AN EXPLORATORY STUDY INTO THE WORLD OF ANTIBODY DRUG CONJUGATES

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

By

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Under the Supervision and Guidance of

Mr. Rahul Sharma

2024

CERTIFICATE OF INTERNSHIP

This internship program certificate is proudly awarded to

Kriti Shrivastava

For her outstanding completion of the compulsory internship program at Octavus Consulting as an Intern Analyst from 18th March to 18th June 2024.

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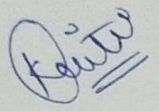
DECLARATION BY STUDENT

I hereby declare that this dissertation **AN EXPLORATORY DIVE INTO THE WORLD OF ANTIBODY DRUG CONJUGATES** is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text .



Name of Student: Kriti Shrivastava

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CERTIFICATE

This is to certify that dissertation titled **"An exploratory dive into the world of Antibody-Drug conjugates"** is a record of the research work undertaken by **Ms. Kriti Shrivastava** in partial fulfillment of the requirements for the award of the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur under my guidance and supervision and her approach to the research study has been sincere, scientific, and analytical.

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Abstract:

Title: An Exploratory Study into the World of Antibody Drug Conjugates

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Keywords: Antibody Drug Conjugates, Targeted therapies, cancer treatment, immunology, clinical trials, cytotoxic payload'

Background:

Antibody-drug conjugates (ADCs) are an exciting class of targeted therapeutics that have changed cancer therapy and show promise for applications in immunology, haematology and infectious diseases. ADCs are composed of an antibody linked to a cytotoxic molecule designed to selectively deliver the latter payload into target cells while reducing systemic toxicity. This paper aims to give a comprehensive review of ADCs, including their components, the mechanisms that they act through and finally evidence from drugs in development and approval. We surveyed recent studies and clinical trial data from databases including the National Institutes of Health, PubMed, Scopus, ClinicalTrials. the Web of Science and Google Scholar, respectively. Submission of the heavy and light chain sequences allows us to search for many components common to ADCs, particularly because the antibody portion is often an IgG1 subclass due high specificity and robust binding affinity.

Crucial elements of ADCs, such as the IgG1 subclass for its specificity and strong-binding affinity contributing to the antibody component or any cytotoxic payload were our targets. We asked what makes ADCs so an excellent means of targeting the cancer lung, created a complete database of well-known ADC molecules in various stages love pre-clinical, DOG and examined into likelihood for drug indication beyond just melanoma. It also presents the expanding landscape of ADCs in a wide range of therapeutic areas, including new research that demonstrates their growing legacy on contemporary clinical practice.

Objective:

1. To make a comprehensive summary of ADCs who are in clinical phase along with their Antibody, Linker, and payloads
2. To investigate approved ADC from 2020-2024 along with their targeted indications.
3. To assess the growth and increasing trend of ADCs across various therapy areas over time
4. To examine different Indication for which ADCs are approved

Results:

Our results strongly suggest that ADCs have bright therapeutic prospects, and the targeted therapy which involves higher precision of treatment will provide new tricks to improve efficiency. Specifically targeted technology could likely lead to superior patient outcomes with fewer side effects and is an attractive prospect for current and future medical therapies. This work highlights the significant therapeutic potential for ADCs across many diseases and predicts transformative improvements in patient outcomes.

Conclusion:

ADCs are a revolutionary class of targeted therapeutic agents in oncology and beyond. The current analysis has illustrated their sophisticated architecture incorporates both "naked antibodies and immunoconjugate: that include antibodies, linkers and cytotoxic payloads to provide differential target delivery of tumor cells, facilitating better treatment efficacy.

In summary, while ADCs hold massive promise in precision medicine, continued interdisciplinary cooperation and rigorous investigation will be paramount in fully realizing their therapeutic potential and defeating current limitations in clinical practice.

ACKNOWLEDGEMENT

I would like to use this opportunity to thank everyone that has been there for me throughout this project.

First of all, I am hugely obliged to my university mentor Mr. Rahul Sharma, Assistant Professor, at IIHMR University. He provided solid support and understanding, guidance and his beneficial feedback has been valuable. His wide knowledge and experience have completely improved my understanding of the subject matter while his help has kept me focused.

Furthermore, I extend my sincere appreciation to my industry mentor Mr. Himanshu Sehgal, CEO and Director Project Delivery at Octavus Consulting Pvt. Ltd., Noida; it is through his backing that intellectual knowledge gets translated into practical execution. His proficiency and willingness in sharing professional insights contributed significantly toward the success of the project.

Also, I admit the cooperation and help from colleagues and fellows during this project and how they supported me in developing my work.

I also want to share my thankfulness with my family members and friends who have always supported me without demanding out in their efforts to recognize what I was going through.

Lastly, I appreciate IIHMR University and the organization where I achieved my industry project for providing me with the vision and resources to undertake this project. The experience has been greatly rewarding and has provided me with valuable insights and skills that I will carry forward in my professional endeavors.

Thank you all for your support and encouragement.

Kriti Shrivastava

Date: 02/06/2024

Place: Jaipur

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CHAPTER 1

INTRODUCTION

1. **Introduction**:

The novel family of biopharmaceuticals known as "antibody-drug conjugates," or ADCs, are complex compounds made up of an antibody and a physiologically active cytotoxic payload or drug. Although the projected application of these medications is as targeted therapies for illness management, ADCs are currently significantly employed in the management or treatment of cancer. Many methods, including "chemotherapy," "immunotherapy," "radiation therapy," "stem cell therapy," "laser treatment," and "surgery," have been devoted in the past to treat cancer. Among these, "chemotherapy" is the best-known therapy area for cancer conduct. They have a very poor therapeutic index, despite the fact that they destroy healthy cells in addition to aiming cancerous ones. To resolve this issue, a novel idea known as antibody drug conjugates has been formed and presented [1].

1.1. History of ADC:

Chemotherapy's strength in struggling illness is merged with the accuracy of antibodies in a new type of medications known as antibody-drug conjugates, or ADCs. The idea of ADCs was first suggested by Paul Ehrlich in 1913. Ehrlich believed that antibodies acted like "magic bullets," able to find identifiable targets inside cells and destroy them without harming healthy tissue. Ehrlich further proposed that the therapeutic specificity of antibodies be improved by binding toxins to them [1].

Traditional" chemotherapeutic agents like "methotrexate", "vinblastine", and "doxorubicin" were used as cytotoxic" contents in the initial generation of ADC medicines. However, these early ADCs met barriers such as insufficient effectiveness "against cancer cells, lack of selectivity" for tumors tissues, and "low collection within target cells," resulting in grim clinical outcomes. Second-generation ADCs had fascinating tubulin inhibitors such as maytansine, which are "effective against actively dividing tumour cells". However, these ADCs "are less effective against static cancer cells", limiting their efficiency. Furthermore, despite its great antiproliferative effectiveness, maytansine produced severe "side effects such as neurotoxicity and gastrointestinal reactions," which prevented it from being allowed as a single cancer therapy. To stunned this issue, "third-generation ADCs utilise DNA detrimental agents (like enediyne, topoisomerase I

inhibitors, and pyrrolo benzodiazepines") as cytotoxic payloads.These drugs can target cells during the cell cycle and cause tumour cell death using mechanisms such "double strand breaking, alkylation, chimerism, and cross-linking of DNA structures.[2]"

The FDA approved Mylotarg (Gemtuzumab ozogamicin), established by Wyeth-Ayerst Research (now Pfizer) and Celltech Chiroscience, in 2000, ushering in the ADC era in cancer-targeted therapy. This innovative drug was designed to treat CD33+ acute myeloid leukaemia by delivering a effective chemotherapeutic chemical "directly to cancer cells, minimising damage to healthy cells. [2]

Despite the promising mechanism, Pfizer removed Mylotarg off the US market at the FDA's request in 2010, claiming safety concerns and a lack of established clinical benefits. The breakthrough occurred "in 2017 when the FDA reapproved Mylotarg for a different patient population, with a changed dosage regimen of three doses of 3 mg/m² instead of a single 9 mg/m² dose." This change considerably reduced the drug's maximum plasma levels, adjusting its safety profile and giving patients new hope.[1]

The accomplishment of ADCs expanded "to the treatment of solid tumours with the approval of Kadcyla" (ado-trastuzumab emtansine) by Genentech/Roche in 2013. Kadcyla was the first ADC approved for adjuvant treatment in "patients with HER2+ early breast cancer who had previously collected trastuzumab (Herceptin) and a taxane, either alone or in combination."[1]

Antibody-drug conjugates (ADCs) are a promising therapeutic method due to their ability to target cancer cells and their "potential in" modulating "the immune system". ADCs are "designed to deliver" therapeutic payloads, such as glucocorticoids or other anti-inflammatory drugs, "immediately to sites of inflammation or immune dysregulation" during immunomodulation. With this tailored delivery, the potential side effects of these powerful drugs are minimized while the therapeutic impact is optimized.[2]

For instance, ADCs can specifically target and distribute glucocorticoids to inflamed tissues in autoimmune disorders such as rheumatoid arthritis and myasthenia gravis, where inflammation plays a fundamental role in disease pathogenesis. Compared to the conventional systemic administration of glucocorticoids, this focused strategy may have a

number of benefits, such as less systemic exposure and associated side effects such as immunosuppression, osteoporosis, and metabolic disturbances.[2]

In this sector, researchers are now studying several ADC approaches that are appropriate for specific diseases and conditions marked by inflammation and immunological dysregulation. [2]

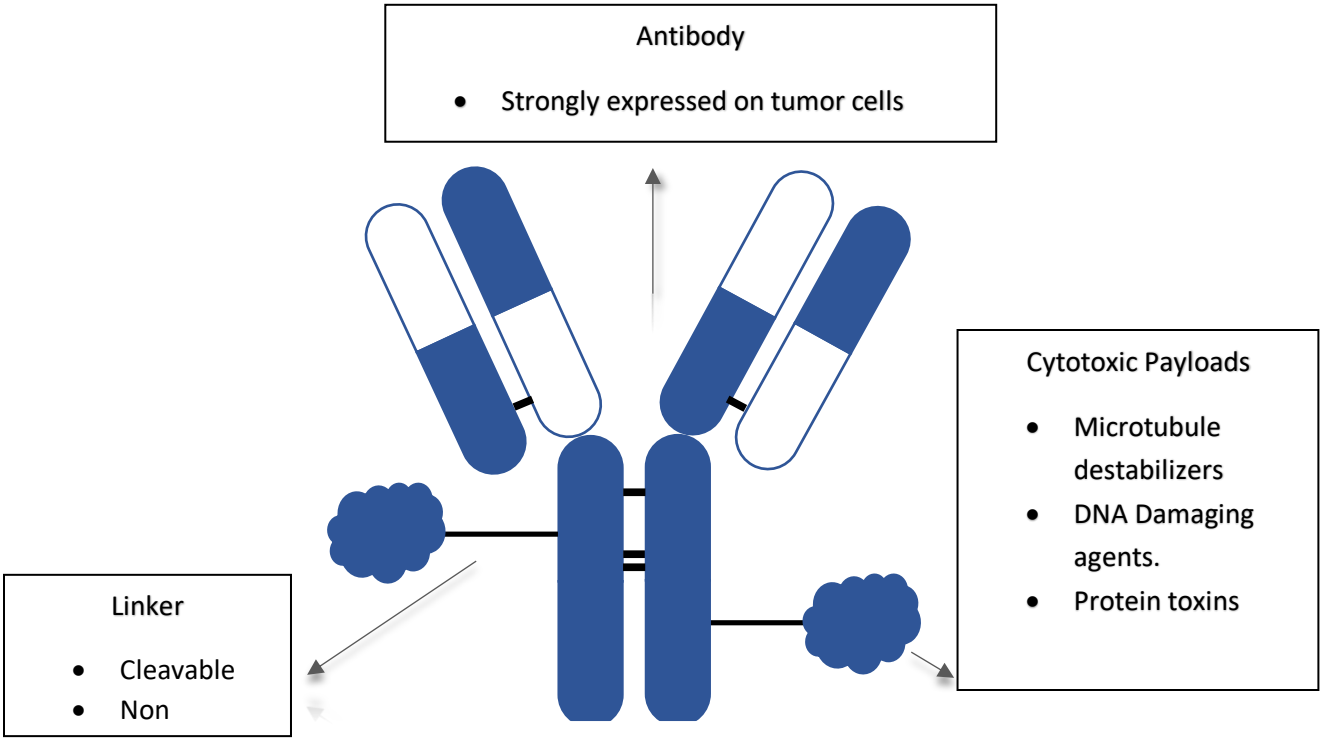

Fig:1.1 – Antibody Drug Conjugates

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1.2. Components of ADC's:

An antibody-drug conjugate (ADC) consists of three major components: an antibody, a linker, and a cytotoxic agent. "The antibody" selectively targets cancer cells, the chemical linker joins the antibody to the medicine, and the active drug, the cytotoxic molecule, kills the cancer cells. This combination enables ADCs "to deliver the drug directly to cancer cells while minimising damage to healthy cells."

ing the antibody component's target selectivity and selecting adequate cytotoxic payloads or anti-inflammatory medicines to accomplish the intended therapeutic effects. [3]

1.2.1. Antibody

"The antibody is the main component of the ADC design; it should have the following characteristics: the first is target specificity, which means the antibody should transport the deadly chemical to the tumour cell (18). The second need is target-binding affinity, which means that the antibody should have a high binding affinity for tumour cell-surface antigens.[3]

Furthermore, the antibody should have good retention, low immunogenicity, little cross-reactivity, and good linkage-binding characteristics (19). This is an crucial component in developing ADC as they specifically target the antigen due to which the harm to healthy cell decreases. They precisely deliver the drug to the antigen's cell. Thus, it enable the treatment efficiency and efficacy.[3]

Human serum have five types of antibodies, the widely available serum is, immunoglobulin G (IgG), which is 70-85% of the total and have half-life of 21 days. IgG is commonly used in the production of antibody-drug conjugates (ADCs) due to its abundance and robust immune response capabilities. IgG contains four subclasses: IgG1, IgG2, IgG3, and IgG4, with IgG1 being the most widely employed in ADCs due to its high capacity to elicit immunological responses. Antitumor antibody drugs use the Fc (fragment crystallizable) part "of the antibody to trigger" the body's "immune" responses, which they do in three ways: first, "antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP)."[4]

These immune functions are essential for effective antitumor activity, requiring a high expression of target antigens on tumor cells. Each IgG antibody subclass differs in the length of “its hinge region, the number and arrangement of its interchain disulfide bonds, and its specific Fc-effector functions. In comparison to other IgG subclasses, IgG1 have great affinity for Fc gamma receptors (FcγRs), that enhances its capability to stimulate ADCC and CDC. IgG1 is an excellent choice for ADC development because of its potent immunological properties and long serum half-life. [4]

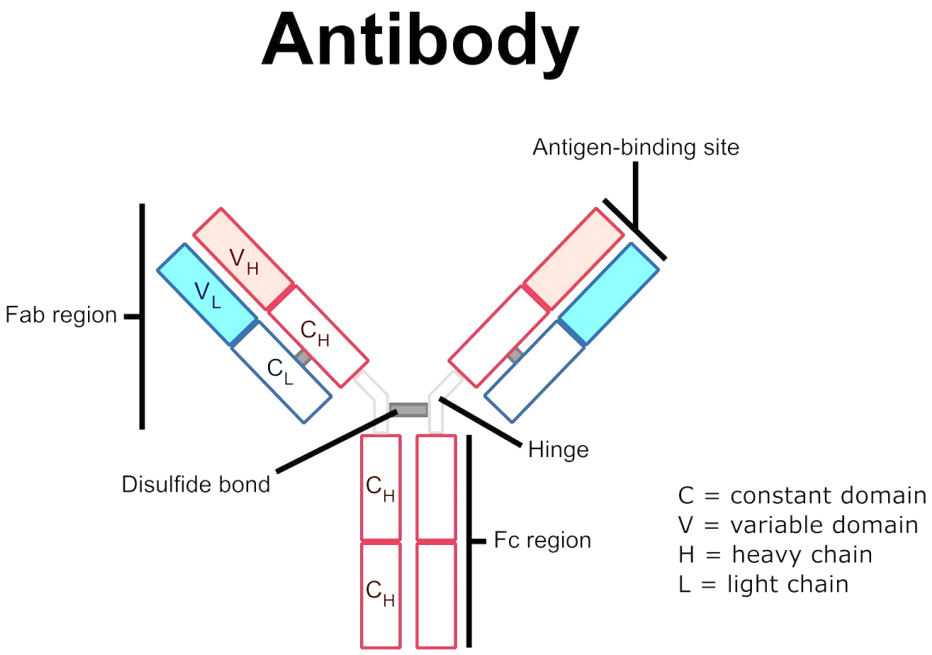

Fig: 1.2 Antibody

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1.2.2. **Linkers**:

As its name suggests, the linker connects the monoclonal antibody (mAb) to the cytotoxic drug. One of the primary challenges in developing ADCs is selecting an appropriate linker to attach the cytotoxic payload to the mAb. Linker chemistry significantly affects various ADC properties, including toxicity, specificity, stability, and potency, prompting extensive research into different linker structures. Linkers can be broadly categorized as either cleavable, where the payload detaches from the mAb at the tumor site, or non-cleavable, where the payload and mAb remain connected, and the mAb is degraded after internalization. This classification influences the mechanisms of action of individual ADCs. When the ADC complex circulates in the bloodstream, the linker must be stable to prevent the premature release of the cytotoxic drug in non-target tissues, keeping the conjugate inactive and non-toxic while bound to the antibody. Simultaneously, the linker must be capable of releasing the cytotoxic drug upon internalization [5].

1.2.2.1. Cleavable Linkers:

Cleavable linkers are designed to release the cytotoxic drug from the antibody once the ADC reaches the target tumor cells. This release can be triggered by specific conditions present in the tumor environment, such as acidic pH, the presence of certain enzymes. This offers a precise way of drug release enhancing the efficacy of ADC's. These are of three types:

- **pH-sensitive linkers**: These linkers break down in the acidic environment of the tumor or inside cellular compartments like lysosomes. A common example is the hydrazone linker, used in the ADC gemtuzumab ozogamicin, which releases the drug in acidic conditions.
- **Enzyme-sensitive linkers**: These linkers are cleaved by enzymes that are often overexpressed in tumor cells. For instance, the valine-citrulline (val-cit) linker, used in the ADC brentuximab vedotin, is cleaved by cathepsin B, an enzyme found in high amounts in certain cancer cells.
- **Disulfide linkers**: These linkers are cleaved in the presence of high levels of intracellular glutathione, which is more prevalent in tumor cells. An example of an ADC with a disulfide linker is disulfide-linked calicheamicin. [5]

1.2.2.2. Non-cleavable Linkers

Non-cleavable linkers are designed to keep the cytotoxic drug attached to the antibody until the entire ADC is internalized and degraded inside the target cell. This means that the drug remains linked to the antibody fragment even after the ADC is taken up by the cancer cell, ensuring that the toxic effect is confined to the inside of the target cell. They are generally thioether linkers.[5]

Thioether linkers: The thioether linker found in trastuzumab emtansine (T-DM1) is a well-known example. The cytotoxic medication, DM1, is released by this linker only after the entire ADC has been internalised and broken down within the cancer cell. It stays stable in the circulation.[5]

1.2.2.3. **Payload cytotoxicity:**

The cytotoxic payloads, commonly referred to as "warheads," are extremely powerful medications that are included into antibody-drug conjugates (ADCs) in order to specifically target and eliminate cancer cells. Because they directly destroy cancer cells, "these payloads are crucial for the effectiveness of ADCs." By using a chemical linker to join the payload to the antibody, the medication is delivered to the cancer cells only, causing the least amount of harm to healthy tissues. which makes ADC an prominent class for treatment. [5]

Types of Cytotoxic Payloads

Cytotoxic payloads can be broadly classified into three main types: microtubule inhibitors, DNA-damaging agents.

DNA damaging agents are an extensive group of chemicals that can disrupt the normal function of DNA in a variety of biological processes. One example is duocarmycins, that are found in Antibody Drug Conjugates (ADCs). Duocarmycins connect to the minor groove of DNA, inducing DNA alkylation. This contact causes structural damage to the DNA molecule, which eventually leads to the cell's collapse. Calicheamicins are additional type of DNA-damaging agent found in ADCs. Like duocarmycins, calicheamicins bind to the minor groove of DNA. However, rather than making DNA alkylation, calicheamicins inhibit DNA replication, encouraging cell death by this route. Doxorubicin, a member of another class of DNA-damaging compounds found in ADCs, works by disrupting DNA synthesis. It achieves this by implanting itself between nucleic acid base pairs, thereby hindering the normal progression of DNA synthesis. [5]

In addition to DNA-damaging compounds, ADCs use microtubule unsettling agents like MMAE from auristatin. These drugs disturb the process of "cell division by blocking the polymerization of tubulin," a protein needed for the development of the cell's structure. The breakdown of tubulin polymerization halts cell cycle growth and produces apoptosis, or programmed cell death. Maytansinoids are a different kind of drug which damages microtubules in ADCs. Maytansinoids, like MMAE, hinder tubulin polymerization, causing cell division to finish during mitosis and eventual cell death. ADCs also use potent

derivatives of maytansinoids as cytotoxic agents, proving the adaptability and selectivity of these DNA-damaging and microtubule-disrupting agents in treating numerous disorders [5].

1.2.3. Mechanism of action:

The mechanism of action of ADCs involves several key steps:

1. **Targeting Specific Antigens**: "ADCs specifically target the antigens that are overly expressed on the surface of the cancer cell. By this, the health cell remains safe and undisturb. They only attack on the cancer cell
2. **Internalisation:** After the antibody component of the ADC binds to the target antigen on the cancer cell surface, the entire complex is infused into the cancer cell via receptor-mediated endocytosis. This attachment step permits the ADC to enter the cancer cell while minimising interaction with healthy cells.
3. **Intracellular Release of the Cytotoxic Drug**: With internalisation, the ADC begins intracellular processing within the cancer cell. This includes eliminating the linker molecule which links the antibody to the cytotoxic drug. Once inside the cancer cell, the ADC can release the lethal drug via a variety of processes, including enzymatic cleavage and reduction.
4. **Cytotoxic Effect**: The cytotoxic chemical attacked on the cancer cell once it is released by the ADC leading to DNA damage, production of microtubule decreases, and also distrub the biological processes which are important for cell survival and proliferation. various drugs work by preventing cell division or causing apoptosis, two processes that result in cell death. [6,7]

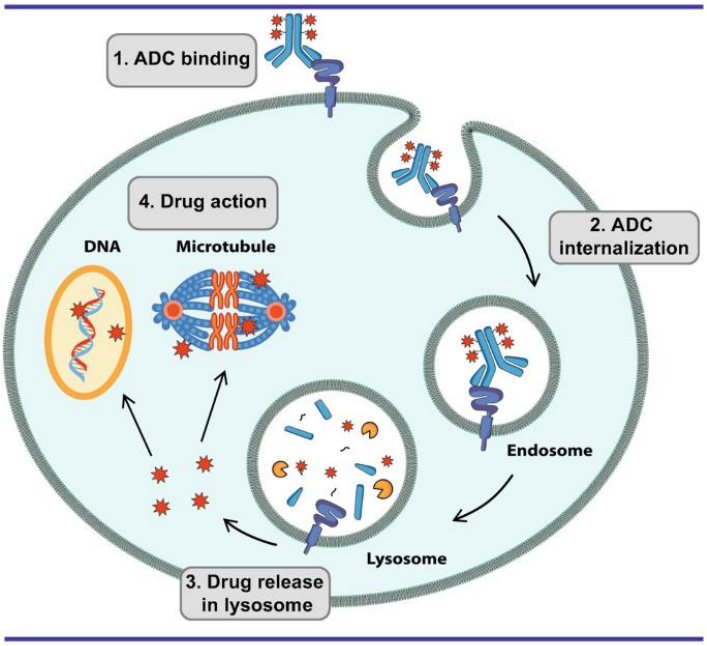

Fig: 1.3 Mechanism of Action

CHAPTER 2

REVIEW OF LITERATURE

A literature review discusses issued information in a specific subject area, and sometimes information in a particular subject area within a certain time. A literature review can be just a regular summary of the sources, but it typically has an organizational plan and relates both summary and synthesis.

1. **"Antibody–drug conjugates as novel anti-cancer chemotherapeutics" Christina Peters". Et al; 2015:** This paper reviews the "current knowledge and recent developments in ADCs", focusing on their design, efficacy, and challenges. ADCs utilize mAbs to target tumor-specific antigens, delivering cytotoxic agents "directly to cancer cells while minimizing damage to healthy tissues". The discussion highlights the importance of predictive biomarkers, innovative linker technologies, and combination therapies to enhance ADC effectiveness. Future research aims to improve target selection, increase cytotoxin potency, and develop new strategies to overcome resistance, paving the way for more effective and stable ADCs in cancer treatment.
2. **Antibody-drug conjugates—an emerging class of cancer treatment; Nikolaos Diamantis; 2016:** The reviewed paper discusses the significant "potential of antibody-drug conjugates (ADCs) as targeted "anticancer agents that merge the specificity of targeted therapies with the potency of chemotherapy. Additionally, combination therapies involving ADCs and other treatments are being actively investigated. Key discussion points include the need for predictive biomarkers "to identify patients most likely to benefit from ADCs, and" overcoming obstacles like low delivery efficiency, normal tissue antigen expression, and tumor heterogeneity.

   "Despite these challenges, advancements in technology and research are paving the way for more stable and effective ADCs in the future".
3. **Recent Developments in ADC Technology: Preclinical Studies, Signal Future Clinical Trends; Penelope M. Drakes; 2017:** This study discusses the advancements in antibody-drug conjugates (ADCs), highlighting a shift from traditional methods to innovative strategies aimed at improving efficacy and reducing toxicity. The discussion centers on overcoming current challenges, optimizing ADC components, and expanding applications beyond oncology to include infectious and chronic diseases, with novel approaches like targeting non-internalizing antigens and advanced linker technologies for precise drug delivery.

4. **Antibody-drug conjugates: promising and efficient tools for targeted cancer therapy; "Hadi Nasiri"; 2017:** This study evaluations the advancements and challenges "in the development of antibody-drug conjugates (ADCs) for cancer therapy. The review also deliberates the mechanisms of resistance that can limit ADC efficacy and highlights the need for continued research in emerging new linkers, efficient cytotoxic agents, and recognizing cancer-specific antigens. The stability and biodistribution of ADCs, as well as their tumor penetration and drug release mechanisms, are critical factors that contribute to their unique therapeutic properties.
5. **Cleavable linkers in antibody–drug conjugates; Jonathan D. Bargh; 2019:** This study attentions on the critical role of cleavable linker technologies in the development and efficacy of antibody-drug conjugates (ADCs) for cancer treatment. The review highlights how the linker, which connects the antibody to the cytotoxic payload, is crucial for the controlled release of the drug at the target site. Future research is predicted to further explore alternative mechanisms of action, comprising exogenous stimuli, and to validate enzyme-cleavable linkers such as glycosidase- and phosphatase-cleavable linkers, which have shown auspicious preclinical results.
6. **Antibody–Drug Conjugates: The Last Decade ;2020:** Over the past decade, the field of Antibody-Drug Conjugates (ADCs) has seen considerable advancements, particularly in improving the stability and specificity of these therapies. Additionally, ADCs are now being investigated for potential submissions beyond oncology, comprising the treatment of infectious diseases, signifying a promising future for these targeted therapies.
7. **What makes a good antibody–drug conjugate? Martin De Cecco; 2021:** Since 2010, the acceptance rate for Antibody-Drug Conjugates (ADCs) in clinical trials increases which increases the possibility of more approved molecules, the approval rate increases from 2019. The paper's discussion foci how continuing research and technical progresses are influencing the direction that ADCs may take in the future, consolidating gains while tackling obstacles to improve patient outcomes and their clinical relevance.
8. **The Evolving Landscape of Antibody–Drug Conjugates: In Depth Analysis of Recent Research Progress; Janet M. Sasso; 2023:** The paper provides a complete overview of antibody-drug conjugates (ADCs), importance their role as targeted

immunoconjugates that association the cytotoxic potency of drugs with the specificity of monoclonal antibodies. “Overall, the account aims to serve as a respected resource for understanding the current state and future guidelines of ADC research, advocating for continued advancements to appreciate their full therapeutic potential across various medical disciplines.”

9. **Antibody–drug conjugates: in search of partners of choice; Jesús Fuentes-Antrás; 2023:** Antibody–drug conjugates (ADCs) have shown significant antitumor efficacy as single agents, leading to regulatory approvals for various cancers. Improving therapeutic indices through optimized drug-to-antibody ratios and selecting patients based on predictive biomarkers are essential. Strategic approaches are needed to identify the most effective ADC-based combinations for specific patient populations and disease settings.
10. **Precision Medicine in Rheumatic Diseases: Unlocking the Potential of Antibody-Drug Conjugates; Zhiwen Huang; 2024:** In the era of precision medicine, Antibody-Drug Conjugates (ADCs) have become a revolutionary therapeutic approach. Despite limited literature, the potential of ADCs in targeting immune components for rheumatic diseases offers novel insights for developing low-risk, efficient treatments. Further efforts are needed to identify disease-specific targets,” develop stable linkers and potent payloads, and improve immune conjugation technologies to maximize ADCs' therapeutic potential in rheumatic diseases.

CHAPTER: 3
METHODOLOGY

The title of this paper is "An exploratory dive into the world of Antibody- drug conjugates", that are a specific class of drugs which are designed to provide a targeted therapy for treating various oncology and non-oncological indication . These are designed to target and treat only the affected cells in the body. The goal of this study is to provide a deep understanding of ADCs, their components, mechanism of action, as well as about the drugs that are currently reviewed by regulatory bodies and are in clinical phases and those that have already been approved .

3.1 Research Question

What is the current status of ADCs molecules that are in clinical stages and those that have already been approved and how do the components of ADCs, contribute to their efficacy and safety profile.

3.2 Objectives

1. To make a comprehensive summary of ADCs who are in clinical phase along with their Antibody, Linker, and payloads
2. To investigate approved ADC from 2020-2024 along with their targeted indications.
3. To assess the growth and increasing trend of ADCs across various therapy areas over time
4. To examine different Indication for which ADCs are approved

3.3 Hypothesis

"The targeted delivery of cytotoxic payloads by antibody-drug conjugates (ADCs)" will improve treatment accuracy and effectiveness across various therapy area, leading to advancements in therapeutic outcomes in oncology and beyond.

3.4 Research Design

This study employs an observational study-based approach through retrospective literature review.

3.5 Study Setting

As this is a literature-based study, there is no physical study setting involved.

3.6 Study Population

- **Inclusion Criteria**: This study involves recent studies and publications (within the last five years) related to antibody-drug conjugates (ADCs). It includes data from ongoing clinical trials provided by companies.

- **Exclusion Criteria**: Studies which are not directly related to ADCs or not meeting the predefined inclusion criteria are excluded.

3.7 Research Procedures/Approaches

- Quantitative assessment involves analysing numerical data from clinical trials and studies linked to ADCs. This may include results such as the number of antibody-drug conjugates licensed by regulatory authorities, as well as the number of ADC clinical studies in various stages, i.e. I, II, and III Phases
- Qualitative evaluation entails analysing and synthesising qualitative data from literature, reviews, and expert opinions. This will include information about the mechanisms of action, unique payloads and linkers, and the broader implications of ADCs in a range of therapeutic settings.

3.8 Sample Size Calculation

The sample size for this study encompasses all relevant studies and publications meeting the inclusion criteria. The methodical review methodology safeguards that all available literature within the defined timeframe i.e., 5 years and criteria is considered, maximizing the completeness of the review.

3.9 Sampling Techniques

Convenience sampling is used to select literature from well-known databases such as NIH, PubMed, Scopus, ClinicalTrials.gov, Web of Science, and Google Scholar. This method permits quick retrieval of relevant papers while offering comprehensive coverage of the available literature on Antibody-Drug Conjugates.

3.10 Study Instruments

The key instrument for data collection is a comprehensive literature search using predefined inclusion and exclusion criteria. This search strategy is planned to gather relevant scientific articles, reviews, clinical trials, and research papers that donate to understanding ADCs, their components, mechanisms, and clinical applications.

3.11 Operational Definitions

- **Antibody-Drug Conjugates (ADCs)**: Defined as a class of biopharmaceutical drugs considered to selectively deliver cytotoxic payloads to target cells, typically cancer cells, while minimalizing systemic toxicity.
- **Targeted Therapies**: Refers to therapeutic tactics that specifically target diseased cells or biological pathways, aiming to improve treatment efficacy and reduce side effects associated to conventional therapies.

3.12 Statistical Methods

Data analysis involves qualitative and quantitative methods to identify and analyze trends, mechanisms of action, and therapeutic efficacy of ADCs. Statistical tools may include meta-analysis for quantitative data and thematic analysis for qualitative data to extract meaningful insights and conclusions from the literature.

3.11 Ethical Considerations

- **Informed Consent**: Not relevant
- **Voluntary Participation**: Not relevant.
- **Data Security and Confidentiality**: Ensured through adherence to ethical guidelines in handling and citing literature sources to recognise intellectual property rights and retain confidentiality of information obtained from databases.

3.12 Implications of Research

This systematic review aims to provide a comprehensive understanding of ADCs by:

- Summarizing recent knowledge on ADC components, mechanisms of action, and safety profiles.
- Compiling a database of ADCs in clinical phases, including indications, trial statuses, and disease areas.
- Assessing the therapeutic potential of ADCs other than oncology, exploring applications in immunology, hematology, infectious diseases, and other areas.

CHAPTER: 4
RESULTS

ADC	ANTIBODY	LINKER	PAYLOAD	TARGET	ACTION	INDICATION
Trastuzumab Deruxtecan (DS-8201a)	Humanized-HER2	Cleavable	Camptothecin	HER2	DNA damaging Agent	Breast Cancer
Sacituzumab govitecan	Humanized-IgG1	Cleavable	SN-38	TROP2	DNA damaging Agent	Breast Cancer
Mirvetuximab Soravtansine (IMGN853)	Humanized-IgG1	Cleavable	DM4	FOLR1	Microtubule disrupting agent	Ovarian cancer
Enfortumab Vedotin	Humanized-IgG1	Cleavable	MMAE	Nectin-4	Microtubule disrupting agent	Urothelial cancer
Trastuzumab Duocarmazine (SYD985)	Humanized-IgG1	Cleavable	Duocarmycin	HER2	DNA damaging agent	Breast cancer
GSK2857916	Humanized-IgG1	Non-Cleavable	MMAF	BCMA	Microtubule disrupting agent	Multiple Myeloma
Glembatumumab Vedotin	Humanized-IgG2	Cleavable	MMAE	GPNMB	Microtubule disrupting agent	Recurrent Osteosarcoma
Anetumab Ravtansine	Humanized-IgG1	Cleavable	DM4	Mesothelin	Microtubule disrupting agent	Mesothelioma
PSMA ADC	Humanized-IgG1	Cleavable	MMAE	PSMA	Microtubule disrupting agent	Prostate cancer
Coltuximab ravtansine (SAR3419)	Humanized-IgG1	Cleavable	DM4	CD19	Microtubule disrupting agent	B-cell lymphoma

Table 4.1- Comprehensive Summary of Clinical stage ADCs

With the aim of understanding their different parts and uses, this research examined a varied range of antibody-drug conjugates (ADCs). The results appear in Table 1, in which the various ADCs are grouped on the basis of the individual antibody, linker, payload, target antigen, mechanism of action and clinical use.[8]

It is aimed at providing clear overview how does ADC get made and what it does as well illustrating how intricate developing processes behind these targeted therapeutics can be. This study wants to express the functions that each part individually plays such as antibody part, linker component and the role played by payload in overall functioning of an ADC. "The key objective of an ADC is to enable accurate targeting through recognizing antigens commonly expressed on cancer cells."[8]

The cytotoxic payload's stability and its release onto cancer cells upon uptake are determined by the linker which serves as a link between them; it also determines how stable the cytotoxic payload will be. However, to lower toxicity to normal tissues while killing cancer cells at very low doses containing non-cancerous cell damage; such toxins are used as payloads. In designing a treatment for cancer with greater specificity than previous monoclonal antibodies had allowed for some degree of selectivity in order to minimize undesired side effects due to healthy tissue but most often found only on tumour cells making them to be good candidates for targeted therapy of cancers (Deeks et al., 2011). [8]

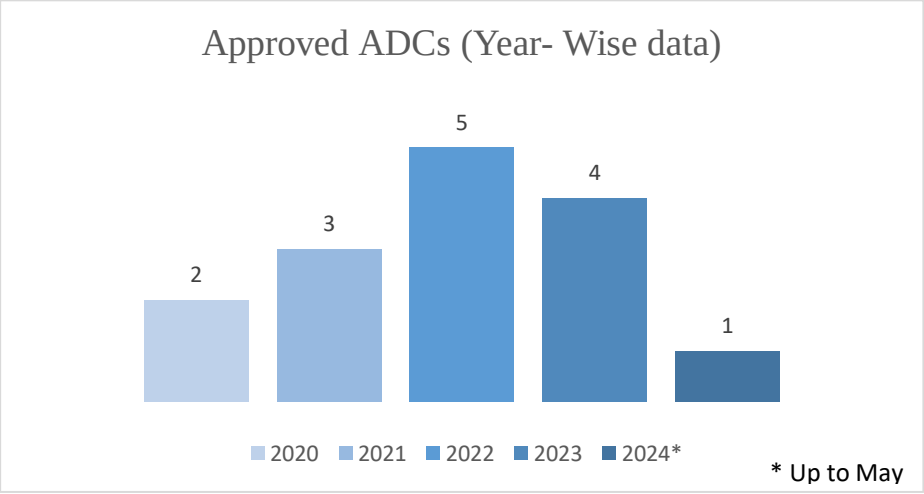

Fig: 4.1 Approved ADC's

The chart presents numbers of approved ADCs per annum from 2020 to 2024 (see fig.1). In 2020, two were approved and it rose to three in the following year of 2021. The highest number of approvals was recorded in 2022 with five ADCs' approval. It decreased slightly to four in the subsequent year {order} but as for this year there is only one approval up to May and more may be approved later. The graph shows that there was a peak in 2022, after which the number of approvals declined progressively in subsequent years toward the end of the period. There are also chances for other FDA-approved ADC's.[9]

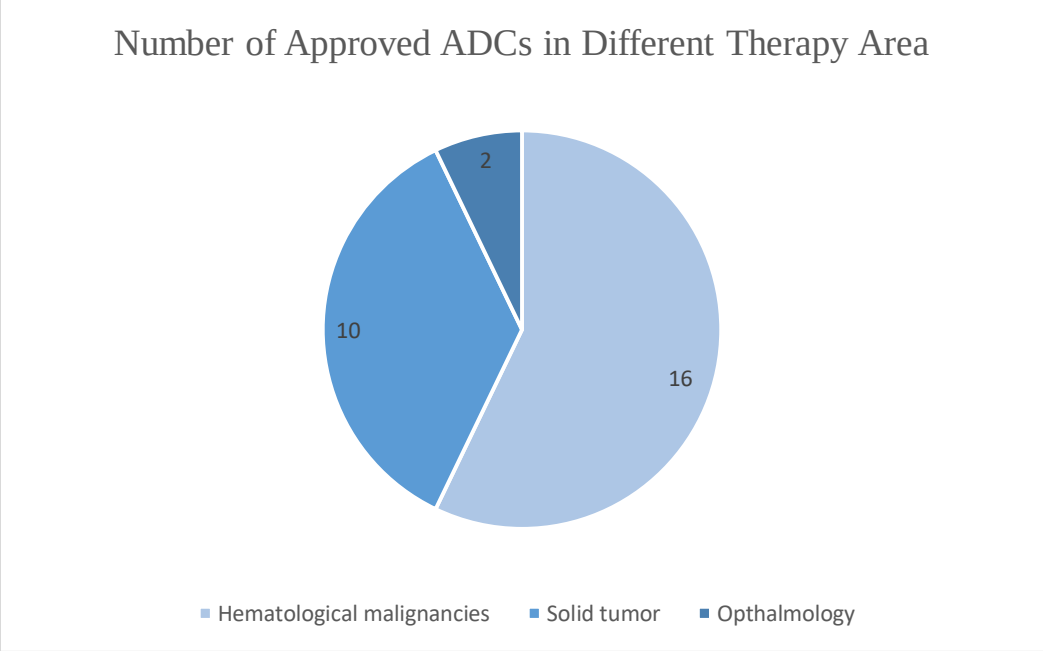

Fig: 4.2 Number of Approved ADC in different Therapy Area

The first pie chart analysis (Fig: 1) depicts a clear pattern of distribution of approved antibody-drug conjugates (ADCs). Hematological malignancies account for 62% of all approved molecules, indicating the strong interest in developing ADCs for hematological cancers based on well-known target antigens and therapeutic successes. This is followed by solid tumor at 28%, illustrating that efforts are being made to extend ADC applications into other areas in oncology. Meanwhile, ophthalmology represents 10% of the population, which suggests that this modality is still in its infancy when it comes to targeting ocular diseases. Taken together, the discussed pie chart reveals the potential role of ADCs in

hematology malignancies and growing preferences to use them against other types of cancer and possibly non-cancer indications including eye conditions.[9]

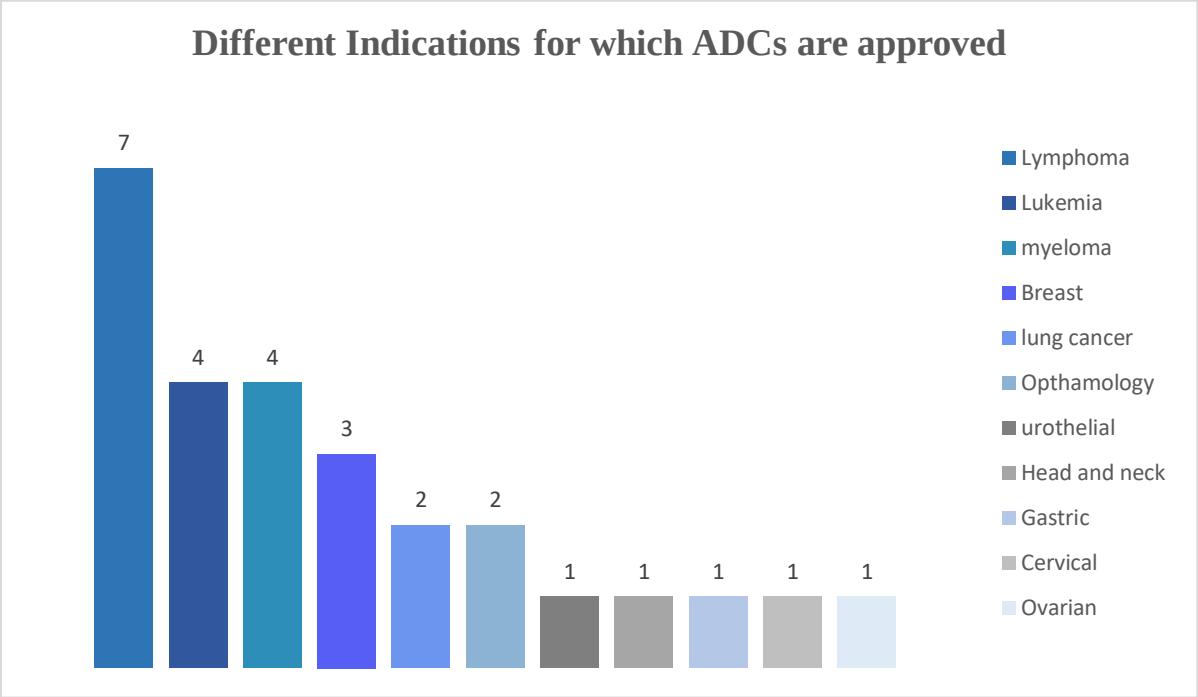

Fig: 4.3 Different Indication for which ADCs are approved

Figure 2, a column chart above is presented showing various indications for that "antibody-drug conjugates (ADCs) have got approval". The chart demonstrates how different medical conditions have varying numbers of approvals.[10]

Lymphoma tops the list with 7 ADCs approved in total. This big number shows a strong focus and success in targeting lymphoma through ADC therapies. Leukemia and myeloma also have considerable figures which are four each indicating notable developments in these areas.[10]

Next is breast cancer with three approvals. Similarly, urothelial cancer, lung cancer, and ophthalmology each have two approved ADCs thus telling us they are moderately developed for use in this direction.[11]

On the other hand, ovarian cancer, head and neck cancer, gastric cancer and cervical cancer each has one approved ADC. This show either emerging interest or difficulties developing ADCs for these indications hence providing potential avenues for further research and development to be explored.[11]

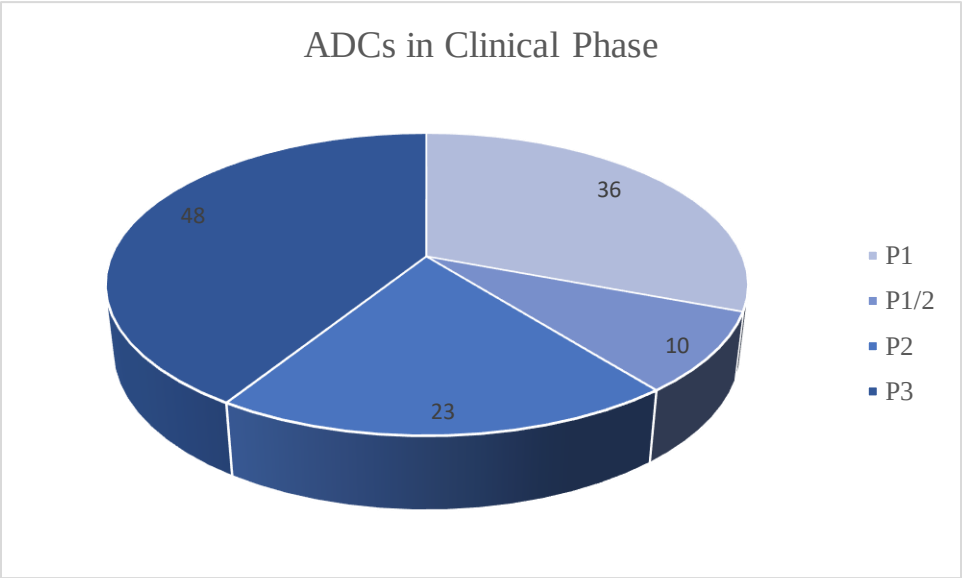

Fig: 4.4 (ADCs in Clinical Phase)

This pie chart provides a detailed illustration of ADC developmental stages among 10 drug companies. It should be noted that the fraction of 48 ADCs in Phase 3, which is critical before it can be given approval to be used in clinical settings, shows how advanced they are in the drug development pipeline. Also, there are 28 that have been approved to treat different diseases.[11]

A total of 46 ADCs at earlier stages are moving through Phase I (36 ADCs) and Phase I/II (10 ADCs). These steps represent active research studies and an initial evaluation aimed at refining and optimizing ADC therapies. Many drugs at these phases indicate the current endeavors towards developing more efficient and safer new treatments based on alternative methods which would ultimately benefit future patients. [11]

CHAPTER:5
DISCUSSION

The investigation of the ADC presents a thorough breakthrough analysis of this new type of cancer therapy, pointing out their individual parts, mechanisms, and clinical use. The data from Table 1, in turn, demonstrate the fine structure of ADCs, which include an antibody, a linker, and a carcinogen entail. These three components collaborate to end the attracted delivery and efficacy of the agent, with the antibody recognizing only the antigens of the tumor cells, the linker making the system stable and also controlling the release of the cargo, and the cytotoxic agent killing the targeted cells off. [12]

The bar chart (Fig 4.3) as well as the doughnut chart (Fig 4.4) show that a large number of ADCs are in stages of development by pharmaceutical companies. This comes because of the increased eagerness and financial allocations to direct research and development in enemy-cells that aim at increasing their therapeutic withdrawal capacity and alleviating their clinical outcomes. [12]

The bar graph (Fig.4.3) is one clinical trial of ADCs in cancer and non-oncology areas. It confirms their active and enormous potential in the treatment of diseases aside from cancer.[13]

Between 2020 and 2024, we have seen the peak of the approval of monoclonal antibodies that are conjugated to drugs (ADCs) in 2022, to be followed by a sharp decline in the subsequent years. [13]

However, there is still the possibility of other Global Medicines ADCs to be approved in 2024, which shows that there are still some explorations and improvements on ADC therapies ongoing.[14]

Besides that, more new technologies such as BiTEs and T-cells (TCEB or TIDE) are being investigated for the purpose of increasing the treatment effectiveness of ADCs. BiTEs connect T-cells to cancer cells, hence, make tumor cells a target for a precise immune response, whereas TiDEs direct specific T-cell activation. The forecasted advancements in this field are to cut down the risk of untarget effects on other tissues and therefore raise the chances of better treatment. The bedrock of new cancer therapies is the full integration of these technologies with ADCs.[14]

Also, the presence of ADCs in experimental tests among the other indications simultaneously with cancer is to be noted by the patient. Among them are the autoimmune diseases that studies focus

on. The reason for choosing ADCs in this case is the real effectiveness of liver transplants. It can be mentioned that this technology has the potential for providing new treatment methods for autoimmune diseases through targeting and modifying immune cells. ADCs can be used to treat diseases like rheumatoid arthritis and lupus because of this possibility. The topical aspects in the study include severe skin diseases that are usually treated by specific therapeutic approaches. The products are the ones that they are agents in the future. Their multiline product category classification is their bright perspective. [15]

5.1 Limitations:

Some limitations of this projects are discussed below:

- **Temporal Limitation:** The information on approved ADCs is covered only from 2020-2024.
- **Limited Scope of Research:** Scope of Research: The research did not cover all the areas of ADCs such as long-term safety profiles, resistance mechanisms, and cost-effectiveness.
- **Data Source Bias:** One of the problems of this study is that it mainly relies on the published literature and the official documentation of the drug profiles as the references to be evaluated for the trustworthiness of the drug.

5.2 Future Perspectives:

- Expanded Indications: Other advanced studies can also be performed in other cancer areas with the definite approval of ADCs for different cancer types.

- Improved Payloads: Payloads: In the future, the main issue of the research will be the production of new cytotoxic payloads with higher strength and lower side effects.
- Enhanced Targeting: In addition, the ability of antibody engineering to develop more exact targeting means will make it possible to have weaker effects on other tissues and consequently improve the patient's situation.
- Combination Therapies: Further use of immunotherapies, radiotherapies and other treatments along with ADCs will open the way for the best treatment method.[16,17]

CHAPTER:6
CONCLUSION

In conclusion, antibody-drug conjugates (ADCs) is a transformative class of targeted therapies in oncology and beyond. This analysis has highlighted their advanced design, combining antibodies, linkers, and cytotoxic payloads to realize precise tumor targeting and improve therapeutic efficacy. The evolution from first to third-generation ADCs signifies substantial progress in improving payload potency and target specificity, promising enhanced treatment results with minimized side effects.

Additionally, the study emphasizes a robust pipeline of ADCs across several developmental stages, signaling their ability extension into non-oncological fields like autoimmune diseases and dermatological conditions. Developing technologies like Bi-specific T-cell Engagers (BiTE) and T-cell engaging bispecific antibodies (TiDE) are prepared to further enhance ADC efficacy, potentially transforming treatment approaches across therapeutic domains.

However, the investigation is inhibited by the temporal limitation of focusing solely on ADC approvals between 2020 and 2024, potentially missing broader, long-term trends and future developments. Moreover, reliance on distributed literature and available data sources may present biases and oversee unpublished research findings. Moving forward, inclusive research efforts should incorporate broader datasets and real-world sign to explore long-term safety profiles, resistance mechanisms, and cost-effectiveness of ADCs. These activities are necessary for improving treatment strategies and maximizing the clinical effect of ADC therapies through diverse patient populations.

In summary, while ADCs hold huge promise in precision medicine, continued interdisciplinary collaboration and rigorous investigation will be paramount in fully understanding their therapeutic potential and defeating present limitations in clinical practice.

CHAPTER:7
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