The Use of Antibody as Drug Carrier in Cancer Chemotherapy

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Abstract
Antibodies are large Y-shaped immunoglobulins, produced by plasma B cells in response to invading pathogen termed antigen. They are used by the body defence (immune) system to recognize and neutralized specific antigen. Antibodies are also considered as gift of nature without which body is defenceless. Antigens are substances capable of triggering an immune response. Cancer cells are also known to be associated with specific antigens which are over expressed preferentially. These antigens are now exploited pharmaceutically to develop new class of cancer chemotherapy termed, antibody drug conjugate (ADC). The aim of this study was to review the various applications of antibodies as drug delivery vehicles in cancer chemotherapy and their therapeutic benefits. For the conventional chemotherapy to remain clinically relevant, the adverse drug reaction associated with these cytotoxic agents must be curtailed. Incorporating by conjugating known cytotoxic agents with antibodies that can recognize specific surface tumour associated antigens is one of the possible strategies that are being exploited to a great success clinically today. The use of antibodies as drug carriers (antibody-drug conjugates) enhances specificity, selectivity thereby improving pharmacokinetic profile, by decreasing the volume of distribution and prolonging the distribution and elimination phases. The reduced toxicity and improved therapeutic outcome, has led to an increase research interest and are of growing significance in cancer therapy, as evidenced by increasing numbers of antibodies-based pharmaceuticals been approved for oncologic indications by the FDA. However, the production of antibodies drug conjugates is limited by the availability of suitable linkers, vital for successful attachment of the cytotoxic agent to the antibodies. Despite this drawback, the use of ADC for cancer treatment will become more relevant as more researches unfold the best production methods and conditions.

Keywords: Antibodies, Linkers, Cytotoxic agent, ADC, Cancer chemotherapy.

Introduction
Cancer is the name given to a collection of related diseases. In all types of cancer, some of the body’s cells begin to divide and proliferate on their own without stopping and may spread into surrounding tissues or organs (Varricchio, 2004). A cancer cell is an abnormal cell that disregards the normal rule of cell division, growth, proliferation, differentiation and death. And in most cases cancer cell develops its own autonomy and rules leading to uncontrolled growth and proliferation (Hanahan and Weinberg, 2000)

Cancer arises from host cell via neoplastic transformation or carcinogenesis i.e. deregulation of genes that regulate cell growth. Cancer is clonal in origin, that is to say it originates from a single abnormal cell with altered DNA sequence; however, it is a multi-gene, and muti stage disease. Uncontrolled proliferation of a single abnormal cell may be followed by a second mutation leading to the aberrant stage. However, successive and continuous rounds of mutation and proliferation of these cells results in the formation of tumour mass (Scott et al., 2012).
Figure 1: Clonal expansion of Cancer.

Cancer is among the most common causes of morbidity and mortality worldwide, with an estimated 14 million new cases and 8 million deaths in 2012; projected to rise by at least 70% by the year 2030 (Ferlay et al., 2015). An ever-increasing cancer burden is expected in the coming years, particularly in low and middle income countries (LMIC), like Nigeria, with over 20 million new cancer cases expected annually as early as 2025 (Bray, 2014 and Forman et al., 2013).

Cancer poses a major threat to public health worldwide, and despite repeated campaigns to defeat cancer, such as Nixon’s War on Cancer, all have failed, because cancer is not a single and simple disease. In fact, it is a collection of highly complex diseases characterized by unregulated cell proliferation that can arise from contributions from numerous causative factors, including nutrition, genetic and environmental (Chabner and Roberts, 2005). Cancer alone caused over 8 million deaths worldwide in 2013 and has moved from the third leading cause of death in 1990 to the second leading cause behind cardiovascular disease in 2013 (Lozano et al., 2013; Murray and Lopez 1997).

The incidence rates have increased in most countries since 1990. The trend if not addressed quickly, may become a serious threat to many developing nations with poor health systems characterized with ill-equipped and trained specialist oncologist to deal with the complex and expensive cancer treatments.
Figure 2: Global Cancer incidence
Figure 3: Global Cancer mortality.

The current strategies to combat cancer depend on the type, location and grade of the cancer as well as the patient's health and preferences. These strategies include surgery, chemotherapy, immunotherapy, radiation therapy, and hormonal therapy.

After the first promising results of cytotoxic treatment during the 1940s there was a tremendous surge of activity to discover new anticancer agents in the hope of finding the ideal drug that would eradicate the tumour whilst having no harmful effects on normal tissue. Decades later this hope is yet to be fulfilled, but the search for new cytotoxic agent has yielded many thousands of compounds with possible therapeutic applications, (Stenvang et al., 2013). Presently plethoras of chemotherapeutic cancer drugs exist for treatment of haematological and other solid tumours. These drugs are divided into six major classes which include: alkylating agents, anti-metabolites, anti-tumour antibiotics, topoisomerase inhibitors, corticosteroids and mitotic inhibitors, (Jain, 1990; Dubowchik & Walker 1999).

The goal of cancer chemotherapy is to selectively and completely kill the cancerous cells using cytotoxic agents, without negatively affecting normal healthy cells. The use of conventional cytotoxic agents is however limited clinically by various adverse drug reactions reported by the patients. These adverse drug reactions are mainly as a result of indiscriminate distribution and lethal effects of the cytotoxic agents on normal healthy cells. There is therefore the need for selective and targeted drug delivery to the tumour cells thereby increasing concentration of the cytotoxic drug in the tumour areas relatively to other parts of the body (Wu and Senter, 2005).

One of the current most useful strategies is the use of antibody as carrier (delivery vehicle) of cytotoxic agent. This strategy is particularly useful in improving the selective delivery of cytotoxic drugs since the vehicle (antibodies) can reorganize and bind selectivity to tumour associated antigen thereby delivering the cytotoxic drugs to the tumour cells through passive and active internalization, (Waldmann, 2003). Conjugation of cytotoxic agent
with antibody has been reported to improve the pharmacokinetic profile, by decreasing the volume of distribution and prolonging the distribution and elimination phase of the attached cytotoxic agents (Cheng and Xu, 2008). Additionally, Antibody – drug conjugates (ADC) offer a sustained release of the attached drug from the carrier results in a prolonged high intra-tumoural drug levels (Wu and Senter, 2005).

### Table 1: Some identified Tumour cells associated antigens

<table>
<thead>
<tr>
<th>Types of Cancer</th>
<th>Associated Surface Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>CD20, CD22 and HLA-DR</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>EGFR, A33 and Carcinoembryonic antigen (CEA)</td>
</tr>
<tr>
<td>Renal Carcinoma</td>
<td>G250</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>HER2</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>CD56</td>
</tr>
<tr>
<td>Solid Tumour</td>
<td>Vascular endothelial growth factor (VEGF) and VEGF2</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>Prostate-specific membrane antigen</td>
</tr>
</tbody>
</table>

**Therapeutics Monoclonal antibodies**

Uses of monoclononal antibodies as therapeutic agent for the treatment and management of various types of cancer has become established over the past two decades and is now one of the most successful and important strategies for treating patients with haematological malignancies and solid tumours. The fundamental basis for the use of monoclonal antibodies as therapeutic agent dates back to the original observations of antigen expression by tumour cells through serological techniques in the 1960s (Rettig and Old, 1989). The definition of cell surface antigens that are expressed by human cancers has revealed a broad array of targets that are over expressed, mutated or selectively expressed compared with normal tissues (Van den Eynde and Scott, 1989).

Monoclonal antibodies are immunoglobulins produced by single clone of cells (cells that are derived from to a single progenitor and genetically identical) and are identical to one another, in terms of weight as well as chain structure. Therefore, they are highly antigen binding specific and offer more consistent efficacy and predictable toxicity in vivo (Delmonico and Cosimi, 1988).
F\textsubscript{ab} = Fragment antigen-binding domain
- Consist of variable (V) and constant (C) domains
- Antigen binding CDR domains found at this terminal
- Very useful for recognition and binding to antigen

F\textsubscript{c} = Fragment crystallizable/constant domain
- Ideal location for drug conjugation
- Consist of a CH\textsubscript{2} and CH\textsubscript{3} domains

The earliest monoclonal antibodies examined in animal and clinical studies were murine antibodies. Because of their non-human origin, they are immunogenic in humans (they have a tendency to elicit a human anti-murine antibody (HAMA) response). HAMA response is an immune response generated against a mouse antibody. They also have been shown to have much shorter clearance rates than human monoclonal antibodies. One approach to overcome these problems has been to cleave the antibody (e.g. by papain digestion) into its respective fragments, (FC and FAB), (Myers and Ron, 1992).

In general, the FAB fragments are less immunogenic compared with corresponding intact antibodies and their smaller molecular size may facilitate penetration into tumour tissue resulting in a longer systemic half-life (Larson et al., 1983). FAB fragment uses is however limited, since they often lose some of their antigen recognition and binding capacity and in some cases, the therapeutic effect may depend on the FC portion of the antibody (Kohler and Milstein, 1975).

Among the feature unique to monoclonal antibodies are their ability to be produced in unlimited quantities, their ability to bind to a specific antigen and their homogeneity.

Monoclonal antibodies abilities to; recognize, bind, attack, and eradicate specific antigens, is today utilized in combating some tumour types with great clinical success, (Peter, 2011).

The development of first fully human therapeutic antibody follows years of logical drug design through application of recombinant DNA
technology which has made it possible to produced fully human antibodies and humanized antibodies. Both human and humanized monoclonal antibodies are today the template on which therapeutic antibodies are built, (Reily et al., 1994; Winter and Harris 1993). At present, there are various therapeutic monoclonal antibodies approved for the treatment and management of various types of cancer. The mechanism of their anti-tumour effect is thought to include complement dependent cytotoxicity, antibody-dependent cellular cytotoxicity and steric hindrance of the function of the target antigens, and a large number of additional therapeutic antibodies are currently being tested in early stage and late-stage clinical trials (Reff et al., 2002).

The tumour killing ability of therapeutics antibodies can be summarized as being due to several mechanisms: direct action of the antibody (through receptor blockade or agonist activity, induction of apoptosis, or delivery of a drug or cytotoxic agent); immune-mediated cell killing mechanisms (including, complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and regulation of T cell function); and specific effects of an antibody on tumour vasculature and stroma. The FC portion of monoclonal antibodies is particularly important for mediating tumour cell killing through CDC and ADCC. All of these approaches have been successfully applied therapeutically. For example Cetuximab and Trastuzumab mechanism is by abrogation of tumour cell signalling; while Rituximab is by the induction of effect or function primarily through ADCC; however Ipilimumab works by immune modulation of T cell function. These are the approaches that have been most successful therapeutically, and that have led to the approval of antibodies using these mechanisms.

Table 1: FDA approved therapeutic monoclonal antibodies, the target antigens and their clinical indications.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary name</th>
<th>Antigen</th>
<th>Year of approval</th>
<th>Clinical indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Rituxin®</td>
<td>CD20</td>
<td>1997</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin®</td>
<td>HER-2</td>
<td>1998</td>
<td>Metastatic Breast Cancer</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Vectibix™</td>
<td>EGFR1</td>
<td>2006</td>
<td>Merkel Cell Carcinoma</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Arzerra™</td>
<td>CD20</td>
<td>2009</td>
<td>Refractory Chronic Lymphocytic Leukaemia</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Yervoy™</td>
<td>CD152</td>
<td>2011</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Perjeta™</td>
<td>EGFR2, HER-2</td>
<td>2012</td>
<td>Breast Cancer</td>
</tr>
</tbody>
</table>

Antibody-drug conjugates (ADC)
A common theme in drug discovery and development is to address limitations in current anticancer therapies by designing novel formulations of these well known cytotoxic drugs. Several limitations to the effective uses of therapeutic monoclonal antibodies include; biochemical barriers such as antibody receptor affinity and antigen. In addition to these problems, the therapeutic efficacy can be limited due to the inability of antibodies to
marshal an immune response sufficient to cause target cell death (Wu and Senter, 2005 and Ruiz-Cabella et al., 2002). The emphasis is now on the use of monoclonal antibodies as delivery vehicles for toxic agents (Herbertson, et al., 2009 and Wu and Senter, 2009).

Since, monoclonal antibodies are generally generated against specific antigens, and as such when conjugated to cytotoxic drugs, can selectively deliver drugs to cancer cells while minimizing damage to normal cells; and of all the carrier systems available, monoclonal antibodies are gaining more relevancies because of their high specificity. Antibody-drug conjugates (ADC) as the name implies, are covalently linked cytotoxic agent and monoclonal antibodies (mAbs) formulated to selectively deliver the cytotoxic agent to tumour cells utilizing the ability of the mAbs to recognized, and selectively bind to specific tumour associated antigens, thereby reducing systemic toxicity and increasing the cell-killing potential of monoclonal antibodies.

Interestingly, ADC have been shown to have high potency in haematological malignancies, and the list of approved ADC by the regulatory authorities is growing daily, for example, Brentuximab Vedotin is an ADC used in patients with CD30-positive Hodgkins (Hughes, 2010: Weiner, et al., 2010 and Youne et al., 2010). Most ADCs use either IgG or IgG1 isotype antibody as the drug delivery vehicle due to their favourable pharmacokinetic properties when compared to other antibody types. Only a few of the ADCs contain IgG2 or IgG4, as is AGS-16M8F (anti-ENPP3 IgG2-MMAF) and Inotuzumab Ozogamicin (anti-CD22 IgG4-calicheamicin) respectively. (McDonagh et al., 2008).

![Elements of an Antibody-Drug Conjugate](image)

**Figure 3: Structural representation of ADC**

The successful development of an ADC involves a complex process of scientific and preclinical evaluations, informed by deep understanding of cancer biology and the properties of antibodies in vivo. Essential pre-clinical characterization including identification of the physical and chemical properties of the antibody; detailed specific analysis of antigen expression using panels of normal and malignant tissues; study of the immune effect and functions, effect of antibodies on cell signalling pathways; in vivo analysis of the antibodies localization and distribution in transplanted or syngeneic tumour systems; antibodies chimerization and humanization (or the use of phage display and
xenomice to produce fully human antibodies); and observation of the in-vivo therapeutic activities of the antibodies conjugated with cytotoxic agents or radioactive isotopes. For effective formulation of an ADC the target antigen must be carefully selected since both the safety and therapeutic efficacy depend on effective binding of ADC to the target antigen.

The ‘ideal’ target antigen must have a high-level expression in cancer cells, little to no expression in normal cells, exclusively expressed on the tumour cell surfaces, and there must be no shedding into the blood by cleavage of the antigen from cancer cell surfaces (Deckert, 2009 and Ellis and Hicklin, 2008). Optimal drug - antibodies ratio, (DAR) is also critical in successful development of an ADC. Attaching sub optimal amount of the drug molecules will lead to decreased efficacy, likewise attaching too many may make the ADC to become unstable, negatively alter the pharmacokinetic properties, increased plasma clearance, reduced half-life and increased systemic toxicity.

The nature and type of linker to be used, the reaction temperature, as well as, cytotoxic drugs to be use in ADC formulation must contain a suitable functional group for conjugation reactions and must be stable under physiological conditions, (Sedlacek et al., 1992). Two classes of drugs used to construct, ADCs in cancer therapy are discussed below:

1. Microtubule inhibitors (MIT)
Microtubules are important cellular targets for anticancer therapy because of their key role in mitosis. Microtubule inhibitors (MTI) such as Taxanes, Vinca Alkaloids, and Epothilones stabilize (up regulation) or destabilize (down regulation) microtubules, thereby suppressing microtubule dynamics required for proper mitotic function, effectively blocking cell cycle progression and resulting in apoptosis. Pharmaceutical formulation of MTIs as ADCs is a good strategy that ensures maxima benefits are obtained from MTIs by providing higher efficacy with limited systemic toxicity. This also helps overcome tumour resistance to conventional MTIs (Perez, 2012).

Monomethyl Auristatin E (MMAE, Vedotin) is a very good potent MTI candidate that inhibits cell division by blocking the polymerisation of tubulin. MMAE is 100-1000 times more potent than Doxorubicin (Adriamycin/Rubex) and as such it must not be used alone but rather as an ADC (Asundi et al., 2011; Younes et al., 2011; Junutula, 2008 and Francisco et al., 2003).

2. DNA-damaging agents
The discovery of the alkylating-like platinum agents had a significant positive impact on anticancer drug research. Cisplatin was discovered by accident in the 1960s, when a magnetic field generated by platinum electrodes was shown to block E. coli cell division (Rosenberg et al., 1965).

DNA integrity is critical for proper cellular function and proliferation. Tumour cells are capable of ignoring normal cell-cycle checkpoints, allowing the cells to achieve high proliferation rates; this also makes them more susceptible to DNA damage. The concept of aiming at DNA as a target for anticancer drugs inspired the development of numerous anticancer compounds, such as Cisplatin, Doxorubicin, 5-Fluorouracil, Etoposide, and Gemcitabine (Fischhaber et al., 1999). All of these drugs function by binding the minor groove of DNA and causing DNA stand scission, alkylay, or cross-linking (Sievers and Linenberger, 2001). The two most successful DNA- damaging agents are Cisplatin and Doxorubicin.

Cisplatin, as its name implies, contains a platinum core with two chloride leaving groups and two amine non-leaving groups. After internization of Cisplatin into the tumour cells, equation of the chloride groups allows the platinum to bind guanine residues and, to a lesser extent, adenine residues to form adducts on DNA.

When more than one platinum adducts form on adjacent bases on the same DNA strand, they form intra-strand cross-links (Siddik, 2003). Cisplatin therapy can cure over 90% of all testicular cancer cases and also has good efficacy in the treatment of ovarian, bladder, head and neck, and cervical cancers; however, Cisplatin is extremely toxic to the
kidney and the nervous system thereby limiting its clinical uses (Kelland, 2007).

Series of efforts were made with little success, at reducing the nephrotoxicity and neurotoxicity by developing Cisplatin analogs. Recently Cisplatin was formulated and evaluated as an ADC incorporating Cisplatin and monoclonal antibody. The problems of adverse drug reactions all cited above were completely solved and Cisplatin ADC is of great clinical success today (Baruah et al., 2004).

In a similar fit, Doxorubicin an Anthracycline antibiotic with Antineoplastics activities via the poisoning of topoisomerase II, and intercalate into DNA, generate free radicals, bind and alkylate DNA, crosslink DNA, interfere with helicase activity, and induce apoptosis (Cutts et al., 2005). Doxorubicin is derived from Streptomyces peucetius and it is widely used to treat breast cancer, small-cell lung tumours, soft tissue sarcomas and lymphomas, and acute lymphoblastic or myeloblastic leukemias. Doxorubicin and the newer Anthracyclines such as Epirubicin and Idarubicin have become mainstays of cancer chemotherapy (Minotti et al., 2004). All Anthracyclines are however extremely cardio toxic, including cardiomyopathy and congestive heart failure (CHF) as a result of their multiple mechanisms of action, (Olson and Mushlin 1990).

Trastuzumab-doxorubicin conjugate (T-Dox) an ADC was shown to selectively target HER2-expressing cells and reduced the adverse drug reaction experience with the use of doxorubicin in low HER2 expressing human cardiomyocytes. Since Doxorubicin is an established chemotherapeutic agent, T-Dox provides unique value for cancer patients with high HER2 expression, who showed benefit from Doxorubicin (Nigyan et al., 2013).

Figure 4: Three basic composition of an ADC
ADC | Antigen Target | Antibody isotype | Cytotoxic agent used | Indications
---|---|---|---|---
Pinatuzumab vedotin (DCDT2980S, RG7593) | CD22 | Hz IgG₁ | MMAE | NHL/DLBCL
Inotuzumab ozogamicin (CMC-544) | CD22 | Hz IgG₄ | Calicheamicin | ALL
Trastuzumab emtansine (Kadcyla®, T-DM1) | HER2 | Hz IgG₁ | DM1 | HER2+breast cancer
BT-062 | CD138 | Hz IgG₁ | DM4 | Multiple myeloma
Glembatumomab vedotin (CDX-011) | GPNMB | Hu IgG₂ | MMAE | Breast cancer/Melanoma
SYD985 | HER2 | Hz | Duocarmycin | Breast cancer
Lorvotuzumab mertansine (IMGN-901, huN901-DM1) | CD56 | Hz IgG₁ | DM1 | SCLC


**Linkers**
Pharmaceutical development and formulation of ADC requires an in-depth understanding of target tumour associated antigen, conjugate internalization process, drug potency and most importantly stability of the linker attaching the cytotoxic drug to the antibody. Additionally, understanding the conjugation methods, drug-to-antibody ratio (DAR), the effects of drug conjugation on antibody properties and type of linker are critical in formulation development of safe and effective ADCs, (Ravandi, 2011). The biggest challenge in the development of antibody-drug conjugates is the selection of suitable linkers that will offer high drug-linker stability in systemic circulation, thereby preventing dose duping of the cytotoxic agent (Carter and Senter, 2008). An ideal linker should be stable in systemic circulation, and must allow rapid release of attached drug within the tumour cells. Linkers can be broadly categorized into Cleavable and Non-cleavable.

While cleavable linkers are stable in systemic circulation, but they, rapidly release the attached drug within the tumour cells upon cleavage by lysosomal acid, lysosomal enzymes or intracellular glutathione ((Ducry and Stump, 2010). Based on their mechanism of cleavage, cleavable linkers are further sub-classified into acid-labile linkers, Protease-cleavable linkers and disulfide linkers with their respective examples as hydrazone, valine-citruline and SPP (N-succinimidyl-4-(2-pyridyldithio) pentanoate). However, in non-cleavable linkers the release of the cytotoxic agent dependent on internalization of the ADC and degradation of the ADC solely by lysosomal enzyme (Carter and Senter 2008).

There are several conjugation techniques of which the most current and frequently used involves limited reduction of intra or inter-chain disulfide bonds by the addition of reducing agents into the buffer containing the antibody. Limited reduction of the intact antibody results in the formation of free thiols without changing the structural characteristics of the antibody and antigen binding domain. With its structure and typical binding domain preserved the antibody will retain its ability to discriminate between healthy and tumour cells. Other conjugation methods are as in table 3.
Table 3: Different conjugations/Linker reactions used in constructing ADCs

<table>
<thead>
<tr>
<th>Linker</th>
<th>Drug Release Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfide Linkage</td>
<td>Designed to cleave the bond between antibody and the cytotoxic drug by disulfide exchange with intracellular thiol such as glutathione.</td>
</tr>
<tr>
<td>Thioester</td>
<td>The drug is release by intracellular proteolytic degradation of the ADC</td>
</tr>
<tr>
<td>Hydrazine</td>
<td>Hydrazone linkage is systemically stable, the cytotoxic drug is release by acid degradation within the tumour cells cytoplasm</td>
</tr>
<tr>
<td>Peptide</td>
<td>The drug is released from the ADC by enzymatic hydrolysis by the lysosomal proteases e.g cathepsin</td>
</tr>
</tbody>
</table>

Chemically labile linkers, such as hydrazones and disulfides, may offer limited plasma stability. Peptide-based linker technologies may offer better controlled drug-linker stability and drug release. Peptidic bonds are also expected to have good serum stability. Cleavable dipeptide linkers like Val-Ala and Val-Cit rely on processes inside the cell to liberate the payload, as they undergo rapid hydrolysis in the presence of lysosomal extracts (Sanderson et al., 2005). The selection of the linker depends on the tumour associated antigen targeted, therefore pre-formulation studies is critical to determine the optimal combination of the correct linker, the target antigen and optimum drug-antibody ratio (ADR) (Younes et al., 2012).

Mechanisms of action of ADC

After administration of an ADC, the monoclonal antibody component of the ADC directs the transportation of ADC to the cancer cells and binds to the target antigen on the surface of the cancer cells to produce antibody-drug conjugate-antigen complex (stage 1). The second stage involves the internalization of the antibody-drug conjugate-antigen complex into the tumour cell. Consequently, the antibody-drug conjugate -antigen complex fuses with tumour cells endosome, to initiate the release of the antigen from the antibody-drug conjugate. At this stage, the antigen may be recycled back to the cell membrane. This process is crucial for eventual activity of the cytotoxic drug (Chames et al., 2009).
The third stage involves internalization of the ADC which is transported through the late endosome pathway to the intracellular compartment of a lysosome, where it is degraded to release the cytotoxic drug. It is important that the ADC must release the attached cytotoxic drugs after internalization, by exploiting the differences in intracellular pH, reduction potential or enzyme concentration to trigger the release of the cytotoxic in the cell. The cytotoxic drug thereafter enters the cytoplasm, where it binds to its molecular target. The interaction of the cytotoxic drug with DNA and microtubules initiates a chain of events leading to apoptosis (Chames et al., 2009).

Conclusion
It will not be out of context to refer to these ADCs as smart bomb against various types of cancer. Their ability to recognize tumour associated antigens and provide a platform for targeted delivery of neoplastic agents is unparalleled. ADC has opened up some unlimited possibilities, and its use has significantly advanced cancer research in diverse fronts with sole aim of completely eradicating cancer. In 2008 there were more than 100 monoclonal antibody based biologic drugs in hundreds of clinical trials. It is reasonable to therefore assume that the future of therapeutic management of cancer patients is bright with the use of ADCs.

References


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