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# An Approach Using Monoclonal Antibodies to Increase Cancer Treatment Effectiveness

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**ABSTRACT**
Currently, Cancer is the second most leading cause of mortality in worldwide. Scientists and researchers recognised around 277 types of cancer, having a number of genetic mutations. This genetic mutation leads to abnormal cell propagation. According to International Agency for Research on Cancer there are abundant proof of carcinogenicity in human being like, human immunodeficiency virus,T-cell lymph trophic virus, hepatitis C virus, hepatitis B virus, human papilloma virus, human herpes virus andEpstein-Barr virus.These findings deliver new leads to drug design and drug-development of therapeutic approaches involving monoclonal antibodies or associated antibody drugs for malignancies treatment. This research article focus on the evolution and existing use of potential antibody drugs as effective ways of cancer treatment. Additionally, the development of potential antibody-drug conjugates with monoclonal antibodies.

**KEYWORDS-**Monoclonal antibody, Cancer, Chemotherapy,Tumor, Clinical trial.

**LIST OF ABBREVIATIONS**

| | |
|---|---|
| Conc. | Concentration |
| HER2 | Human epidermal growth factor receptor 2 |
| MoAb | Monoclonal antibody |
| Sub | Substance |
| Yr | Year |
| Gm | Gram |
| WHO | World Health Organization |
| Hrs | Hours |
| CHOP | Cyclophosphamide,hydroxycholide,oncovin and prednisolone |
| HCL | Hydrochloride |
| e.g. | For example |
| i.e. | That is |
| Str | Structure |
| MOA | Mechanism of Action |
| Mg | Milligram |
| IV | Intravenous |
| Min | Minute |
| Fig | Figure |
| IgG | Imunoglobulin |
| VA | Vincristine –dactinomycin |
| AE | Adverse effect |
| OS | Overall survival |
| PFS | Progression free survival |

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## I. INTRODUCTION

According to the World Health Organization cancer is a leading cause of death in world, accounting for nearly 10 million deaths or about one in six deaths. It is a generic term for large group of diseases that can affect any part of the body.In cancer cells divide continuously and excessively. Cell division is tightly regulated via multiple evolutionary-conserved cell cycle control mechanisms to ensure the production of two genetically identical cells. Cell cycle checkpoints operate as DNA surveillance mechanisms that prevent the accumulation and propagation of genetic errors during cell division [1]. Checkpoints can delay cell cycle progression or, in response to irreparable DNA damage, induce cell cycle exit or cell death. Cancer-associated mutations that perturb cell cycle control allow continuous cell division chiefly by compromising the ability of cells to exit the cell cycle. Continuous rounds of division however, creates increased reliance on other cell cycle control mechanisms to prevent catastrophic levels of damage and maintain viability. New detailed insights into cell cycle control mechanisms and their role in cancer reveal how these dependencies can be best exploited in cancer treatment.Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body [2]. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Changes are sometimes called "drivers" of cancer. Various factors can affecting cancer cells (Table 1).Cancer is a genetic disease that is caused by changes to genes that control the way our cells function, especially how they grow and divide. The genetic changes that contribute to cancer tend to affect three main types of genes- proto-oncogenes, tumor suppressor genes, and DNA repair genes [3].

Table 1- Factor effecting of Cancer

| | |
|---|---|
| External factor: Physical carcinogens | radiation, uv ,etc. |
| Chemical carcinogens | cigarette, pollution, alcohol Biological carcinogens |
| Biological carcinogens | viruses, bacteria, parasites |

- **Carcinoma-** Cancer begins in the skin or in tissues that line or cover internal organs.
- **Sarcoma**- Cancer begins in the connective or supportive tissues such as bone, cartilage, fat, muscle or blood vessels
- **Leukemia**-Cancer of the white blood cells. It starts in the tissues that make blood cells such as the bone marrow.
- **Lymphoma and myeloma**-Cancers begin in the cells of the immune system
- **Brain and spinal cord cancers**-These are known as central nervous system cancers Some common cancers are:
- Skin cancer.
- Lung cancer.
- Prostate cancer.
- Breast cancer.
- Colorectal cancer.
- Kidney (renal) cancer.
- Bladder cancer.
- Non-Hodgkin's lymphoma.

## II. TREATMENT OF CANCER (TABLE 2)

Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cells in human body. It is most often used to treat cancer, since cancer cells grow and multiply much more quickly than most cells in the body.It usually works by keeping the cancer cells from growing, dividing, and making more cells. Many different chemotherapy drugs are available.Chemotherapy may shrink your cancer or slow down its growth, which may help you live longer and help with your symptoms. For a small number of people with borderline respectable cancer, chemotherapy may shrink the cancer enough to make surgery to remove the cancer possible.Some other treatment for cancer are surgery, radiation therapy, Bone marrow transplant, immunotherapy, hormone

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therapy,cryoablation and targeted drug therapy (Fig 1). Classification of anti-cancer drug are in Fig 2.Side effects of chemotherapy drugs can be significant. Each drug has different side effects, and not every drug causes every side effect Nausea, Vomiting, Diarrhea, Hair loss, Loss of appetite, Fatigue, Fever, Mouth sores, Pain, Constipation, Easy bruising, Bleeding [4, 5].

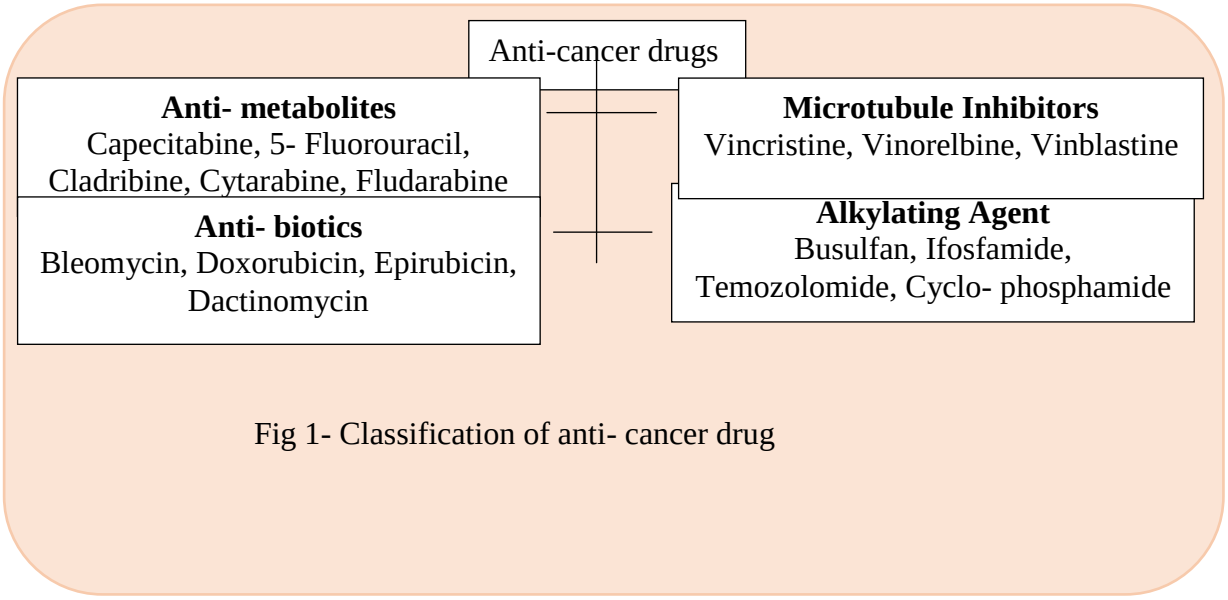


Fig 1- Classification of anti- cancer drug


Fig 2 - Treatment of cancer

## III. MATERIALS AND METHODS

### MONOCLONAL ANTIBODY IN CANCER TRATMENT

Monoclonal antibodies are laboratory-produced molecules engineered to serve as substitute antibodies that can restore, enhance, modify or mimic the immune system's attack on cells that aren't wanted, such as cancer cells. They are designed to function in different ways. A particular drug may actually function by more than one means. Monoclonal antibodies can also be modified further to be more effective [6]. One approach is to create bi-specific antibodies. Instead of attaching to just a cancer cell, bi-specific antibodies attach to a cancer cell and a type of immune cell called a T cell.Another approach is to attach a chemotherapy drug to a monoclonal antibody. These are called antibody-drug conjugates. “With this approach, chemotherapy is

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delivered to the cancer cells while avoiding healthy cells." An example is trastuzumab emtansine, which combines the HER2 monoclonal antibody trastuzumab with the chemotherapy drug emtansine. When trastuzumab connects with HER2 antigen expressed on the cancer cells, emtansine enters inside the cancer cell and kills it. Target cells of monoclonal antibody during cancer treatment and their mechanism of action are gather in table 2 [7, 8].

**Table 2- Monoclonal antibody in Cancer Treatment [5-8]**

| Name of monoclonal antibody | Antigenic target | MOA | Main cancer indication(s) |
|---|---|---|---|
| Rituximab | CD20 | ADCC, CMC, induces apoptosis | Non-Hodgkin's lymphoma |
| Alemtuzumab | CD52 | Induces apoptosis, CMC, ADCC | Chronic lymphocytic leukaemia |
| Tositumomab | CD20 | ADCC, induces apoptosis | Non-Hodgkin's lymphoma |
| Cetuximab [9] | EGFR | ADCC, inhibition of EGFR signaling | Colorectal cancer, head and neck cancer |
| Bevacizumab [10] | VEGF | Inhibition of VEGF signaling | Lung cancer, renal cancer, colorectal cancer, brain cancer, breast cancer |
| Panitumumab [9] | EGFR | Inhibition of EGFR signaling | Colorectal cancer |
| Catumaxomab [11] | EpCAM | ADCC, T-cell mediated lysis, phagocytosis via FcγR accessory cells | Malignant ascites in patients with EpCAM $^{+}$ve cancers |
| Ofatumumab [12] | CD20 | ADCC, CMC | Chronic lymphocytic leukaemia |
| Denosumab [13] | RANKL | Inhibition of RANKL signaling | Breast cancer, prostate cancer |
| Ipilimumab | CTLA-4 | - | Melanoma |
| Pertuzumab | HER2 | Inhibition of HER2 signalling | Breast cancer |

## IV. MATERIALS AND METHODS

**DRUG DETAILS**

**1. TRASTUZUMAB**
**Brand-** Eleftha (Intas), **Strength-** 440 mg, **Batch-** 26030095, **Expiry-** 8/23

**2. RITUXIMAB**
**Brand-** Mabtas (Intas), **Strength**-500mg/50ml, **Batch-** 12030333, **Expiry-** 3/25

**3. PACLITAXEL**
**Brand** - Mitotax (Dr.Reddy'S), **Strength-** 300mg/50ml, **Batch-** NN14824, **Expiry-** 10/23

**4. CYCLOPHOSPHAMIDE**
**Brand** - Endoxan(Zydus), **Strength**-1000mg, **Batch-** BUY1029, **Expiry-** 12/23

**5. VINCRISTINE**
**Brand-** Unicristin(united biotech), **Strength-** 1mg/1ml, **Batch-** UCIK1A4, **Expiry-** 10/23

**6. DOXORUBICIN**
**Brand-** Adrib(Adley), **Strength-**50mg/25ml, **Batch-** BDRI2204YB, **Expiry-** 02/24

**7. BEVACIZUMAB**
**Brand-** Bevacirel(Reliance), **Strength-** 400mg/4ml, **Batch-** BMV1B21008, **Expiry-** 10/24

**STUDY PARTICIPANTS**

Data of consenting cancer patients treated between November2021 and June 2022 were assessed between December 2021 and July 2022. We found 95 patients who had received both

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CHOP preparations and mAb at any time during their treatment (Table 3).

All patients had an ECOG performance status of 0 to 2, and no patient was ineligible based on comorbidities (ie, no evidence of refractory hypertension, internal bleeding, danger of perforation, or treatment with mAb within 4 weeks of surgery). Details of treatment with mAb or VA preparations, including dates, doses, routes of administration, concomitant medications, and associated AEs, along with demographic, diagnosis, and disease progression data were extracted. Patients were assigned to 1 or more of 3 treatment groups based on documented timing of treatment with mAb and VA preparations.

Note that it was possible for patients to be assigned to different treatment groups at different times throughout their treatment. If a CHOP preparation and mAb therapy were received by a patient on the same day, the patient was described as receiving combined therapy. A patient was described as receiving CHOP therapy if they received one or more CHOP infusions, where they did not receive mAb for at least 1 month either side of the VA application. Likewise, mAb therapy refers to a patient not receiving a VA infusion for at least 1 month either side of treatment with mAb. A 1-month washout period was specified to eliminate any carryover effects and to avoid confusion over the causality of delayed or enduring AEs. Because of the complex nature of cancer treatment, some patients in all 3 groups received concomitant chemotherapy or supportive therapies (eg, antiemetic or pain medication).

Patients were excluded from the study if they did not meet the criteria for at least 1 of the 3 treatment groups or if they had missing or invalid information regarding dates of treatment with mAb and CHOP preparations, specific drug names, concomitant medications, database identification number, date of birth, gender, date of diagnosis, or ICD-10 code. Although data for all routes of administration and types of CHOP preparations and targeted therapies were collected, our analysis was limited to intravenously administered CHOP preparations and intravenously administered mAb.

**Table 3- Characteristics of participants**

| **Characteristic** | **n (%)** |
|---|---|
| Middle Age (range) | 34 years old (18-50) |
| Gender | |
| Male | 5 |
| Female | 6 |
| Clinical staging | |
| II | 2 |
| IV | 5 |
| International prognostic index | |
| 0-1 | 1 (14.3) |
| 2 | 4 (57.1) |
| 3 | 2 (28.6) |
| Bulky disease (longest diameter ≥ 7.5 cm by CT scan) | |
| Mediastinum | 5 (71.4) |

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| Table 3- Characteristics of participants | |
|---|---|
| **Characteristic** | **n (%)** |
| Abdominal cavity | 2 (28.6) |
| B symptoms | |
| Weight lose | 2 (28.6) |
| Fever | 1 (14.3) |
| Laboratory abnormalities | |
| LDH ( >240 IU/L) | 6 (85.7) |
| C-reactive protein increased | 6 (85.7) |

## V. RESULT AND DISCUSSION

### TREATMENT OF CHOP+RITUXIMAB

Patients treated with CHOP received the combination of 750 mg of cyclophosphamide per square meter of body-surface area on day 1; 50 mg of doxorubicin per square meter on day 1; 1.4 mg of vincristine per square meter, up to a maximal dose of 2 mg, on day 1; and 40 mg of prednisone per square meter per day for five days. They were treated every three weeks for eight cycles of CHOP. Patients treated with CHOP plus rituximab also received rituximab, at a dose of 375 mg per square meter, on day 1 of each of the eight cycles of CHOP. The rituximab infusion was interrupted in the event of fever, chills, edema, congestion of the head and neck mucosa, hypotension, or any other serious adverse event and was resumed when such an event was no longer occurring. No radiation therapy was scheduled or recommended at the end of treatment.

Patients who had grade 4 (severe) neutropenia or febrile neutropenia after any cycle of chemotherapy were given granulocyte colony-stimulating factor. If grade 4 neutropenia persisted during the next cycle, the doses of cyclophosphamide and doxorubicin were decreased by 50 percent. For patients with grade 3 (moderate) or 4 thrombocytopenia, the doses of cyclophosphamide and doxorubicin were decreased by 50 percent. If the neutrophil count was lower than 1500 per cubic millimeter or the platelet count was lower than 100,000 per cubic millimeter before a scheduled cycle, the cycle was delayed for up to two weeks, and then treatment was stopped. The doses of rituximab were not modified, but rituximab was discontinued when CHOP was stopped. Treatment was stopped if lymphoma progressed or the patient declined to continue or at the discretion of the investigator in cases of intercurrent illness or adverse events.

### RESPONSE TO TREATMENT AND ADVERSE EVENTS

Tumor responses were assessed after eight cycles of chemotherapy or at the end of treatment and were classified as complete response, unconfirmed complete response, partial response, stable disease, or progressive disease according to the International Workshop criteria. Complete response was defined as the disappearance of all lesions and of radiologic or biologic abnormalities observed at diagnosis and the absence of new lesions. An unconfirmed complete response was defined as a complete response with the persistence of some radiologic abnormalities, which had to have regressed in size by at least 75 percent. Partial response was defined as the regression of all measurable lesions by more than 50 percent, the disappearance of nonmeasurable lesions, and the absence of new lesions. Stable disease was defined as a regression of any measurable lesion by 50 percent or less or no change for the nonmeasurable lesions, but without growth of existing lesions or the appearance of new lesions. Progressive disease was defined as the appearance of a new lesion, any growth of the initial lesion by more than 25 percent, or growth of any measurable lesion that had regressed during treatment by more than 50 percent from its smallest dimensions.

All adverse events reported by the patient or observed by the investigator were collected from the case-report form in predefined categories. An adverse event was defined as any adverse change from the patient's base-line condition, whether it

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was considered related to treatment or not. Each event was graded according to the National Cancer Institute Common Toxicity Criteria grading system. All grade 3 and 4 events plus grade 2 infection were recorded in detail. Grade 1 and 2 adverse events were not extensively described.

**TREATMENT OF CHOP+BEVACIZUMAB**

Patients were to receive 6–8 cycles of ACHOP followed by 8 cycles of maintenance bevacizumab (MA), as outlined below. Bevacizumab 15 mg/kg was administered on day 1 over 90 min ($1^{st}$ cycle), 60 min ($2^{nd}$ cycle) and 30 min for the subsequent cycles. CHOP (cyclophosphamide750 mg/m2; doxorubicin 50 $mg/m^2$; vincristine 1.4 $mg/m^2$ (max 2 mg); prednisone 100 mg daily on d 1–5) was administered on day 1 of a 21 day cycle. Radiographic response was assessed after cycles 3, 6, and 8 of ACHOP and after cycle 8 of MA. Patients received 6 cycles of ACHOP if they achieved a CR after 3 cycles, 8 cycles if they achieved a PR after 3 cycles. Non responders were removed from the study. ACHOP responders received maintenance bevacizumab 15 mg/kg every 21 days for 8 cycles. Response criteria were based on the International Workshop to Standardize Criteria for Non-Hodgkin's Lymphoma [14]. All patients, regardless of eligibility status, were followed for development of secondary cancers.

**RESPONSE TO TREATMENT**

The primary endpoint of this study was the 1 year PFS rate, which was defined as the proportion of patients who were progression free and alive at 1 year from registration. A 1-year PFS rate of 30% was considered non-promising and 50% was considered promising. A one-stage design was used because of the limited treatment options available for these patients. The study was to accrue 43 patients in order to have 39 eligible. According to the above assumptions, ACHOP would be considered promising for further study if 16 of 39 patients were progression free at 1-yr.

The probability of concluding that the regimen is effective is 0.90 assuming a true underlying 1 year PFS rate of 50% and is 0.09 if the true underlying 1 year PFS rate is 30%.

Baseline patient characteristics were listed with descriptive statistics (mean, median, percentage). PFS was defined as the time from registration to the progression, relapse or death. Overall survival (OS) was measured from registration to death of any cause. The response rate was reported for overall response and CR/CRu with 95% confidence intervals (CI). Comparisons between histology groups were conducted among eligible patients with a log-rank test. Toxicity and secondary primary cancers were evaluated for all patients regardless of eligibility. Due to poor accrual the study was amended in 2008 to allow patients who had received one prior cycle of CHOP to enroll.

**Treatment Of Trastuzumab+Doxorubicin And Paclitaxel**

**PHASE1**: Patients receive doxorubicin hydrochloride IV and cyclophosphamide IV over 20-30 minutes on day 1. Treatment repeats every 3 weeks for 4 courses. Patients then receive paclitaxel IV over 1 hour beginning on day 1 of week 13 and continuing weekly for 12 courses in the absence of disease progression or unacceptable toxicity. Within 5 weeks after completion of paclitaxel, patients may undergo radiotherapy. All postmenopausal ER- or PR-positive patients receive oral tamoxifen or an aromatase inhibitor once daily for 5 years beginning no later than 5 weeks after the last dose of paclitaxel. Patients may also receive an aromatase inhibitor once daily for 5 years after 5 years of daily tamoxifen. Patients who receive tamoxifen once daily for less than 4.5 years may receive an aromatase inhibitor daily until they have received a total of 5 years

**PHASE2**: Patients receive doxorubicin hydrochloride, cyclophosphamide, and paclitaxel as in Phase I. Patients then receive trastuzumab (Herceptin®) IV over 30-90 minutes beginning on day 1 of week 25 and continuing weekly for 52 courses in the absence of disease progression or unacceptable toxicity. Within 5 weeks after completion of paclitaxel, patients may undergo radiotherapy. All postmenopausal ER- or PR-positive patients receive oral tamoxifen or an aromatase inhibitor once daily for 5 years beginning no later than 5 weeks after the last dose of paclitaxel. Patients may also receive an aromatase inhibitor once daily for 5 years after 5 years of daily tamoxifen. Patients who receive tamoxifen once daily for less than 4.5 years may receive an aromatase inhibitor daily until they have received a total of 5 years of adjuvant hormonal therapy adjuvant hormonal therapy.

**PHASE3**: Patients receive doxorubicin hydrochloride and cyclophosphamide as in Phase I. Patients then receive paclitaxel IV over 1 hour and trastuzumab IV over 30-90 minutes beginning on day 1 of week 13 and continuing weekly for 12 courses. Patients then receive trastuzumab IV over 30 minutes beginning on day 1 of week 25 and continuing weekly for 40 courses in the absence of disease progression or unacceptable toxicity.

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Within 5 weeks after completion of paclitaxel, patients may undergo radiotherapy. All postmenopausal ER- or PR-positive patients receive oral tamoxifen or an aromatase inhibitor once daily for 5 years beginning no later than 5 weeks after the last dose of paclitaxel. Patients may also receive an aromatase inhibitor once daily for 5 years after 5 years of daily tamoxifen. Patients who receive tamoxifen once daily for less than 4.5 years may receive an aromatase inhibitor daily until they have received a total of 5 years of adjuvant hormonal therapy.

**Rituximab+CHOP(Cyclophosphamide,doxorubicin,vincristine,prednisolone) for treatment of B-cell lymphoma (Table 4)**

Three randomized clinical trials (RCT) and one population-based registry trial have shown a significant improvement in cure rate when rituximab is added to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP, R-CHOP regimen) or CHOP-like chemotherapy [15-18]. Two of the RCTs (Group d'Etude des Lymphomas de l'Adulte [GELA] and E4494) were conducted in patients older than 60 years of age with advanced-stage diffuse large B-cell lymphoma (DLBCL). In an update of the original GELA report, the 5-year overall survival (OS) rate was 58% in patients who received rituximab plus CHOP (R-CHOP) compared to 45% (P <.007) in those receiving CHOP[19]. The US intergroup trial, E4494, confirmed these results and demonstrated a 3-year OS of 67% in R-CHOP patients compared to 58% (P = .05) in CHOP patients [16- 17]. No additional benefit for maintenance rituximab after R-CHOP therapy was observed.

The third RCT was conducted in patients under the age of 60 who had one or fewer adverse prognostic factors [17]. The chemotherapy was either CHOP or cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP). The estimated 3-year OS was 93% in the rituximab–chemotherapy patients compared to 84% (P = .0001) in the chemotherapy-alone patients. Population-based analysis, performed in the province of British Columbia, revealed a marked improvement in 2-year OS after the introduction of R-CHOP therapy: 78% versus 52% (P <.0001). In summary, these studies show that the addition of rituximab to CHOP chemotherapy improved the OS in the three RCTs by 9% to 13% in absolute terms.

Since OS can be influenced by factors unrelated to the treatment under investigation (such as the effectiveness of salvage regimens), progression-free survival (PFS) is considered a better end point for evaluating the efficacy of a regimen. When analyzed by PFS, the impact of rituximab is even more striking, with absolute improvements ranging from 13% to 24%.

Table 4- Trials Comparing Rituximab Plus CHOP to CHOP for Patients

| Study Group | Study Type | N | Follow-up | PFS | | OS | |
|---|---|---|---|---|---|---|---|
| | | | | R-CHOP | CHOP | R-CHOP | CHOP |
| BCCA [16] | Registry | 292 | 2yr | 68% | 51% | 78% | 52% |
| US intergroup [17] | RCT | 632 | 3yr | 52% | 39% | 67% | 58% |
| International [18] | RCT | 824 | 3yr | 79% | 59% | 93% | 84% |
| GELA [19] | RCT | 399 | 5yr | 54% | 30% | 58% | 45% |

**Bevacizumab+CHOP for treatment of anaplastic large cell lymphoma and T-cell lymphoma (Fig 3) (Table 5)**

Patients were to receive 6–8 cycles of ACHOP followed by 8 cycles of maintenance bevacizumab (MA), as outlined below. Bevacizumab 15 mg/kg was administered on day 1 over 90 min (1st cycle), 60 min (2nd cycle) and 30 min for the subsequent cycles. CHOP (cyclophosphamide750 mg/m2; doxorubicin 50 mg/m$^2$; vincristine 1.4 mg/m$^2$ (max 2 mg); prednisone 100 mg daily on d 1–5) was administered on day 1 of a 21 day cycle. Radiographic response was assessed after cycles 3, 6, and 8 of ACHOP and after cycle 8 of MA.

Patients received 6 cycles of ACHOP if they achieved a CR after 3 cycles, 8 cycles if they achieved a PR after 3 cycles. Non responders were removed from the study. ACHOP responders received maintenance bevacizumab 15 mg/kg every 21 days for 8 cycles. Response criteria were based on the International Workshop to Standardize Criteria for Non-Hodgkin's Lymphoma [14]. All patients, regardless of eligibility status, were followed for development of secondary cancers.

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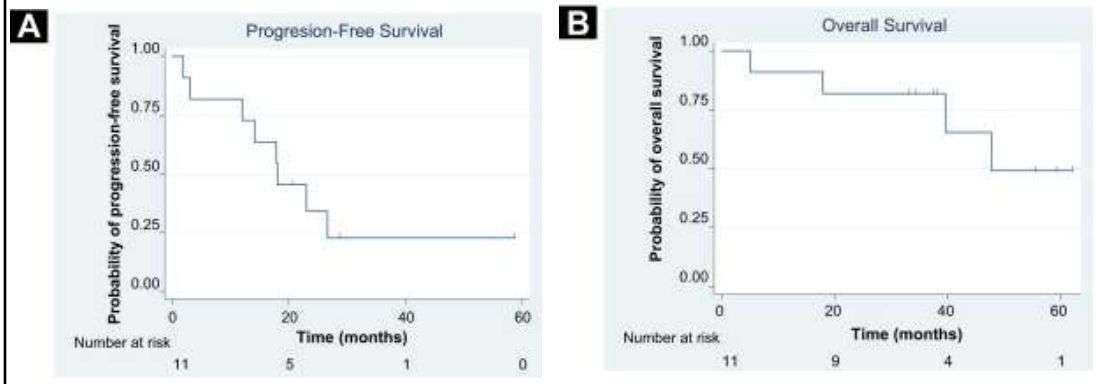


Fig 3- Graphical representation of with or without bevacizumab

**Table 5: Safety and efficacy of bevacizumab combined with R-CHOP regimen in seven patients with untreated diffuse large B-cell lymphoma**

| No. | 1st assessment after cycles 1-4 | 2nd assessment after cycles 5-8 | Bevacizumab maintaining times | Radiotherapy (Gy) | 3rd assessment |
|---|---|---|---|---|---|
| 1 | CRu | CR | 0 | 40.6 | CR |
| 2 | CRu | CR | 7 | 40 | CR |
| 3 | CRu | CR | 7 | 36 | CR |
| 4 | PD | NA[a] | 0 | No | NA |
| 5 | CRu | CR | 6 | 42 | CR |
| 6 | CRu | CR | 4 | 42 | CR |
| 7 | PR | Cru | 0 | 50 | CR |

CR: complete remission, CRu: complete remission unconfirmed, PR: partial remission, PD: progressive disease. NA, not assessed. [a]Patient No. 4 withdrew after the first assessment.

**Transtuzumab + doxorubicin,paclitaxel and cyclophosphamide in treatment of breast cancer (Fig 4)**

AT was administered as an i.v. bolus of 60 mg/m$^2$ doxorubicin followed 15 min later by 150 mg/m$^2$ paclitaxel by infusion over 3 h. Both drugs were administered every 3 weeks for three cycles, followed by nine cycles of weekly paclitaxel (80 mg/m$^2$) by infusion over 1 h. Patients received a paclitaxel premedication of i.v. dexamethasone (10 mg), i.v. diphenhydramine (50 mg), and i.v. cimetidine (300 mg) 30 min before administration of any active drug.

Trastuzumab was administered as a 4 mg/kg loading dose followed by 2 mg/kg weekly. Treatment was initiated with the AT regimen in cohort 1: the first dose was administered as a 90-min infusion 24 h after AT in cycle 1; in cycles 2 and 3, trastuzumab was administered as a 30-min infusion followed by doxorubicin 15 min later and

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paclitaxel 15 min after the end of the doxorubicin infusion; in cycles 4–12, trastuzumab infusion was followed immediately by paclitaxel infusion. In cohort 2, trastuzumab was initiated with cycle 4 (first cycle of paclitaxel alone). Trastuzumab was administered until disease progression or 52 weeks of therapy but could be continued beyond 1 year until disease progression at the discretion of the investigator. Patients were followed for another 36 months.

Dose adjustment criteria for doxorubicin and paclitaxel were predefined.

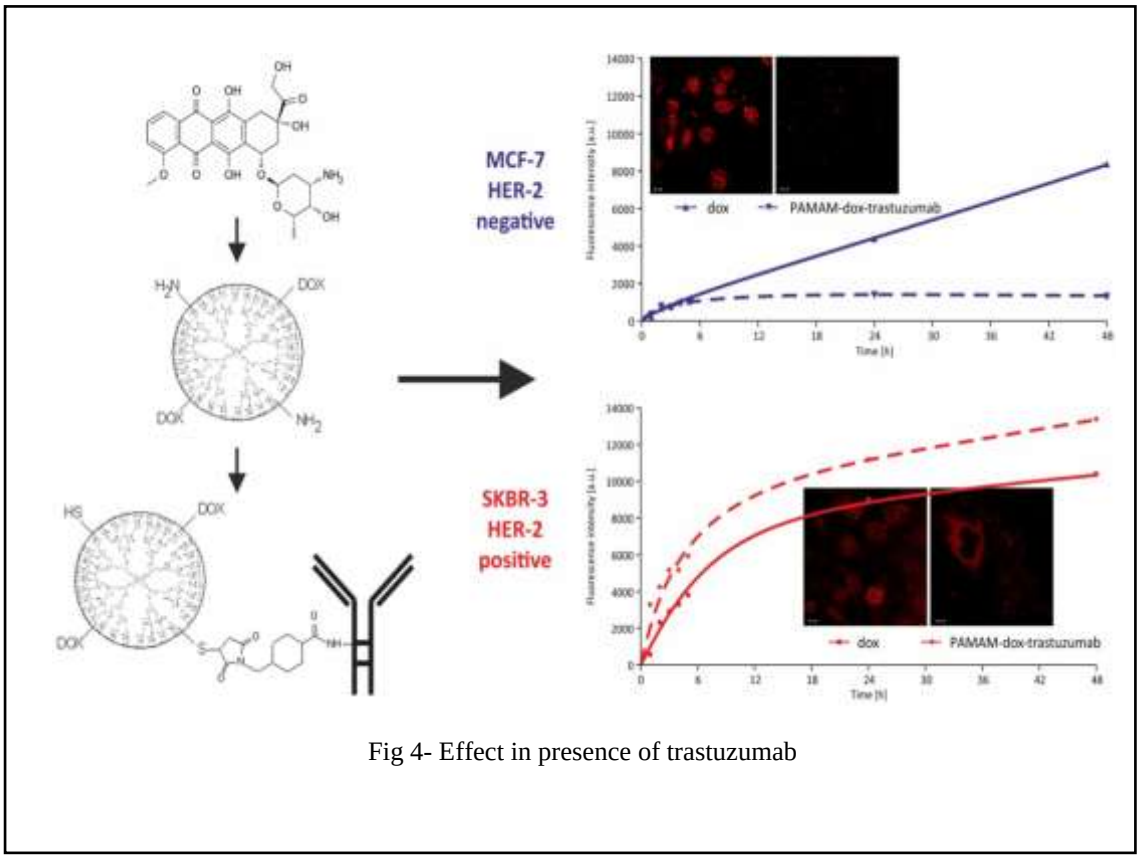


Fig 4- Effect in presence of trastuzumab

The role of angiogenesis in PTCL provided the rationale for evaluating bevacizumab in combination with CHOP chemotherapy. While the response rate was 90% (CR 49%), the 3-year PFS and OS were 16% and 37%, respectively. In addition, the ACHOP combination was associated with excess cardiac toxicity as previously reported [20]. Smaller experiences with ACHOP in combination with rituximab in DLBCL suggested that the combination was well tolerated and were not associated with changes in the pharmacokinetics of rituximab and bevacizumab [21].

However, two recent larger studies also reported significantly increased cardiac toxicity leading to premature closure of the MAIN trial [22, 23]. Our results are not better than those achieved with CHOP alone as suggested in a meta-analysis of 31 studies of patients with PTCL treated with CHOP (n=2912) excluding ALCL, which reported an estimated 5-yr OS of 38.5% (95%CI 35.5–41.6) [24]. Our results are also inferior to contemporary anthracycline-based therapies which have incorporated etoposide.

The German Study Lymphoma Group reported the outcome of 265 patients with PTCL, excluding ALK-positive ALCL, with a 3-yr OS for patients treated with CHOEP (CHOP with etoposide) of 53.9–67.5%, depending on the T-cell lymphoma subtypes [25]. A trend to improved EFS was seen in the ALK negative subgroup mainlyinin patients who were < 60 years old and had a normal LDH. In another study reported by Niitsu and colleagues, 84 PTCL patients were treated with the CyclOBEAP (cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin, prednisolone) regimen with a 5-year OS of 72% and a PFS of 61% [26]. The 5-yr OS was 93% for patients with

ALK positive ALCL compared to 74% and 63% for AITL and PTCL-NOS, respectively.

When evaluating responses according to histology, patients with ALK-negative ALCL had the best outcome, which is consistent with all other reports [25, 26]. PTCL-NOS patients had a worse prognosis than patients with AITL. Eight of 17 (47%) patients with AITL continued on to MA, as compared to only 27% of patients with PTCL-NOS. Interestingly, the majority of AITL have strong VEGF expression, both in the lymphoma cells and the benign macrophage population [27].

In addition, the AITL express strong hypoxia inducible factor-1α (HIF1-α), which could generate hypoxic conditions and further stimulate tumor vasculogenesis through an upregulation of VEGF [27]. Therefore, one can speculate that there might be a role for bevacizumab in AITL incorporating non-anthracycline based chemotherapy.

Results from our observational study found a reduced incidence of AEs following exposure to mAb with CHOP compared to mAb without CHOP and no unexpected AEs. These results are in line with the prediction, based on theoretical considerations, of no significant interactions occurring between CHOP and mAb. Future research should focus on investigating combined use of CHOP with specific mAb, in larger and more homogeneous patient groups in order to further elucidate the safety and effectiveness of this approach. Overall, the current results suggest that combined therapy with CHOP and mAb is safe. It is important to acknowledge a number of limitations of our study. First, of the 95 medical records initially reviewed, 36 patients were excluded for not satisfying the 1-month washout period. Specification of a washout period was important for this study because many of the observed AEs can have a delayed onset or be long-lasting (eg, leucopenia, acneiform rash). However, this resulted in small sample sizes for both the individual therapy groups and a consequent decrease in statistical power. Because of the retrospective and nonrandomized nature of this study, patient characteristics and diagnoses were not balanced across treatment groups. Factors considered as potential confounders (ie, age, gender, UICC stage, concomitant chemotherapy, and supportive therapies) were included in multivariable analysis; however, it is likely that unmeasured confounders, such as previous surgery or unmeasured comorbidity, exist. Furthermore, although mechanistically it would make sense to assess different mAb separately and to also consider the role of therapy dose, small sample sizes and heterogeneity prevented us from doing this.

Overall, although our results must be interpreted with care, they provide a first picture of the current application and toxicity profile of a combination strategy involving CHOP and mAb. Furthermore, to our knowledge, this is the first attempt to investigate the safety of such a strategy.

## REFERENCE

[1]. Mohamed, A.; Amer, E.; Eldin, N.; Hossam, M.; Elmasry, N.; Adnan, G.T. The impact of data processing and ensemble on breast cancer detection using deep learning. J. comput. commun. 2022, 27-37.

[2]. Naik, A.; Decock, J. Targeting of lactate dehydrogenase C dysregulates the cell cycle and sensitizes breast cancer cells to DNA damage response targeted therapy. Mol. Oncol. 2022, 885-903.

[3]. Fonseca, V.B.; da. Silva. Sopezki. M.; Yunes, J.S.; Zanette, J. Effect of a toxic Microcystis aeruginosa lysate on the mRNA expression of proto-oncogenes and tumor suppressor genes in zebrafish. Ecotoxicol. Environ. Saf. 2018, 161:729-34.

[4]. Nastasi, N.; Bruno, G.; Favre, C.; Calvani, M. Role of β3-Adrenergic Receptor in Bone Marrow Transplant as Therapeutical Support in Cancer. Front. Oncol. 2022, 12:889634.

[5]. Kruszewska, J.; Krzywdzińska, S.; Grymowicz, M.; Smolarczyk, R.; Meczekalski, B. POI after chemotherapy and bone marrow transplant may mimic disorders of sexual differentiation–a case report of a patient with primary amenorrhea and 46, XY karyotype. Gynecol. Endocrinol. 2020, 36(6):564-6.

[6]. Zahavi, D.; Weiner, L. Monoclonal antibodies in cancer therapy. Antibodies. 2020, 20;9(3):34.

[7]. Nandy, S.K; Thakur, S. Molecular Signaling Pathways Of Several Cancers And Natural Compounds Prevent Cancer With Molecular Targets.Int. Res. J. Mod. Eng. Technol. 2021.

[8]. Marcinkowska, M.; Stanczyk, M.; Janaszewska, A.; Sobierajska, E.; Chworos, A.; Klajnert-Maculewicz, B. Multicomponent conjugates of anticancer drugs and monoclonal antibody with PAMAM dendrimers to increase efficacy

of HER-2 positive breast cancer therapy. Pharm. Res. 2019, 36(11):1-7.

[9]. Bardelli, A.; Siena, S. Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. J. Clin. Oncol. 2010, 28(7):1254-61.

[10]. Ferrara, N.; Hillan, K.J.; Gerber, H.P.; Novotny, W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat. Rev. Drug Discov 2004, 3(5):391-400.

[11]. Seimetz, D.; Lindhofer, H.; Bokemeyer, C. Development and approval of the trifunctional antibody catumaxomab (anti-EpCAM× anti-CD3) as a targeted cancer immunotherapy. Cancer Treat. Rev. 2010, 36(6):458-67.

[12]. Cheson, B.D. Ofatumumab, a novel anti-CD20 monoclonal antibody for the treatment of B-cell malignancies. J. Clin. Oncol 2010, 28(21):3525-30.

[13]. Smith, M.R.; Saad, F.; Oudard, S.; Shore, N.; Fizazi, K.; Sieber, P.; Tombal, B.; Damiao, R.; Marx, G.; Miller, K.; Van, Veldhuizen. P. Denosumab and bone metastasis–free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J. Clin. Oncol. 2013, 31(30):3800.

[14]. Ober, R. J.; Radu, C. G.; Ghetie, V; Ward, E. S. Differences in promiscuity for antibody-FcRn interactions across species: implications for therapeutic antibodies. Int. Immunol. 2001, 13, 1551–1559 (2).

[15]. Zou, W. Regulatory T cells, tumors immunity and immunotherapy. Nature Rev. Immunol. 2006, 6, 295–307.

[16]. Pardoll, D. Does the immune system see tumors as foreign or self? Annu. Rev. Immunol. 2003, 21, 807–839.

[17]. Shablak, A. Conn, "A case of fatal cetuximab-induced interstitial lung disease during the first weeks of treatment. Target. Oncol. 2014, vol. 9, no. 2, pp. 177–180.

[18]. Cunningham, D.; Humblet, Y.; Siena, S.; Khayat, D.; Bleiberg, H.; Santoro, A.; Bets, D.; Mueser, M.; Harstrick, A.; Verslype, C.; Chau, I. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004, 351(4):337-45.

[19]. Kohler, G.; Milstein, C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975, 256:495–497.

[20]. Shawler, D. L.; Bartholomew, R. M.; Smith, L. M.; Dillman, R. O. Human immune response to multiple injections of murine monoclonal IgG. J. Immunol. 1985, 135, 1530–1535.

[21]. Kipps, T.J.; Parham, P.; Punt, J.; Herzenberg, L.A. Importance of immunoglobulin isotype in human antibody-dependent, cell-mediated cytotoxicity directed by murine monoclonal antibodies. J. Exp. Med. 1985, 161(1):1-7.

[22]. Presta, L.G. Engineering of therapeutic antibodies to minimize immunogenicity and optimize function. Adv. Drug Deliv. Rev. 2006, 58(5-6):640-56.

[23]. Morrison, S.L.; Johnson, M.J.; Herzenberg, L.A.; Oi, V.T. Chimeric human antibody molecules: mouse antigen-binding domains with human constant region domains. Proc. Natl. Acad. Sci. 1984, 81(21):6851-5.

[24]. Jones, P.T.; Dear, P.H.; Foote, J.; Neuberger, M.S.; Winter, G. Replacing the complementarity-determining regions in a human antibody with those from a mouse. Nature. 198, 321(6069):522-5.

[25]. De, Saint. Basile. G.; Menasche, G.; Fischer, A. Molecular mechanisms of biogenesis and exocytosis of cytotoxic granules. Nat. Rev. Immunol. 2010, 10(8):568-79.

[26]. Nimmerjahn, F.; Ravetch, J.V. Analyzing antibody–Fc-receptor interactions. Innate Immun 2008, 151-162.

[27]. Eischen, C.M.; Leibson, P.J. Role for NK-Cell-Associated Fas Ligand in CellMediated Cytotoxicity and Apoptosis. Res. Immunol. 1997, 148:164–169.