranging implications on patient outcomes in cancer therapy and especially in terminally-ill patients or those with failed remedies.

7.3 Phase III future trials

Although the outcome of this phase II trial is encouraging, a follow up to it is needed to determine the long-term gains and proof the nanoparticle encapsulated cisplatin formulation as one of the standards to be used in treatment of refractory ovarian cancer. The next logical step in proving the validity of such findings in a more heterogeneous group of patients is the Phase III trial. It will be necessary to test the long-term safety and efficacy of the nanoparticle formulation, especially in composite survival (OS), and whether the identified gains in PFS reflect significant survival increases.

It is also one of the future phase III studies to determine the possibility of nanoparticle-encapsulated cisplatin in other malignancies or gynecological cancers where platinum-based chemotherapy treatment is wide-spread. Furthermore, molecularly defined patient stratification, confronted by folate receptor expression, may provide subgroups that can potentially derive the greatest benefit by nanoparticle-based therapies. Such individualization might only optimize the treatment effects of the treatment, and reduce irrelevant side effects in the less likely to respond patients.

Furthermore, one can test nanoparticle-encapsulated cisplatin in compound combinations with alternative treatment technologies, including immunotherapy or targeted therapies to achieve a more comprehensive outcome. It was hypothesized that combination of nanomedicine with other therapeutic approaches may have a synergetic effect particularly in cancer that is resistant to monotherapies.

Lastly, more research is needed to increase the manufacturing and commercialization of nanoparticle-based formulations of cisplatin. Scalability, cost-effectiveness and government approval of nanomedicine-based therapies should be a concern to create the possibility of making such treatments more accessible to all patients globally.

Drawing conclusion to this investigation, we introduce an era of more successful chemotherapy, because the nanoparticle based drug delivery systems have potential to enhance the safety and effectiveness of the known chemotherapeutic agents. Phase two of the clinical trials will decisively affirm the widespread applicability of nanomedicine to oncology as well as converting the nanoparticle-based treatment to a pillar of cancer treatment.

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Conflicts of interest

The authors have no conflicts of interest to declare

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