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For your patients with very low T-score (e.g. less than −3.0) or with other serious risk factors, start with EVENITY® followed by PROLIA® to help build and protect her bones.¹

For your patients with history of fragility fracture or low T-score (e.g. less than −2.5) with other risk factors, start with PROLIA® to help strengthen her bones.²³

---

¹ For your patients with very low T-score (e.g. less than −3.0) or with other serious risk factors, start with EVENITY® followed by PROLIA® to help build and protect her bones.

² For your patients with history of fragility fracture or low T-score (e.g. less than −2.5) with other risk factors, start with PROLIA® to help strengthen her bones.

---

**Very High Fracture Risk**

< −3.0 T-score²

of recent fracture or multiple fractures

fracture while on medication

**High Fracture Risk**

≤ −2.5 T-score³

of history of fragility fracture of the hip/spine
MEET HER THERE
other serious risk factors, start with
For your patients with
very low T-score
to help build and protect her bones.1

have been reported in patients receiving Prolia. Patients should be advised to report new or unusual thigh, hip, or groin pain.

Mineral Metabolism:
Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating...

INDICATIONS
are back pain and constipation.

ARCH=Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BMD=Bone mineral density.

or other clinically significant allergic reaction occurs, appropriate therapy should be initiated and use of romosozumab should be discontinued.

if the prescriber and patient agree that the benefit outweighs the risk. If a patient experiences a myocardial infarction or stroke during therapy, treatment with romosozumab should be discontinued.

Hypocalcemia and pregnancy, as well
The

PEDIATRIC, GERIATRIC AND RENAL IMPAIRMENT

CONTRAINDICATIONS

Hypersensitivity to the active substance(s) or to any of the

PREGNANCY

Scanned sectional radiographs of bone showing

PREGNANCY AND LACTATION

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium-free.

Pregnancy:

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Myocardial infarction and stroke:

Recent fracture

Fracture Risk†

Very High

Myocardial infarction;

Atypical low-energy or low trauma fracture of the femoral shaft, which can occur spontaneously, has been reported rarely in patients receiving romosozumab. Any patient who presents with new

Atypical low-energy or low trauma fracture of the shaft

Any

The

CONSIDERATIONS

Atypical low-energy or low trauma fractures of the femoral shaft, which can occur spontaneously, have been reported rarely in patients receiving romosozumab. These fractures can be serious and may involve surgery to stabilize the bone.

In clinical trials treatment with

The

The

INDICATIONS

are back pain and constipation.

ARCH=Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; BMD=Bone mineral density.

The

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The Cover Shot

A Sunset Scene in Hong Kong.

In the months of October and November, numerous locals and visitors gather at Tsuen Wan West seaside to watch the awesome scenes of sunset over Ting Kau Bridge. In fine weather, the golden sun sets behind the bridge creating intriguing silhouettes of the bridge cables, traffic vehicles, and incoming flights intersecting its set path.

This cover photo captured an image of the glamorous setting sun, silhouettes of heavy traffic and an inbound flight which together conjured up a gratifying scene testifying to the return of prosperity to Hong Kong after three long years of hardship under the Covid pandemic.

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IKEMA²: SARCLISA® + Kd vs Kd (N=302)

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HR=0.58
(95.4% CI: 0.42-0.79)

ICARIA²: SARCLISA® + Pd vs Pd (N=307)
mPFS 11.53 mo
vs 6.47 mo with Pd alone
HR=0.596
(95% CI: 0.44-0.81; P=0.001)

Most common adverse reactions², ⁴

- In IKEMA, the most frequent adverse reactions (≥20%) were neutropenia (47%), infusion reactions (38%), pneumonia (31%), upper respiratory tract infection (28%), diarrhea (26%), and bronchitis (24%)

- In ICARIA, the most frequent adverse reactions (≥20%) were infusion reactions (46%), hypertension (37%), diarrhea (36%), upper respiratory tract infection (36%), pneumonia (29%), fatigue (28%), dyspnoea (28%), insomnia (24%), bronchitis (23%), and back pain (22%)

SARCLISA® is indicated:

- In combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy

- In combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

*Assessment by masked independent review committee (IRC)


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 societal benefit of therapy for the wider. Afterwards, substances could be used during breast-feeding if clinically needed. Inducible effects: oxaliplatin in combination with gemcitabine and dexamethasone. Most common adverse reactions reported: leukemia, upper respiratory tract infection, dyspepsia, fatigue, feeling of infection, for other tolerable effects, please refer to the full prescribing information. Preparation the provision of the infusion solution must be done under aseptic conditions. Local, regional, or systemic anesthesia for the local area of the primary lesion. Reference. The drug is used for treatment of solid tumors, including advanced ovarian cancer, endometrial cancer, non-small-cell lung cancer, and other breast cancer patients. The drug is an injectable formulation and is usually administered intravenously. The recommended dose is 25 mg/m² of body surface area (BSA) given every 3 weeks. The drug is a small molecule inhibitor that targets the KDR (VEGFR-2) and FLT-3 receptors, which are involved in the proliferation and survival of cancer cells. The drug is approved for use in combination with capecitabine for the first-line treatment of patients with metastatic breast cancer. The drug is a monoclonal antibody that binds to the PD-1 receptor on T cells, preventing it from being activated by the PD-L1 ligand on cancer cells. The drug is approved for the treatment of patients with advanced or metastatic melanoma who have previously received ipilimumab treatment.
Therapeutic approaches for cancers have evolved in the past two decades, and many novel anti-cancer treatment modalities are highly effective and have excellent safety profiles. Among them, immunotherapy is increasingly being used for the treatment of many different cancers, including haematological malignancies. The term “cancer immunotherapy” can be broadly defined as treatment that harnesses the anti-cancer activities of the immune system to kill neoplastic cells. In this issue of the Hong Kong Medical Diary, various forms of immunotherapy for the treatment of haematological malignancies are discussed.

By unleashing the inhibition exerted by neoplastic cells and tumour micro-environment on the body’s immune surveillance, immune checkpoint blockade therapy restores the anti-cancer activities of patients’ own T-cells. In his article, Prof Kwong Yok-lam has discussed the use of immune checkpoint blockade therapies in haematological malignancies, including classical Hodgkin lymphoma and NK/T-cell lymphoma.

Monoclonal antibodies targeting specific cancer surface antigens are incorporated into the therapeutic regimens for different haematological malignancies. The anti-CD20 antibody rituximab is the prototype and is used for the treatment of almost all B-cell neoplasms. In addition to “naked” monoclonal antibodies, antibody-drug conjugates and bispecific antibody T-cell engagers are armamentaria used to improve the treatment outcomes of patients. Dr Carol Cheung has given an overview of the use of these agents in haematological malignancies, and Dr Karen Tang has discussed in detail the applications of monoclonal antibodies in the treatment of multiple myeloma.

Allogeneic haematopoietic stem cell transplantation (HSCT) has been used for more than decades in the management of leukaemias. With its associated graft versus tumour effect, HSCT represents a form of adoptive cellular immunotherapy. Dr Joyce Sim and Dr Garret Leung have reviewed the recent advances in allogeneic HSCT focusing on haploidentical HSCT. A more target-specific adoptive cellular immunotherapy is chimeric antigen receptor (CAR)-T cell therapy that harnesses the anti-cancer activities of patients’ own T-cells. In his article, Prof Kwong Yok-lam has discussed the use of CAR-T cell therapy and discussed its use in lymphoid neoplasms.

In Haematology and Oncology, we often talk about precision medicine. For good watches, precision is also the key! In the Lifestyle of this Issue, Dr Herman Liu would share with the readers his extraordinary collection of wrist watches, showcasing a number of beautiful and highly sought-after timepieces.
Immune Checkpoint Blockade in the Management of Haematological Malignancies

Prof KWONG Yok-lam

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Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

INTRODUCTION

Immune checkpoints provide a regulatory mechanism to control the activation of effector cells in the immune response. Generally, these immune checkpoints are represented by receptors on effector cells, which on ligation with their cognate ligands, transduce signals that inhibit cellular functions. Immune checkpoints play important roles in maintaining a balance in immune reactions. Malignant cells may hijack these regulatory pathways by over-expressing the cognate ligands of immune checkpoint receptors. Hence, although immune effector cells may recognise and target neoantigens on these malignant cells, ligation of the immune checkpoints with their cognate ligands expressed on malignant cells result in inhibition of the immune response. This immune escape leads to suppressed immunosurveillance, enhancing the proliferation of malignant cells. Blockade of immune checkpoint receptors or their cognate ligands restores immunoreactivity of effector cells, thus constituting an innovative approach to cancer immunotherapy.

THE PD1-PDL1/L2 PATHWAY

The programmed cell death protein 1 (PD1) is an immune checkpoint receptor expressed on activated CD4+ and CD8+ T-cells, B-cells, natural killer (NK) cells, macrophages and dendritic cells. It binds to two ligands, PDL1 and PDL2. On binding its ligand, PD1 inhibits immune cellular function. Blockade of the PD1/PDL1 pathway is currently the predominant immunotherapeutic strategy for haematological malignancies.

MECHANISMS OF PD-L1/L2 OVER-EXPRESSON IN HAEMATOLOGICAL MALIGNANCIES

The prototypes of haematological malignancy over-expressing PDL1/L2 are classical Hodgkin lymphoma (cHL) and lymphomas infected with the Epstein Barr virus (EBV). In the neoplastic Hodgkin Reed-Sternberg cells of cHL, amplification of chromosome 9p24.1 (where the gene loci of PDL1/L2 are located) and JAK/STAT pathway activation are typically found. Both mechanisms lead to PDL1 and PDL2 over-expression. In EBV-positive lymphomas, the viral oncoprotein LMP1 transactivates the PD-L1 gene, resulting in PD-L1 over-expression. Hence, targeting the PD1-PDL1/L2 pathway is an effective treatment for these malignancies.

PD1 BLOCKADE IN cHL

Two anti-PD1 antibodies nivolumab and pembrolizumab have been found to be highly effective for relapsed/refractory cHL, both now considered a standard-of-care for these patients. An overall response rate (ORR) of 69%-75% and complete response rates (CR) of 16% - 23% were achieved in pivotal clinical trials in relapsed/refractory patients. More recently, pembrolizumab has shown promising results when combined with standard chemotherapy in newly-diagnosed cases of cHL.

LOW-DOSE ANTI-PD1 BLOCKADE IN cHL

The standard doses of pembrolizumab and nivolumab for treating cHL are respectively 200 mg every three weeks (Q3W) and 240 mg Q2W or 480 mg Q4W. However, a direct dose-response relationship has not been established for anti-PD1 antibodies. High doses of anti-PD1 antibodies do not improve outcomes. However, adverse events are increased. Furthermore, health costs are substantially elevated.

At Queen Mary Hospital, we have adopted a low-dose anti-PD1 approach in treating cHL. Pembrolizumab is used at 100 mg Q3W, whereas nivolumab is used at 40 mg Q2W. In relapsed/refractory cHL, low-dose pembrolizumab and nivolumab achieved ORR of 100%, and CR of 67%-73%. Results are at least comparable with, if not actually superior to, those in pivotal clinical trials. These results were achieved with very low rates of adverse events and significantly lower health costs. This low-dose approach has been validated independently by other researchers.

PD1/PDL1 BLOCKADE IN NK (NATURAL KILLER)/T-CELL LYMPHOMA

NK/T-cell lymphomas are universally infected by EBV, representing the prototype of EBV-infected lymphoid malignancy. In the first series of patients with...
relapsed/refractory NK/T-cell lymphoma, treatment with pembrolizumab resulted in an ORR of 100% and a CR of 71%.14 Treatment with nivolumab also resulted in high efficacies.15 These results have been validated in a smaller number of patients treated with pembrolizumab.16 In treating these patients, we have again adopted a low-dose approach with pembrolizumab and nivolumab, and shown that such a strategy is also effective in NK/T-cell lymphomas.13,15

Two other antibodies targeting the PD1/PDL1 pathway have also been evaluated in relapsed/refractory NK/T-cell lymphoma. The anti-PD1 antibody sintilimab induced an ORR of 68% in 28 patients.17 The anti-PDL1 antibody avelumab induced an ORR of 38% with a CR of 24% in another study.18

These results have established the blockade of the PD1/PDL1 pathway as a standard salvage option for NK/T-cell lymphoma. Preliminary results indicated structural changes in the 3'-UTR of the PDL1 gene to be associated with a more favourable response to pembrolizumab.19 However, further studies are needed to define better clinicopathologic or genetic markers predictive of response to PD1/PDL1 blockade.

**PD1 BLOCKADE IN OTHER LYMPHOMAS**

Primary mediastinal large B-cell lymphoma (PMBCL) is a specific B-cell lymphoma localised to the mediastinum, with a predilection for young women. Relapsed/refractory PMBCLs respond very poorly to conventional therapy. In two clinical trials studying 74 patients with relapsed/refractory PMBCL, treatment with pembrolizumab led to an ORR of 46% and CR of 19%,20 representing very good efficacy for these largely incurable patients.

Besides these results, blockade of the PD1/PDL1 pathway in other lymphomas has only shown anecdotal success. Reported lymphoid malignancies to respond to pembrolizumab included Richter transformation of chronic lymphocytic leukaemia (ORR: 44%),21 relapsed/refractory mycosis fungoides/Sezary syndrome (ORR: 38%; CR: 8%);22 double-hit lymphoma,23 post-transplantation lymphoproliferative diseases,24 and anaplastic large cell lymphoma25 after allogeneic haematopoietic stem cell transplantation (HSCT).

Nivolumab has also been shown anecdotally to be effective in primary central nervous system diffuse large B-cell lymphoma,26,27 testicular lymphoma,26 and T-lymphoblastic lymphoma after allogeneic HSCT.28

**ADVERSE EFFECTS OF PD1/PDL1 BLOCKADE**

Blockade of the PD1/PDL1 pathway results in a distinctive array of adverse events, collectively known as immune related adverse events (irAE).29,30 Virtually every organ in the body may be affected, but frequently affected sites include the skin, gut, liver, endocrine organs, lungs, kidneys, and the nervous system (Table 1).29,30 Many of these irAEs resemble autoimmune conditions. Hence, patients with a history of autoimmune diseases are generally considered not suitable for PD1/PDL1 blockade. Furthermore, treatment with anti-PD1/PDL1 may exacerbate graft-versus-host disease after allogeneic HSCT.31 Hence, a washout period is mandatory in patients treated with PD1/PDL1 blockade before undergoing allogeneic HSCT.

The severity of irAEs correlates with the dosage and duration of anti-PD1/PDL1 treatment. With our low-dose approach, irAEs are relatively mild and uncommon, with the lungs, thyroid and pituitary glands most often affected.11 We recommend routine chest radiographs, thyroid function test and morning cortisol levels before each anti-PD1 treatment, in addition to vigilance against other known irAEs.

**Table 1. Immune-related adverse events (Developed by author)**

<table>
<thead>
<tr>
<th>Site or organ</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Rashes, dermatitis, Stevens-Johnson syndrome, vitiligo</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Oral mucositis, xerostomia, pancreatitis, colitis, enteritis, hepatitis</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Hypothyroidism, hypophysitis, diabetes mellitus, hypoadrenalism</td>
</tr>
<tr>
<td>Lungs</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Encephalitis, meningitis, peripheral neuropathy</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthritis, myositis, vasculitis</td>
</tr>
<tr>
<td>Kidneys</td>
<td>nephritis</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Anaemia, thrombocytopenia</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Myocarditis, pericarditis, heart failure</td>
</tr>
</tbody>
</table>

**THE CD47/SIRPα PATHWAY**

The signal regulatory protein alpha (SIRPα) is an immune checkpoint receptor on macrophages, which on activation transduces an inhibitory signal that prevents phagocytosis.32 Its cognate ligand is CD47, which is expressed on a variety of cells and constitutes a “don’t eat me” signal preventing macrophage mediated phagocytosis. Malignant cells may express CD47, thereby avoiding their phagocytosis by macrophages.

Treatment with the anti-CD47 antibody magrolimab was first reported to be active when combined with rituximab in relapsed/refractory lymphomas, inducing an ORR of 40% (CR: 30%) in diffuse large B-cell lymphoma, and an ORR of 71% (CR: 43%) in follicular lymphoma.33 Another CD47 targeting molecule TTI-621 (SIRPaFc serving as a decoy receptor) has also shown promising efficacies in phase 1 studies for a variety of hematologic malignancies34 and mycosis fungoides/Sezary syndrome.35

Most of the development of anti-CD47 is now focused on myeloid malignancies, including acute myeloid leukaemia and myelodysplastic syndrome.32,36 Clinical trials are conducted in combining anti-CD47 with hypomethylating agents, and have shown promising results.
TARGETING OTHER IMMUNE CHECKPOINTS IN HAEMATOLOGIC MALIGNANCES

Other important immune checkpoints that have been considered therapeutic targets include lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin domain 3 (TIM3), and T cell immunoreceptor with Immunoglobulin and ITIM domains (TIGIT). The targeting of these immune checkpoint proteins is tested in ongoing clinical trials in various haematological malignancies, including lymphomas and leukemias.

IMMUNE CHECKPOINT TARGETING AND CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR-T) THERAPY

CAR-T cell therapy is a novel cellular therapy currently developed and approved for the treatment of B-cell malignancies. Over-expression of immune checkpoint receptors on CAR-T cells is one of the mechanisms for the failure of the therapy. Accordingly, patients failing CAR-T cell therapy have been treated with anti-PD1 antibodies, leading to modest results. Further work is therefore required to understand how immune checkpoint blockade may improve the therapeutic efficacy of CAR-T cells.

CONCLUSION

Immune checkpoint blockade is rapidly becoming a standard-of-care in haematological malignancies. However, many malignancies do not respond to such a strategy. Furthermore, for malignancies that respond, predictive markers have still not been defined. More studies are therefore needed in these areas, so that the efficacy of immune checkpoint blockade and the spectrum of responding haematological malignancies can be improved.

References

Controlled Uptake Mechanism

- Ferric ions (Fe$^{3+}$) are converted into ferrous ions (Fe$^{2+}$) by dudenal Cytochrome B
- Controlled physiological absorption as Ferrous ions
- Converted back into Ferric ions by Hephaestin and transported in the bloodstream by Transferrin

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Immune Checkpoint Blockade in the Management of Haematological Malignancies" by Prof KWONG Yok-lam and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2022. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Cancer cells may evade immune surveillance by over-expressing the cognate ligands of immune checkpoint receptors.
2. Immune checkpoint blockade therapy directly targets cancer cells leading to cancer cell apoptosis.
3. Programmed death protein ligand 1 (PD-L1) is the only ligand for PD1.
4. Anti-PD1/PD-L1 antibodies are the only available immune checkpoint blockade therapeutic agents available in the market.
5. Anti-PD1 antibodies are highly effective for relapsed/refractory classical Hodgkin’s lymphoma with an overall response rate of around 70-80%.
7. PD-1 immune checkpoint blockade is largely ineffective in the treatment of primary mediastinal B-cell lymphoma.
8. There is no safety concern for the use of PD1/PD-L1 immune checkpoint blockade therapy in patients after allogeneic haematopoietic stem cell transplantation.
9. Cancer cells may express CD47, which binds signal regulatory protein alpha (SIRPα) on macrophages and inhibits phagocytosis by macrophages.
10. Chimeric antigen receptor T-cell (CAR-T) therapy is another form of immune checkpoint blockade therapy.

ANSWER SHEET FOR DECEMBER 2022

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Immune Checkpoint Blockade in the Management of Haematological Malignancies

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1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] 8 [ ] 9 [ ] 10 [ ]

Name (block letters): ___________________________ HKMA No.: ___________ CDSHK No.: ___________
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Answers to November 2022 Issue

Management of Psoriasis - Where Are We Now?

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- Nearly Doubled Median Event-Free Survival\(^\text{4}\)
  - 17.3 months (95% CI, 13.4-30.0) 
  - with MYLOTARG + chemo
  - vs 
  - 9.5 months (95% CI, 8.1-12.0) 
  - with chemotherapy alone

- More Than Doubled Median Relapse-Free Survival\(^\text{4}\)
  - 28.0 months (95% CI, 16.3-NE) 
  - with MYLOTARG + chemo
  - vs 
  - 11.4 months (95% CI, 10.0-14.4) 
  - with chemotherapy alone

(*IR*=0.56, 95% CI, 0.46-0.76, P=0.0002)\(^\text{(1)}\)

Fractionated dosing of MYLOTARG delivers efficacy without excessive toxicity and demonstrates a favourable benefit/risk profile\(^\text{3,5}\).

---

\(^{1}\)NCCN: recommended for newly diagnosed patients with AML in combination with daunorubicin and cytarabine. NICE: recommended with daunorubicin and cytarabine, as an option in untreated disease.

\(^{2}\)In elderly patients aged 65 years and above.

\(^{3}\)For patients aged 15 years and above only.

\(^{4}\)Based on two randomized, open-label, Phase 3 studies. Lenz, 2012: 373(9512): 1026-1036.

\(^{5}\)Based on pooled results from three Phase 3 studies (M14/06, M14/10, M14/12).

**MYLOTARC** Summary of Product Information

**WARNINGS & PRECAUTIONS**

- Use in combination with chemotherapy and is contraindicated in patients with severe neutropenia and/or profound thrombocytopenia. Patients with a history of severe neutropenia and/or thrombocytopenia should be monitored closely for signs of infection and bleeding, respectively.

**ADVERSE REACTIONS**

- The most common adverse reactions (≥20%) are infections, fever, pyrexia, anemia, neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, and constipation.

**CONTRAINDICATIONS**

- Contraindicated in patients with severe neutropenia and/or profound thrombocytopenia.

---

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INTRODUCTION

Immunotherapy is gaining importance in the management of haematological malignancies. Indeed, monoclonal antibodies (MAb) have become the standard of care in certain blood cancers for years. Rituximab was the first ever immunotherapy approved for use in cancer and the year 2022 marks the 25th anniversary of its approval by the U.S. Food and Drug administration (FDA). Nowadays, it is the backbone of treatment for various B-cell malignancies. Rituximab is considered a type of "naked" therapeutic monoclonal antibody which is typically bivalent and monoclonal IgG molecule. Modern technology enables the engineering and modification of MAb to enhance their efficacy. In particular, two approaches are commonly adopted, namely bispecific antibodies and monoclonal antibody conjugates. Unlike the naked MAb, bispecific antibodies target two independent antigens or epitopes via various designs, often linking an effector cell, such as T-cell to a target cell. Monoclonal antibody conjugates refer to MAb linked to a specific anti-tumour effector molecule, commonly a cytotoxic drug or radioactive particle. Antibody-drug conjugates (ADC) consist of MAb conjugated to a cytotoxic drug (also known as payload) via a chemical linker. This review will focus on the clinical application of bispecific antibodies and antibody-drug conjugates in the management of haematological malignancies (Table 1).

| Table 1. Immunotherapeutic agents covered in this article (Table prepared by author) |
|-----------------------------------------------|-----------------------------------------------|
| Bispecific antibody | Antibody-drug conjugate |
| Acute lymphoblastic leukaemia | Blinatumomab, Inotuzumab ozogamicin |
| Acute myeloid leukaemia | | |
| Non-Hodgkin B-cell lymphomas | Mosunetuzumab, Glofitamab, Polatuzumab vedotin, Moxetumomab pasudotox-ddk |
| Hodgkin lymphoma and mature T-cell lymphoma | Brentuximab vedotin |
| Multiple myeloma | Belantamab mafodotin-blmf |

ACUTE LYMPHOBLASTIC LEUKAEMIA

Acute lymphoblastic leukaemia (ALL) is a serious, deadly blood cancer. Despite its high initial complete remission (CR) rate with intensive conventional combination chemotherapy, a significant proportion of patients eventually relapse and the long-term survival of adult ALL patients is around 40% only. In recent years, immunotherapy has been formally incorporated into the management of ALL following the approval of two new immunotherapeutic agents, namely blinatumomab and inotuzumab ozogamicin. Both drugs were shown to be superior to conventional chemotherapy in relapsed or refractory ALL, leading to significant improvement in clinical outcomes.

Blinatumomab

Blinatumomab is a type of bispecific antibodies termed bispecific T-cell engager (BiTE®). It has dual specificity for CD3 and CD19. Most B-lineage ALL (B-ALL) blasts express CD19, while CD3 is expressed on the surface of T-cells. By simultaneous binding to CD3-positive cytotoxic T-cells and CD19-positive blasts, blinatumomab activates the patient’s endogenous T-cells to recognise and eliminate the leukaemic cells. Currently, blinatumomab is approved for the treatment of relapsed or refractory CD19-positive B-ALL in adult and paediatric patients, as well as those in first or second remission with minimal residual disease (MRD) greater than or equal to 0.1%. Its efficacy over conventional chemotherapy was established in the landmark TOWER trial. In patients with relapsed/refractory Philadelphia chromosome (Ph)-negative B-ALL, complete remission (CR) rate was significantly higher in the blinatumomab group than the chemotherapy group (44% vs 25%). The blinatumomab group also had a significantly longer median duration of remission and overall survival.

Minimal or measurable, residual disease (MRD) refers to the low-level disease that is below the detection limit of conventional cytomorphology. The role of MRD is increasingly appreciated in the field of malignant haematology and it is considered an important independent prognostic factor in ALL. Blinatumomab has been proven in the BLAST trial to be an effective treatment for the clearance of MRD that persists after standard chemotherapy. In this single-arm study, blinatumomab was given to B-ALL patients who were in haematologic CR with persistent or recurrent MRD greater than or equal to 0.1% after at least three blocks of intensive chemotherapy. Seventy-eight percent of patients achieved a complete MRD response, which was associated with longer relapse-free survival (RFS) and overall survival (OS).

Due to its short half-life, blinatumomab is administered as continuous intravenous infusion for 28 days per
cycle. Its major side effects include cytokine release syndrome (CRS) and neurologic toxicity, with the risks being much lower when given in the MRD setting than relapsed/refractory disease. Outside its licensed indications, the therapeutic role of blinatumomab in the front-line setting has also been actively investigated in recent years, and the clinical data are promising.16-12

Inotuzumab Ozogamicin

Inotuzumab ozogamicin is an ADC directed against CD22, which is expressed in more than 90% of B-ALL patients. It consists of a humanised monoclonal antibody and a cytotoxic agent called calicheamicin, covalently attached together via an acid labile linker. The ADC binds to CD22-expressing ALL blasts, followed by internalisation of the CD22-conjugate and intracellular release of calicheamicin. Calicheamicin induces double-strand DNA breaks, and hence apoptotic cell death. Inotuzumab is approved for the treatment of relapsed or refractory B-ALL in adults. In the phase 3, randomised INO-VATE trial,13 the CR rate was significantly higher in the inotuzumab group than in the conventional chemotherapy group (80.7% vs 29.4%). Progression-free survival (PFS) was also significantly longer in the inotuzumab group.

Inotuzumab is administered intravenously and offers a more convenient treatment schedule than blinatumomab. It is given on day 1, day 8 and day 15 of a 3- to 4-week cycle, dosage and cycle length depending on the response to the treatment. Apart from infusion-related reactions commonly associated with MAb, inotuzumab carries a black-box warning concerning the risk of hepatotoxicity including hepatic veno-occlusive disease (VOD). Almost a quarter of patients who underwent allogeneic haemopoietic stem cell transplantation (HSCT) after inotuzumab treatment experienced VOD. It is postulated that VOD develops as a result of the injury caused to sinusoidal endothelial cells by the calicheamicin component of the ADC. The same toxicity is also observed in gemtuzumab ozogamicin, another ADC containing calicheamicin and used in patients with acute myeloid leukaemia (AML). Due to the risk of VOD, it is recommended that patients proceeding to HSCT should receive no more than two cycles of inotuzumab.

Although the approval of inotuzumab is based on its administration as monotherapy, its safety and efficacy when given as a combination treatment with conventional chemotherapeutic agents as well as blinatumomab have been explored. It is foreseeable that these monoclonal antibodies, together with CAR T-cell therapy, will continue to reshape the treatment landscape of ALL.

ACUTE MYELOID LEUKAEMIA

Acute myeloid leukaemia (AML) is a more common form of acute leukaemia in adults than ALL. For decades, the standard induction therapy for AML had been the “7 + 3 regimen”, comprising 7 days of cytarabine and 3 days of anthracycline. However, a number of new drugs have been approved for the treatment of AML by the FDA since 2017, one of which being gemtuzumab ozogamicin.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is an ADC directed against CD33, which is commonly expressed on myeloid blasts. Similar to inotuzumab, it consists of a MAb covalently linked to the cytotoxic agent calicheamicin. The anti-leukaemic activity of the drug is exerted by the intracellular release of calicheamicin in the CD33-expressing tumour cells, following the binding of the ADC to the tumour cells and internalisation of the ADC-CD33 complex. In fact, GO was first granted accelerated approval by the FDA in 2000 for the treatment of older adults with relapsed CD33-positive AML. At that time, the recommended regimen was 9 mg/m² for two doses 14 days apart. However, its manufacturer voluntarily withdrew the drug from the market in 2010 as a result of safety concerns and lack of clinical benefit in a phase 3 trial which evaluated GO 6 mg/m² in combination with 7+3 induction in newly diagnosed AML patients. Further studies adopted a fractionated dosing schedule to reduce the toxicities. In 2017, GO gained approval again at a lower recommended dose and a different treatment schedule for the treatment of newly diagnosed and relapsed or refractory CD33-positive AML. In the randomised, phase 3 ALFA-0701 trial, a fractionated dose of GO in combination with standard front-line chemotherapy was shown to significantly improve the event-free survival in adult AML patients (median 17.3 months vs 9.5 months).

GO is given as an intravenous infusion. Its dosage and dosing schedule vary according to the indication. For patients with newly diagnosed AML, the recommended dose of GO is 3 mg/m² on Days 1, 4, and 7 in combination with daunorubicin and cytarabine during the induction cycle. GO should be given on Day 1 only in the consolidation cycles. In relapsed/refractory cases, GO is given as a single agent. Apart from hepatotoxicity including VOD, GO is also associated with a higher rate of haemorrhage and a longer median time to platelet recovery. Given the toxicity profile of GO, extra precautions should be taken to mitigate the risks of VOD and thrombocytopenia.

LYMPHOMA

Immunotherapy plays an important role in the management of lymphoma. A number of MAb have been approved for the treatment of various subtypes of lymphoma. While CD20 remains a common target, some MAb are directed to other surface antigens that are frequently expressed on mature B-cell lymphomas, such as CD22 and CD79b. On the other hand, CD30 is expressed in classical Hodgkin lymphoma and certain types of T-cell lymphoma; thus has become the target of immunotherapy.

Non-Hodgkin B-cell Lymphomas

Mosunetuzumab is a novel CD20xCD3 T-cell engaging bispecific antibody. It was granted conditional marketing authorisation by the European Commission (EC) in June 2022 for the treatment of relapsed or refractory follicular lymphoma (FL). It was also granted Priority Review by the FDA, which was expected to decide on the approval by the end of 2022. In the
pivotal phase I/II study, mosunetuzumab was shown to have high complete response (CR) rates and durable remission in heavily pre-treated patients with relapsed or refractory FL.\textsuperscript{25} Unlike blinatumomab, which is a fragment-based bispecific antibody and does not contain an Fc region, mosunetuzumab is a full-length, humanised bispecific antibody. It recruits endogenous T cells to engage and kill CD20-expressing B cells. Its structure confers more favourable pharmacokinetic properties, and the drug can be given intravenously once every 21-day cycle, after the initial step-up phase. Cytokine release syndrome (CRS) is a notorious side effect of T-cell activating therapies such as bispecific T-cell engaging antibodies and adoptive T-cell therapies, and mosunetuzumab is no exception.

Glofitamab is another CD20xCD3 T-cell engaging bispecific antibody of interest. It differs from mosunetuzumab in the number of antigen-binding fragment (Fab) arms: glofitamab has a 1:2 CD3:CD20 ratio, while mosunetuzumab has a 1:1 CD3:CD20 ratio. It is postulated that such CD20 bivalency might be associated with better potency against tumour. Glofitamab has not been approved yet, but the preliminary clinical data are encouraging.\textsuperscript{24}

ADCs approved for the treatment of B-cell lymphoma include polatuzumab vedotin and moxetumomab pasudotox-tdfk. Polatuzumab vedotin is a CD79b-directed ADC. In combination with bendamustine and rituximab, it is indicated for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL). In the randomised trial\textsuperscript{28} that compared polatuzumab in combination with bendamustine and rituximab (pola-BR) versus BR in transplantation-ineligible relapsed/refractory DLBCL, the former had a significantly higher CR rate (40.0\% vs 17.5\%), and longer PFS and OS. Pola-BR was associated with high rates of myelosuppression and peripheral neuropathy. Progressive multifocal leukoencephalopathy (PML) has also been rarely reported after treatment with polatuzumab. The role of polatuzumab in front-line setting has been investigated in the POLARIX trial, which compared pola-R-CHP (polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisone) against the current standard-of-care R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).\textsuperscript{29} While the pola-R-CHP group had a higher EPS, there was no significant difference in the overall response rate and OS.

Moxetumomab pasudotox-tdfk is a CD22-directed immunotoxin and is indicated for the treatment of relapsed or refractory hairy cell leukaemia (HCL) in adult patients. Unlike a typical ADC which comprises a chemical linker connecting the MAb and cytotoxic payload, moxetumomab consists of an anti-CD22 antibody conjugated to a toxin by recombinant DNA technology.\textsuperscript{27} The efficacy of moxetumomab in relapsed/refractory HCL was demonstrated in a multicentre, single-arm, open-label study which led to its FDA approval.\textsuperscript{28} It is associated with unique toxicities including capillary leak syndrome and haemolytic uraemic syndrome, the mechanism of which remains poorly understood.

**OTHER LYMPHOMAS**

**Brentuximab Vedotin**

Brentuximab vedotin (BV) is a CD30-directed ADC. CD30 expression is commonly found in classical Hodgkin’s lymphoma (cHL) and certain types of mature T-cell lymphoma, e.g. anaplastic large cell lymphoma (ALCL). BV is indicated for the treatment of cHL, systemic ALCL, and other CD30-expressing peripheral T-cell lymphomas (PTCL) as well as mycosis fungoides (MF). In the multi-centre, randomised phase 3 ECHELON-1 trial\textsuperscript{29}, BV in combination with doxorubicin, vinblastine and dacarbazine (A+AVD) was shown to result in a higher modified PFS than ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) (82.1\% vs 77.2\%). In the latest updated analysis of ECHELON-1 with 6-year follow-up\textsuperscript{30}, the A+AVD group also significantly reduced the risk of mortality. On the other hand, the efficacy of BV in previously untreated mature T-cell neoplasms including anaplastic large cell lymphoma (ALCL) and other CD30-positive peripheral T-cell lymphomas, was evaluated in the ECHELON-2 trial.\textsuperscript{31} The group using BV plus chemotherapy (cyclophosphamide, doxorubicin and prednisone) had superior PFS than the CHOP group (48.2 months vs 20.8 months). BV carries a similar toxicity profile to polatuzumab vedotin, such as peripheral neuropathy and PML.

**MULTIPLE MYELOMA**

**Belantamab Mafodotin-blmf**

The application of immunotherapy is expanding in multiple myeloma, too. Following approval of several monoclonal antibodies for the treatment of myeloma, namely daratumumab, elotuzumab, and isatuximab, belantamab mafodotin-blmf (belamaf) was the first ADC introduced to patients with relapsed or refractory multiple myeloma. Belamaf is a B-cell maturation antigen (BCMA)-directed ADC using the microtubular inhibitor monomethyl auristatin F (MMAF) as the payload. In the phase 2 DREAMM-2 study, around one-third of heavily pre-treated myeloma patients responded to single-agent belamaf.\textsuperscript{32} Belamaf carries unique ocular toxicity. At its approved dose (2.5 mg/kg as an intravenous infusion once every 3 weeks), a majority of patients developed keratopathy of any grade associated with a change in visual acuity.\textsuperscript{33} These changes in the corneal epithelium were thought to be related to MMAF. Ophthalmic examination should be conducted regularly, and prompt intervention should be offered once corneal events are observed.\textsuperscript{34}

Lastly, BCMA is a major target for immunotherapy in multiple myeloma. A number of BCMA-directed bispecific antibodies are in development\textsuperscript{35} not to mention ciltaclabtagene autoleucel, the BCMA-directed CAR T-cell therapy approved for the treatment of relapsed or refractory multiple myeloma. It is anticipated these novel immunotherapeutic agents will be incorporated into the standard treatment regimens for myeloma.
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CONCLUSION

The past decade has been an exciting time for the field of haematological oncology. Immunotherapy, a new class of drugs, has been introduced to the management of various haematological malignancies and has led to a shift in the treatment paradigm. Some are approved as single-agent therapy (e.g. blinatumomab, belanaf), while others are used in conjunction with conventional chemotherapy (e.g. GO, polatuzumab). With mechanisms of action and pharmacologic properties different from conventional cytotoxic chemotherapy, these bispecific antibodies and ADC do have their unique safety profiles. For example, cytokine release syndrome and neurotoxicity are major side effects observed in bispecific T-cell engaging antibodies such as blinatumomab and mosunetuzumab. The cytotoxic payloads in ADC are often associated with important adverse events, such as VOD in calicheamicin-containing ADCs and keratopathy in MMAF-based ADCs. As the data mature and experience accumulates, it is likely that these immunotherapeutic agents will be moved to earlier lines of treatment to enhance efficacy and to improve long-term clinical outcomes in the years to come.

References


Certificate Course on

Common Diseases in Otorhinolaryngology, Head & Neck Surgery 2023 (Video Lectures)

**Objectives:**
Otorhinolaryngology is a specialty managing diseases over head and neck region and sleep related disorders. This course provides essentials about ENT conditions to health care providers. Participants will have latest information in the related topics to facilitate their daily practice in managing related ENT conditions and collaboration with ENT specialists.

<table>
<thead>
<tr>
<th>Date</th>
<th>Topics</th>
<th>Speakers</th>
</tr>
</thead>
</table>
| 5 January 2023     | ENT Kids: How to Handle Them in Office, and When to Refer? | Dr. Alice KY Siu  
Specialist in Otorhinolaryngology  
Hong Kong Children Hospital  
Clinical Assistant Professor (Honorary)  
Department of Otorhinolaryngology, Head and Neck Surgery  
The Chinese University of Hong Kong          |
| 12 January 2023    | Update on Management of Head and Neck Cancer               | Dr. Eddy Wong  
Chief of Service  
Department of Ear, Nose & Throat  
Prince of Wales Hospital |
| 19 January 2023    | Rhinosinusitis and its Management                           | Dr. Fergus Wong  
Associate Consultant  
Department of Ear, Nose & Throat  
Pamela Youde Nethersole Eastern Hospital |
| 26 January 2023    | Hearing Loss and its Related Treatment                      | Dr. Wai-tsze Chang  
Assistant Professor  
Department of Otorhinolaryngology, Head and Neck Surgery  
The Chinese University of Hong Kong |
| 2 February 2023    | Management of Challenging Voice Disorders                  | Dr. Eric Tang  
Specialist in Otorhinolaryngology  
Clinical Assistant Professor (Honorary)  
Department of Otorhinolaryngology, Head and Neck Surgery  
The Chinese University of Hong Kong |
| 9 February 2023    | Obstructive Sleep Apnea Syndrome -- from Diagnosis to Management | Dr. Fiona Chui-yan Wong  
Specialist in Otorhinolaryngology  
Clinical Assistant Professor (Honorary)  
Department of Otorhinolaryngology, Head and Neck Surgery  
The Chinese University of Hong Kong |

**Dates:** 5, 12, 19, 26 January & 2, 9 February 2023 (Thursday)  
**Time:** 7:00 pm – 8:30 pm  
**Duration of session:** 1.5 hours (6 sessions)  
**Course Feature:** Video lectures (with Q&A platform for participants to post the questions)  
**Language Media:** Cantonese (Supplemented with English)  
**Quiz for doctors:** DOCTORS are required to complete a quiz after the completion of each lecture  
**Course Fee:** HK$1,000  
**Certificate:** Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)  
**Deadline:** 28 December 2022  
**Enquiry:** The Secretariat of The Federation of Medical Societies of Hong Kong  
Tel: 2527 8898  
Fax: 2865 0345  
Email: vienna.lam@fmshk.org

CME / CNE Accreditation in application  
Online Application from website: http://www.fmshk.org
Monoclonal Antibodies in the Management of Myeloma

Dr Karen HK TANG
MBBCh(CUHK), MRCP(UK), FHKAM(Medicine)
Associate Consultant, Division of Haematology and Haematopoietic Stem Cell Transplant, Department of Medicine, Queen Mary Hospital

INTRODUCTION

Significant advancements in the treatment of multiple myeloma (MM) have occurred over the last few years, improving the median survival of patients from 3-4 years to nearly one decade. The key to such great success lies in the introduction of novel therapeutic agents. These drugs include: 1) the immunomodulatory agents (IMIDs) lenalidomide and pomalidomide; 2) the proteasome inhibitors (PIs) bortezomib, carfilzomib, and ixazomib; 3) monoclonal antibodies (MoAbs) daratumumab, elotuzumab, and isatuximab, and 4) antibody drug conjugate (ADC) belantamab mafodotin. These drugs can be used in combinations as triplets or quadruplets, leading to overwhelming response rates of up to 90% in newly diagnosed myeloma patients. In particular, the response rates, progression-free survival (PFS) and overall survival (OS) reached by the use of anti-CD38 MoAbs daratumumab and isatuximab have been unprecedented in MM. This article will focus on the MoAbs that are currently available and more widely used in Hong Kong, including daratumumab, isatuximab and belantamab. Developments in bispecific antibodies which may soon be available, will also be briefly summarised.

DARATUMUMAB

Daratumumab is a first-in-class human immunoglobulin G1 kappa (IgG1κ) CD38-directed MoAb. CD38 is an excellent therapeutic target in myeloma because it is expressed with relatively high surface density on abnormal plasma cells, whereas its expression is lower on normal myeloid and lymphoid cells. Daratumumab can be given by intravenous infusion over 4-8 hours or subcutaneously within 5 minutes. Subcutaneous administration has a lower rate of infusion-related reactions (IRRs) and can significantly reduce drug administration time. The subcutaneous formulation is not yet registered in Hong Kong but will likely be available in 2023. Daratumumab can be used in both transplant-eligible and transplant-ineligible newly diagnosed MM (NDMM) or relapse refractory MM (RRMM). Table 1 summarises the results of key pivotal trials on daratumumab.

Daratumumab in NDMM

Combination of daratumumab, bortezomib, thalidomide and dexamethasone (D-VTd) showed superior response rates, complete response (CR) rates, PFS, and a trend to better OS as compared with VTd, followed by autologous stem cell transplant (ASCT) in the phase III CASSIOPEIA trial. The addition of daratumumab to bortezomib, lenalidomide and dexamethasone (D-VRd) followed by ASCT further increased the rate and depth of response to therapy, with a trend towards improved PFS in the phase II GRIFFIN trial. In these trials, the benefit of daratumumab was observed in patients with both standard and high-risk disease, but was more pronounced in the former group of patients. With the current follow-up data, OS benefit has not been demonstrated with the addition of daratumumab to either triplet regimens. These two trials, approximately one out of three patients in the daratumumab group achieved CR and sustained minimal residual disease (MRD)-negative status at 1 or 2 years, as compared with around only one-tenth of patients in the placebo group achieving the same depth of response.

For transplant-ineligible patients, significant superiority in response rates, CR rate, MRD negativity, PFS and OS with the addition of daratumumab was demonstrated in 2 phase III randomised studies comparing daratumumab, lenalidomide and dexamethasone (DRd) with Rd till disease progression (MAIA trial) and daratumumab, bortezomib, melphalan and dexamethasone (D-VMP) with VMP (ALCYONE trial). Although the comparison between different trials should be made with caution, the median PFS of the patients treated with Rd in the MAIA trial was similar to those treated with Dara-VMP in the ALCYONE trial (33.8 vs 36 months), suggesting better performance of Dara-Rd compared with Dara-VMP in those ineligible for transplant. However, there was a higher incidence of grade 3-4 infective complications in those receiving daratumumab, specifically pneumonia and upper respiratory infection, which should be taken into consideration in the management of elderly and frail myeloma patients.

Daratumumab in RRMM

At first relapse, for patients who are not refractory to lenalidomide, multiple triplet regimens can be considered, including Drd, carfilzomib lenalidomide dexamethasone (K Rd) and ixazomib lenalidomide dexamethasone (IRd). Each of these regimens has shown superiority over Rd in randomised trials. In the phase III POLLUX trial, Drd significantly improved response rates, PFS, and MRD-negativity rates as compared with Rd in patients regardless of cytogenetic risk. The greatest clinical benefit of Drd was also observed in patients that had received one prior line
Table 1: Summary of trials for Daratumumab and Isatuximab (Developed by author)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Combination Therapy</th>
<th>Median follow up, months</th>
<th>CR or better</th>
<th>Median PFS, months</th>
<th>Median OS, months</th>
<th>MRD negativity, 10-5</th>
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<tbody>
<tr>
<td><strong>Daratumumab Trials</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CASSIOPEIA8</td>
<td>Dara VTd vs VTd (first randomisation) -&gt; ASCT -&gt; Dara MTN vs no MTN (second randomisation)</td>
<td>35.4 (from second randomisation)</td>
<td>73% vs 61%, p &lt; 0.0001</td>
<td>NR vs 46.7, p = 0.0001</td>
<td>NR vs NR</td>
<td>59% vs 47%, p = 0.0001</td>
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<tr>
<td>GRIFFIN9</td>
<td>Dara VRd vs VRd -&gt; ASCT -&gt; Dara R MTN vs R MTN</td>
<td>38.6</td>
<td>82% vs 61%, p = 0.0013</td>
<td>NR vs NR (36 months PFS rate 88.9% vs 81.2%)</td>
<td>NR vs NR (36 months OS rate 92.6% vs 92.2%)</td>
<td>62.5% vs 27.2%, p &lt; 0.0001</td>
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<td>MAIA10</td>
<td>Dara Rd vs Rd</td>
<td>56.2</td>
<td>51% vs 30%, p &lt; 0.0001</td>
<td>NR vs 34.3, p &lt; 0.0001</td>
<td>NR vs NR, p = 0.0013 (60 months OS rate 66.3% vs 53.1%)</td>
<td>31% vs 10%, p &lt; 0.0001</td>
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<td>ALCYONE11</td>
<td>Dara VMP -&gt; Dara MTN vs VMP x9 cycles</td>
<td>40.1</td>
<td>46% vs. 25%, p &lt; 0.0001</td>
<td>36.4 vs 19.3, p &lt; 0.0001</td>
<td>75 vs 62, p = 0.0003</td>
<td>28% vs. 7%, p &lt; 0.0001</td>
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<td>POLLUX13</td>
<td>Dara Rd vs Rd</td>
<td>44.3</td>
<td>56.6% vs 23.2%, p &lt; 0.0001</td>
<td>44.5 vs 17.5, p &lt; 0.0001</td>
<td>NR vs NR (42 months OS rate 65% vs 57%)</td>
<td>30.4% vs 5.3%, p &lt; 0.0001</td>
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<td>CANDOR17</td>
<td>Dara Kd vs Kd</td>
<td>27</td>
<td>33% vs 13%, p &lt; 0.0001</td>
<td>28.6 vs 15.2, p &lt; 0.0001</td>
<td>Pending maturity</td>
<td>18% vs 4%, p &lt; 0.0001</td>
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<td>APOLLO18</td>
<td>SC Dara Pd vs Pd</td>
<td>16.9</td>
<td>25% vs 4%, p &lt; 0.0001</td>
<td>12.4 vs 6.9, p = 0.0018</td>
<td>Pending maturity</td>
<td>9% vs 2%</td>
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<td><strong>Isatuximab Trials</strong></td>
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<td>ICARIA26</td>
<td>Isa Pd vs Pd</td>
<td>35.3</td>
<td>9.7% vs 2.7%</td>
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<td>24.6 vs 17.7, p = 0.028</td>
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<td>IKEMA27</td>
<td>Isa Kd vs Kd</td>
<td>44</td>
<td>44.1% vs 28.5%, OR 2.09, 95% CI 1.26 - 3.48</td>
<td>35.7 vs 19.2, HR 0.58, 95% CI 0.42 - 0.79</td>
<td>Pending maturity</td>
<td>33.5% vs 15.4%, OR 2.78, 95% CI 1.55 - 4.99</td>
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<td>GMMG HD728</td>
<td>Isa VRd vs VRd -&gt; ASCT -&gt; Isa R vs R MTN</td>
<td>NA</td>
<td>21.6% vs 24.2%, p = 0.46</td>
<td>Pending maturity</td>
<td>Pending maturity</td>
<td>50.1% vs 35.6%, p &lt; 0.001</td>
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Abbreviations: Dara VTd, daratumumab bortezomib thalidomide dexamethasone; ASCT, autologous stem cell transplant; MTN, maintenance; Dara VRd, daratumumab bortezomib lenalidomide dexamethasone; Dara Rd, daratumumab lenalidomide dexamethasone; Dara VMP, daratumumab bortezomib melphalan prednisolone; Dara Kd, daratumumab carfilzomib dexamethasone; Dara Pd, daratumumab pomalidomide dexamethasone; Isa Pd, isatuximab pomalidomide dexamethasone; Isa Kd, isatuximab carfilzomib dexamethasone; Isa VRd, isatuximab bortezomib lenalidomide dexamethasone; NA, not available; CR, complete response; PFS, progression free survival; OS, overall survival; NR, not reached; MRD, minimal residual disease

Table 2. Safety and Efficacy of bispecifics (adapted from Moreau et al Blood 2022)(Excerpted from Reference 41)

<table>
<thead>
<tr>
<th>Target</th>
<th>Tecristamab(36) N=159</th>
<th>Elranatamab(38) N=50</th>
<th>Talquetamab(39) N=95</th>
<th>Cevostamab(40) N=160</th>
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<td>Administration</td>
<td>SC weekly</td>
<td>SC Q2 weeks</td>
<td>SC weekly or Q2 weeks</td>
<td>IV Q3 weeks</td>
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<td>6</td>
<td>Not reported</td>
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<td>Triple refractory</td>
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<td>RP2D</td>
<td>1.5 mg/kg/week</td>
<td>1 mg/kg</td>
<td>405 μg/kg weekly or 800 μg/kg Q2 weeks</td>
<td>Not reported</td>
</tr>
<tr>
<td>CRS, grade &gt;= 3 (%)</td>
<td>67, 1</td>
<td>83, 0</td>
<td>73, 5 at 405 μg/kg weekly or 78, 0 at 800 μg/kg Q2 weeks</td>
<td>80, 1</td>
</tr>
<tr>
<td>Neurotoxicity, grade &gt;= 3 (%)</td>
<td>2.5, 0</td>
<td>Not reported</td>
<td>Not reported</td>
<td>13.1, 3.8</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>65</td>
<td>70</td>
<td>70 at 405 μg/kg weekly or 71 at 800 μg/kg Q2 weeks</td>
<td>36.7 at 90 mg 54.5 at 160 mg</td>
</tr>
<tr>
<td>DOR (%)</td>
<td>6 months, 90%</td>
<td>92.3% at 6 months</td>
<td>6 months: 67% at 405 μg/kg weekly</td>
<td>Median 15.6 months</td>
</tr>
</tbody>
</table>

Abbreviations: BCMA, B cell maturation antigen; GPRC5D, G protein-coupled receptor, class C group 5 member D; FcRH5, Fc receptor-homolog 5; SC, subcutaneous; IV, intravenous; CRS, cytokine release syndrome; ORR, overall response rate; DOR, duration of response
of therapy supporting the use of DRd in patients with RRMM at first relapse. Although these triplet combinations (DRd, KRd, IRd) have not been directly compared in prospective clinical trial, it is worth noting that DRd has produced the largest reduction in the risk of progression and was apparently better tolerated8.

The effectiveness of other daratumumab triplet combinations has also been evaluated. In the phase III CANDOR trial, patients receiving daratumumab, carfilzomib and dexamethasone (DKd) had superior response rates, MRD negativity and PFS, as compared with those treated with Kd, and the benefits were demonstrated in all cytogenetic risk groups and patients with lenalidomide refractoriness9,10. Subcutaneous daratumumab, pomalidomide and dexamethasone (DPd) resulted in improved response rates, MRD negativity and PFS as compared with Pd in the phase III APOLLO trial11. Comparing the median PFS of patients receiving DKd (28.6 months) and DPd (12.4 months) may give the impression that DKd was superior to DPd. However, the different patient populations recruited in these two studies should be noted; lenalidomide-refractory patients in APOLLO constituted around 80% of the study population, as compared with 30% in the CANDOR trial. Patients with lenalidomide-refractory myeloma have unfavourable prognosis19,20. Quadruplet regimens in single arm studies combining daratumumab, carfilzomib, pomalidomide and dexamethasone (DKPd) have also shown good response rates and PFS in this poor risk group of patients21,22.

How Do We Use Daratumumab?
The cost and the lack of government funding for daratumumab have limited the use of this effective agent in the management of myeloma patients in Hong Kong. In the public sector, daratumumab could be considered a patient self-financed item to combine with either VTd or VRd induction to improve the survival outcome of patients. A clinical trial examining the daratumumab, carfilzomib, lenalidomide and dexamethasone combination (DKRd) with an MRD-response-adapted approach (MASTER trial) has shown that patients with two or more high-risk cytogenetic aberrations lose MRD negative response more readily during the treatment-free period, leading to shorter PFS and OS23. Based on these data and our present limited understanding of disease relapse dynamics, I would suggest high-risk patients (i.e. those with high-risk cytogenetics) continue daratumumab in addition to either lenalidomide or bortezomib maintenance after induction with careful balance and monitoring of their underlying infective risks. For patients not exposed to daratumumab initially, daratumumab-containing regimens should be used in the relapsed/refractory setting.

ISATUXIMAB

Isatuximab is a chimeric humanised IgG1 monoclonal antibody that binds to a specific epitope on the human cell surface antigen CD38. Isatuximab differs from daratumumab in its mechanism of action with higher antibody-dependent cytotoxicity24, and it inhibits the CD38 enzymatic activity via allosteric inhibition25.

Isatuximab is approved for the treatment of RRMM and is given by intravenous infusion. Table 1 summarises the results of clinical studies on isatuximab.

Isatuximab for RRMM

The phase III ICARIA MM study compared isatuximab, pomalidomide and dexamethasone (IsaPd) with PD in RRMM. The overall response rate was much higher in the IsaPd group, with a median PFS of 11.6 months as compared with 6.5 months in the Pd arm26. Another phase III trial IKEMA evaluated the use of isatuximab, carfilzomib and dexamethasone (IsaKd) versus Kd. IsaKd yielded significantly higher rates of CR and MRD negativity. The median PFS was significantly longer in the IsaPd group, 35.7 months, as compared with 19.2 months in the Kd group27. Though PFS associated with IsaKd may appear longer than IsaPd, these two studies again recruited different study populations, with over 90% of patients having lenalidomide-refractory disease in the ICARIA study. Isatuximab is currently not approved for use in NDMM, however promising results have been shown in the GMMG-HD7 phase III trial, with superior MRD negativity rates in the IsaVRd arm as compared with RVd after induction alone in NDMM28.

How Do We Use Isatuximab?
With the increasing use of daratumumab in frontline treatment and RRMM, resistance to daratumumab is becoming a concern, and optimal management is largely unclear. Evidence suggests that daratumumab failure is mediated by clone selection of MM cells with lower CD38 expression as well as CD38 depletion in existing MM cells29. Sequential isatuximab treatment after daratumumab-refractory MM may be of limited benefit. If isatuximab treatment is to be considered after progression on daratumumab, patients with a longer gap of at least six months between daratumumab and isatuximab treatment may respond better30,31. At this point, I would use isatuximab in RRMM patients who are daratumumab-naïve or who have not been on daratumumab maintenance. The role of isatuximab in the treatment of patients with gain/amplification of chromosome 1q32 and soft tissue plasmacytoma33 in subgroup analyses of ICARIA and IKEMA have recently been brought to attention.

BELANTAMAB

Belantamab mafodotin is a first-in-class ADC consisting of an anti-B cell maturation antigen (BCMA) MoAb bound to the microtubule-disrupting agent, monomethyl auristatin F (MMAF). It is approved for patients with RRMM who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. Single agent belantamab gave an overall response rate of 32% and PFS of 11 months in a heavily pre-treated population with a median of seven prior lines of treatment34. Belantamab
can cause changes in the corneal epithelium resulting in alterations in vision, including severe vision loss, corneal ulcers and symptoms such as blurred vision and dry eyes. Ophthalmic examination should be conducted at baseline, before each dose, and promptly for worsening symptoms. Further trials looking into the combination of belantamab with other classes of anti-myeloma drugs are currently in progress, with the aim to maximise efficacy while allowing a more manageable toxicity profile.

**BISPECIFIC T CELL ENGAGERS**

Bispecific T-cell engagers are antibody-like molecules with two binding specificities: CD3 on T cells, and a tumour-associated antigen (this varies among the agents) on the cancer cells. Their use does not require apesrhesis and T-cell manipulation as in chimeric antigen receptor T-cell (CAR-T) therapy. Teclistamab, which targets BCMA, is the most advanced in development. In the MajesTEC-1 trial, 63.0% of the triple-class-exposed patients achieved a response with 39.4% CR. Among patients with CR, 46.2% achieved MRD negativity. The overall duration of response was 18.4 months, and the median PFS was 11.4 months. The development of bispecific antibodies is ongoing, with several other products under investigation. They include other BCMA/CD3, CD38/CD3, FcRL5/CD3 and GPRC5D/CD3 bispecific antibodies (Table 2). If approved, additional off-the-shelf products with novel mechanisms of action will be available for patients with RRMM.

**Positioning Different BCMA Targets**

As of now, belantamab mafodotin is the only agent targeting BCMA available in Hong Kong and is the drug of choice for patients with progressive myeloma that are triple-class refractory. In the near future, when BCMA CAR-T cell therapy and bispecific T-cell engagers are made licensed in Hong Kong, fit patients may be considered for CAR-T therapy first and bispecific antibodies or ADC upon relapse after CAR-T. There are emerging data on retained efficacy of BCMA bispecific antibodies after failing BCMA ADC and BCMA CAR-T cell therapy. On the other hand, bispecific antibodies or ADC may be the initial treatment of choice for frail patients with RRMM.

**CONCLUSION**

Antibody therapy has become an essential component of MM treatment in the past few years. Monoclonal antibodies were initially introduced for RRMM but now have an increasing role in the frontline setting. ADC and bispecific T-cell engagers are beginning to enter the treatment landscape and are needed to overcome resistance after multiple prior lines of therapy. Antibody therapy options for the treatment of MM continue to evolve and are achieving responses that are both deeper and more durable. Future directions should focus on better patient selection and sequencing of treatment regimens to further improve the outcome of patients with myeloma.

**References**


A 37-year-old female presented with acute left lower quadrant abdominal pain and vomiting. There were tenderness and guarding at the left lower quadrant of the abdomen on physical examination, low grade fever with mildly elevated white cell count on blood testing. An abdominal radiograph was performed.

Questions
1. What is the abnormality on the radiograph?
2. What are the most likely differential diagnoses?
3. What is the next step of the investigation?
For your adult patients with lower-risk MDS* or β-thalassemia†-associated anemia

BRING ERYTHROID MATURATION TO LIFE

With REBLOZYL® (luspatercept), the first erythroid maturation agent, you can reduce patients’ RBC transfusion burden.1,2

LOW-RISK MDS*

A SIGNIFICANT INCREASE IN TRANSFUSION INDEPENDENCE WITH REBLOZYL®1

PRIMARY ENDPOINT—
TRANSFUSION INDEPENDENCE FOR AT LEAST 8 WEEKS DURING WEEKS 1-241

37.9% REBLOZYL® (n=58/153)3

13.2% Placebo (n=10/76)3

1 Adult patients with transfusion-dependent anemia associated with very low-, low-, or intermediate-risk MDS.

2 Adult patients with transfusion-dependent anemia associated with β-thalassemia.

† REBLOZYL® was studied in the pivotal phase 3 MEDALLIST trial of 229 patients with IPSS-R very low, low, or intermediate-risk MDS who have ring sideroblasts and require RBC transfusions (≥2 RBC units/8 weeks) who were randomized 2:1 to REBLOZYL® (n = 115) or placebo (n = 114). Patients were required to have had an inadequate response to prior treatment with an ESA, be intolerant of ESAs, or be ineligible for ESAs (e.g., serum EPO >200 U/L). MEDALLIST excluded patients with deletion 5q MDS, white blood cell count >13 Gi/L, neutrophils <0.5 Gi/L, platelets <50 Gi/L, or with prior use of a disease-modifying agent for treatment of MDS. REBLOZYL® was administered 1 mg/kg subcutaneously every 3 weeks. Two dose-level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg) if the patient had an RBC transfusion within the prior 6 weeks. All patients received best supportive care, which included RBC transfusions as needed.

‡ REBLOZYL® was studied in a pivotal phase 3 BELIEVE trial of 236 adult patients with β-thalassemia requiring regular RBC transfusions (≥20 RBC units per 24 weeks) with no transfusion-free period greater than 35 days during that period who were randomized 2:1 to REBLOZYL® (n = 228) or placebo (n = 112). In BELIEVE, REBLOZYL® was administered subcutaneously once every 3 weeks as long as a reduction in transfusion requirement was observed or until unacceptable toxicity. Patients were able to receive BSC as needed, including RBC transfusions; iron-chelating agents; use of antibiotic, antiviral, and antifungal therapy; and nutritional support. The exclusion criteria for this trial included HbS or hemoglobin C disease, major organ damage (liver, heart, or lung disease), or renal insufficiency; recent deep vein thrombosis or stroke; or recent use of ESA, immunosuppressant, or hydroxyurea therapy.1

BSC=best supportive care; ESA=erythropoiesis-stimulating agent; HbS=hemoglobin S; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndrome; RBC=red blood cell.

References:
β-THALASSEMIA†

REBLOZYL® SIGNIFICANTLY REDUCES
RBC TRANSFUSION BURDEN†

EXPLORATORY ENDPOINT—
≥33% REDUCTION IN TRANSFUSION BURDEN COMPARED TO BASELINE OVER ANY CONSECUTIVE 12-WEEK PERIOD†

70.5% REBLOZYL® (n=158/224)4

29.5% Placebo (n=33/112)4

ACTIVE INGREDIENT: Each vial contains 25 mg or 75 mg of luspatercept. After reconstitution, each mL of solution contains 50 mg luspatercept.

INDICATIONS: Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anemia due to very low, low and intermediate-risk myelodysplastic syndromes (MDS) in very low-risk disease (i.e., low IPSS-R score) who had an unsatisfactory response to or are ineligible for erythropoiesis-stimulating agent-based therapy. Reblozyl is indicated for the treatment of adult patients with transfusion-dependent anemia associated with beta-thalassemia. Reblozyl is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia. DOSEAGE & ADMINISTRATION: Myelodysplastic syndromes: The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who are not RBC transfusion-free after at least 2 consecutive doses at the 1.0 mg/kg starting dose, the dose should be increased to 1.33 mg/kg. If patients are not RBC transfusion-free after at least 2 consecutive doses at the 1.33 mg/kg dose level, the dose should be increased to 1.75 mg/kg. The dose increase should not occur more frequently than every 6 weeks (2 administrations) and should not exceed the maximum dose of 1.75 mg/kg every 3 weeks. β-thalassemia: The recommended starting dose of Reblozyl is 1.0 mg/kg administered once every 3 weeks. In patients who do not achieve a response, defined as a reduction in RBC transfusion burden of at least a third after at least 2 consecutive doses (6 weeks), at the 1.0 mg/kg starting dose, the dose should be increased to 1.25 mg/kg every 3 weeks. Method of administration: For subcutaneous use. After reconstitution, Reblozyl solution should be injected subcutaneously into the upper arm, thigh or abdomen. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients. Pregnancy. SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Trancaclitase: In combination with trancaclitase, the dose of trancaclitase should be reduced. In transplant recipients, the dose of trancaclitase should be reduced. In patients with b-thalassemia, the dose of trancaclitase should be reduced. In patients with MDS, the dose of trancaclitase should be reduced. In patients with other hematologic disorders, the dose of trancaclitase should be reduced. In patients with MDS, the dose of trancaclitase should be reduced. In patients with other hematologic disorders, the dose of trancaclitase should be reduced.

Please refer to the full prescribing information before prescribing. Prescribing information is available on request.

Date of revision of the text: September 2021
Capacity Building and Education Programmes on End-of-Life Care

CME Online Courses for Doctors

Target: All doctors including specialists, non-specialists and trainees

CME point* from HKCA, HKCCM, HKCEM, HKCFP, HKCP, HKCPsych, CSHK, CUHK (non-specialist)

*details refer to each video link

Duration: 1 hour

E-learning period:

17 Oct 2022 - 31 Mar 2023

What is Advance Care Plan?

Speaker: Dr. Christopher Lum

Palliative Care for Dying Patients

Speaker: Dr Lam Kwok Kwong

End-of-Life Care for Older Adults

Speaker: Dr Kong Tak Kwan
https://bit.ly/3C7yoRE

Case Study on EOL Care Practice

Speaker: Dr Chan Fei Charles
Allogeneic Haematopoietic Stem Cell Transplantation

Dr Garret MK LEUNG
MBBS(HK), MRCP(UK), FHKAM(Medicine)
Consultant

Dr Joycelyn PY SIM
MBBS(HK), FRCPEdin, FHKAM(Medicine)
Associate Consultant

INTRODUCTION

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is considered the only curative treatment of choice for many high-risk haematological malignancies. It can be seen as an effective form of immunotherapy applied systematically against leukaemia. In addition to the cytotoxic effect of the high-dose pre-transplantation conditioning chemotherapy, the donor-derived stem cells provide allo-immunity that enables a graft-versus-tumour (GVT) effect to eradicate residual disease and prevent relapse. Along with the introduction of the various novel agents, many would have expected allo-HSCT to become a “sunset industry”. Instead, the annual number of allo-HSCT has continued to increase worldwide in the past decade.1-3 Here we shall review the development of allo-HSCT with emphasis on recent new advances and the current situation of allo-HSCT in Hong Kong.

TRENDS IN ALLO-HSCT IN THE PAST 50 YEARS

The first allo-HSCT was pioneered by the 1990 Nobel laureate, Dr E. Donnall Thomas, and reported in the New England Journal of Medicine on September 12, 1957. In the beginning, access to allo-HSCT was limited. This was due to the high transplant-related mortality (TRM) secondary to the high-dose conditioning chemoradiotherapy, the risks of life-threatening infections and bleeding during the cytopenic phase, and the limited treatment strategies for severe graft-versus-host disease. Donor availability was another issue as only patients with a human leukocyte antigen (HLA)-matched sibling could undergo this treatment.

A comparison of transplantations performed over the last two decades would show that survival in allo-HSCT recipients have improved across all age spectra.3 There has been significant improvement in the field of transplantation over the last 50 years, attributable to the introduction of the less toxic reduced-intensity conditioning (RIC), the improved supportive care including more potent antimicrobial agents and better transfusion support, and the newly available FDA-approved drug treatments for both acute and chronic graft-versus-host disease (GVHD). The introduction of unrelated donor and cord blood transplantations, and the subsequent establishment of the international unrelated donor registries and cord blood banks have significantly increased donor availability and have allowed patients who do not have any HLA-matched sibling to benefit from this treatment. All these advancements have led to a dramatic increase in the number of allo-HSCT, especially among “silver hair” patients who were once considered ineligible. According to the CIBMTR database, only 48 patients, representing 2% of all allo-HSCT performed in the year 2000, were aged > 65 years. In 2019, the number of allo-HSCT recipients aged > 65 years had grown to 1,888 patients, representing 26% of the total number of allo-HSCT performed in 2019. Given that the average age of diagnosis of acute myeloid leukaemia (AML), a blood malignancy which is the most common indication for allo-HSCT, is 68 years of age, this advancement has greatly improved the prognosis of the “silver hair” AML patients.4

WHAT IS NEW IN ALLO-HSCT OVER THE LAST DECADE?

Donor availability remains one of the major challenges to the success of allo-HSCT. Only about a quarter of the patients who need the transplant can find an HLA-identical sibling donor. Despite the expansion of the worldwide unrelated donor programme, the complicated search process for an unrelated donor necessitates 4-6 months of lag time from initiation of a search to the actual donation of stem cells. Unrelated cord blood as an alternative donor source offers the advantages of easy procurement and immediate availability; the low cell content poses engraftment problems for transplantation in adult patients.


In contrast, almost all patients who need an HSCT would have at least one identifiable haploidentical donor within his family, nuclear or extended. Biological children, parents, siblings, and frequently even more distant family members who share one haplotype are potentially qualified as donors (Fig. 1). In addition, these donors are often highly motivated and readily willing to adjust their own life plans in order to accommodate to patients’ transplant schedule and changes in clinical conditions.

Yet, because of the increased T-cell mediated allo-reactivity, the early development of haploidentical HSCT (haplo-HSCT) was hindered by the high rates of GVHD and graft failure, resulting in ~10% long-term survival.5

By removing the T-cells from the graft, Reisner and colleagues performed the first successful haplo-HSCT in children with severe combined immunodeficiency (SCID) using T-cell depleted (TCD) haploidentical...
However, the same approach was not applicable to other non-SCID patients, in whom the underlying immune system is generally functional, and a high rate of graft failure due to the unopposed host versus graft (HVG) rejection.

This limitation was later overcome by the use of T-cell depleted (TCD) "megadose" stem cell grafts (containing ~10×10^6/kg CD34+ haematopoietic stem cells). Although the "megadose" TCD approach was able to improve the primary engraftment rate to >90% with comparable GVHD rate as HLA-matched transplants, there was a high non-relapse mortality of >30% observed across studies, largely owing to post-transplant infections and primary disease relapse. As a result, the 2-year event-free survival probability was only ~40 - 50%.

The ultimate breakthrough that led to the widespread use of haplo-HSCT, including in resource-restricted countries, was the introduction of the "post-transplant cyclophosphamide" (PTCy)-based haploidentical transplantation using a T-cell replete (TCR, i.e., non-T-cell depleted) stem cell graft. This immunological effect of PTCy was first observed in the 1960s in animal models of allogeneic skin grafts whereby cyclophosphamide administration within a window of up to 4 days after grafting delayed rejection.\(^7\) It was thought that the PTCy exerts selective deletion of the alloreactive T cells. However, more recent work by Kanakry and colleagues in dedicated murine models suggested that the PTCy mediates its effects through the preferential recovery and expansion of regulatory T cells after PTCy.\(^8\)

Pioneered by the Johns Hopkins group, the first clinical study of unmanipulated haplo-HCT was performed using non-myeloablative conditioning and one dose of PTCy at 50 mg/kg on day +3. The post-transplant PTCy immunosuppressive regimen included mycophenolate mofetil and tacrolimus starting on day +4 in 13 patients (Fig. 2A).\(^9\) Subsequent prospective clinical trials, administering two doses of PTCy on days +3 and +4, demonstrated a trend towards a higher engraftment and a lower risk of extensive chronic GVHD, which has later become the current standard PTCy protocol.

Another TCR haplo-HSCT commonly used is the GIAC approach pioneered by the Peking University People’s Hospital (PUPH) group (Fig. 2B).\(^10\) This approach uses Antihuman Thymocyte Immunoglobulin (ATG) part of the conditioning regimen to overcome the allo-reactivity across the HLA barrier. Owing to its long half-life, ATG exerts a dual effect on both recipient T cells and donor T cells, and therefore facilitating engraftment and preventing GVHD at the same time. The stem cell graft used in the GIAC protocol consists of a combination of G-CSF-primed bone marrow and PBSC. The combination of both marrow and stem cell graft allows a higher CD34+ cells from the PBSC graft that promote engraftment and decrease relapse. In addition, by virtue of inducing differences in cytokine milieu, T-cell polarisation and T-cell hypo-responsiveness, the GCSF-primed bone marrow leads to less acute and chronic GVHD. In the initial study of 171 patients using GIAC, most of whom had acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), or chronic myeloid leukaemia (CML), all patients achieved engraftment with sustained full donor chimerism. The rates of leukaemia-free survival and cumulative incidences of grade II-IV acute GVHD and extensive chronic GVHD were comparable to other conventional alternative donor allo-HSCT.
Allo-HSCT in Hong Kong

Queen Mary Hospital (QMH) is the only adult allo-HSCT centre in Hong Kong. Lie et al. described the landscape of HSCT in Hong Kong in 2009, including 1708 HSCT performed at QMH during the period 1990 to 2008. Adult recipients accounted for 85.8%, and allo-HSCT accounted for 66%. Acute myeloid leukaemia (AML) was the most common indication for adult HSCT, followed by chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) (Table 1). The main donor source was matched sibling at the beginning, with a gradual increase in the number of unrelated donor transplants to about one-third of all allo-HSCT by 2008.

Another major change observed is the increasing use of haplo-identical donor transplantation. Matched sibling and unrelated donors were the main donor source for our patients before 2014. QMH started our adult Haplo-HSCT programme in 2014. The option was offered to patients with high-risk diseases yet lacking suitable matched related or unrelated donors. The haploidentical donor has proven to be a valuable donor source for HSCT during the COVID outbreak. The number of haplo-HSCT even surpassed that of sibling and unrelated HSCT in 2021 (Fig. 5).

A decade on, there have been significant changes in the HSCT practice. Among 893 adult patients who underwent allo-HSCT at QMH during the period 2012 to 2021, AML remained the most common indication (N=388, 43%), followed by ALL (N=221, 25%), then myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) (N=119, 13%) (Fig. 3). Only 5% of patients had allo-HSCT for chronic myeloid leukaemia (CML) as tyrosine kinase inhibitors have become the standard of care since the introduction of imatinib.

We have also observed an increase in the age at which patients received their first transplantation (Fig. 4). Omitting the 16.6% of patients aged < 20 years in the Lie study, the median age-group at transplantation (including auto-HSCT) was 40-49 years, as compared to 50-59 years in the current study accounting for 39% of all allo-HSCT performed during this period. This change can be attributed to the introduction of the less toxic reduced-intensity conditioning to patients deemed unfit for the more toxic conventional myeloablative conditioning.

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Table 1. Top five indications for allogeneic HSCT in Hong Kong (Personal data of the authors)

<table>
<thead>
<tr>
<th></th>
<th>1990-2009*</th>
<th>2012-2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukaemia</td>
<td>24%</td>
<td>43%</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>12%</td>
<td>25%</td>
</tr>
<tr>
<td>Myelodysplastic syndrome/myeloproliferative neoplasm</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>6%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Derived from Lie HKMJ 2009.11

---

Another major change observed is the increasing use of haplo-identical donor transplantation. Matched sibling and unrelated donors were the main donor source for our patients before 2014. QMH started our adult Haplo-HSCT programme in 2014. The option was offered to patients with high-risk diseases yet lacking suitable matched related or unrelated donors. The haploidentical donor has proven to be a valuable donor source for HSCT during the COVID outbreak. The number of haplo-HSCT even surpassed that of sibling and unrelated HSCT in 2021 (Fig. 5).
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Choose IMBRUVICA® first, because life is the ultimate endpoint

The first and only BTKi available with up to 10 years follow-up.

Oral tablets available now

<table>
<thead>
<tr>
<th>Frontline CLL</th>
<th>R/R CLL</th>
<th>R/R MCL</th>
<th>R/R WM</th>
</tr>
</thead>
</table>

* Time of follow-up varies for different indications; median PFS ranged from 39 months for monotherapy to 82.1 months for combination therapy.

**INDICATIONS:**
- Imbruvica as a single agent for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
- As a single agent or in combination with rituximab or obinutuzumab indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).
- As a single agent or in combination with bendamustine and rituximab (BR) indicated for the treatment of adult patients with CLL who have received at least one prior therapy.
- In first line treatment for patients unsuitable for chemo-immunotherapy.
- In combination with rituximab indicated for the treatment of adult patients with WM.

**DOSE & ADMINISTRATION:**
- MCL: 560 mg once daily.
- CLL and WM: either as a single agent or in combination, 420 mg once daily.
- Recommended to administer IMBRUVICA prior to anti-CD20 therapy when given on the same day.

**SIDE EFFECTS:**
- Diarrhoea, neutropenia, musculoskeletal pain, rash, haemorrhage, thrombocytopenia, nausea, pyrexia, arthralgia, and upper respiratory tract infection.

**CONTRAINDICATIONS:**
- Hypersensitivity to the active substance or to any of its excipients.

**WARNINGS & PRECAUTIONS:**
- Use of preparations containing St. John’s Wort is contraindicated in patients treated with IMBRUVICA.

**INTERACTIONS:**
- Avoid co-administration with strong CYP3A4 inhibitors and strong or moderate CYP3A4 inducers. If a moderate CYP3A4 inhibitor must be used, reduce IMBRUVICA dose. Monitor patient closely.

**REFERENCES:**
**Direct ON-TUMOUR Actions**

- Complement-dependent Cytotoxicity
- Antibody-dependent Cell-mediated Cytotoxicity
- Antibody-dependent Cellular Phagocytosis
- Apoptosis via Crosslinking

**IMMUNOMODULATORY Actions**

- Modulation of Tumour Microenvironment
- Increase in Cytotoxic & Helper T Cells
- Depletion of Immunosuppressive Cells

---

**MYELOMA CELL DEATH**

**DARZALEX**: The first human monoclonal IgG1k antibody targeting CD38 antigen which induces myeloma cell death through direct on-tumour and immunomodulatory actions

**IN MULTIPLE MYELOMA**

**CD38**

**DARZALEX** (daratumumab) is indicated:
- in combination with lenalidomide and dexamethasone or with bortezomib and melphalan, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant,
- in combination with thalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant,
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

**See DARZALEX** prescribing information for full indication, including its use as a monotherapy.

---

**Abbreviations:**
- CD38: Cluster of Differentiation 38
- DARZALEX: Daratumumab
- IgG1k: Immunoglobulin G1κ
- FAQs: Frequently Asked Questions

---

**References:**

**Cancer Drug Concentrate for Solution for Infusion 100mg/5mL, 400mg/20mL**

**Address for Information:**

Janssen, a division of Johnson & Johnson (HK) Ltd
13/F Tower 1, Grand Century Place, 193 Prince Edward Road West, Mongkok, Hong Kong.
Tel: 2736 1711 Fax: 2736 1926
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**Additional Information:**
1. Antibody-dependent cell-mediated cytotoxicity, also known as antibody-dependent cellular cytotoxicity (ADCC), is a mechanism by which antibodies activate immune cells to destroy target cells.
2. CD38 is a transmembrane glycoprotein expressed on the surface of myeloma cells.
3. DARZALEX is approved for the treatment of adults with multiple myeloma.
4. The drug is administered intravenously over 3 hours.
5. It is a humanized monoclonal antibody that targets CD38, a molecule expressed on myeloma cells.

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**Key Points:**
- DARZALEX is indicated for the treatment of multiple myeloma.
- It is administered intravenously as a 3-hour infusion.
- It is used in combination with lenalidomide and dexamethasone or with bortezomib and melphalan.
- It is also approved as monotherapy for relapsed and refractory multiple myeloma.

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**Image:** The image contains a diagram illustrating the mechanisms of action of DARZALEX, including its effects on myeloma cells, T cells, and helper T cells. The diagram also highlights the role of DARZALEX in modulating the tumor microenvironment and depleting immunosuppressive cells.

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**Table:** The table provides a summary of the mechanisms of action of DARZALEX, including its effects on myeloma cells, T cells, and helper T cells. The table also highlights the role of DARZALEX in modulating the tumor microenvironment and depleting immunosuppressive cells.
Up until 30 June 2022, a total of 132 adult haplo-HSCT have been performed at QMH. The median age of the HSCT cohort was 48 years (range, 20-66 years). AML and high-risk MDS/MPN again accounted for the majority (55%) of the cohort, followed by ALL (40%), relapsed lymphoma (14%) and CML (3%). Fifty-six percent were in second remission or accelerated phase/blastic crisis, or had active disease or high-risk MDS/MPN at the time of HSCT. Seventeen patients underwent their second transplantation, and two patients their third. Parents were the donors in 24% of haplo-HSCT, haploidentical siblings in 35%, and children in 41%. One patient received haematopoietic stem cells from his nephew.

With a median follow-up of 423 days (range, 42-2049 days) among 95 surviving patients, the 1-year progression-free survival (PFS) and overall survival (OS) were 61% and 77%, respectively (Fig. 6). The main cause of death was post-transplant relapse of the primary haematological disease, accounting for 61% of mortality in the cohort.
CONCLUSION

Despite the many advancements in the field of allogeneic haematopoietic stem cell transplantation we have made during the past 50 years, many challenges remain. With the less toxic reduced-intensity conditioning and the improved supportive care, allo-HSCT is now a much safer treatment option than we first started. On the other hand, relapse of primary disease emerged as the major cause of failure after allo-HSCT (a topic not covered here). Methods of manipulating the graft immune activity to maximise GVL and minimise GVHD will be a new direction which could promote the next breakthrough in allo-HSCT. Novel agents likely serve to complement and build on the immunological GVL platform set up by allo-HSCT, rather than replacing it.

In a survey conducted in United States, transplantation physicians predicted a continued increase in the number of HSCTs performed for malignant as well as benign diseases such as sickle cell disease, autoimmune and genetic disorders in 2023. While the majority (63%) predicted that matched related donors will remain the preferred donor source for adult HSCT recipients, haploidentical donor (21%) ranked second and matched the preferred donor source for adult HSCT recipients, predicted that matched related donors will remain an important weapon in our battle against haematological malignancies in the years to come.

References

ω-3 enriched PN – proven to improve clinical outcomes with excellent safety profile²:
- Significantly reduced length of hospital stay overall by 3 days.
- Significantly reduced infection rate by 39%.

- Extensive compatibility data with micronutrients.

Complete parenteral nutrition therapy with micronutrients:
- All PN prescriptions should include a daily dose of multi-vitamins and trace elements²,³.
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Approved for children ≥ 2 years

References:

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INTRODUCTION

In the last decade, immunotherapy has emerged as a breakthrough in cancer therapeutics. Among all cancers, haematological malignancies are particularly susceptible to manipulation of the immune system because of several reasons: (i) the immune effector cells are usually in constant contact with the malignant cells, allowing maximal interaction between the two parties; (ii) the normal counterparts of the malignant blood cells are often antigen-presenting in nature and are thus more immunogenic; and (iii) the expression of surface molecules in the malignant cells is relatively unique, making these molecules good targets for immunological attack without sacrificing organ function. There are many ways in which the immune system can be harnessed to control blood cancers. Readers can also refer to the other articles of this issue. In the present article, I will focus on the latest form of cell-based immunotherapy, chimeric antigen receptor T-cell (CAR-T cell) therapy.

Cell-based immunotherapy involves modification or transferal of immune cells to fight against cancer cells. Chimeric antigen receptor T cell (CAR-T) therapy is the most successful form of cell-based immunotherapy to date. Autologous or allogeneic T lymphocytes are genetically engineered to express chimeric antigen receptors (CARs), targeting the antigens expressed on the tumour cell surface. CARs are synthetic transmembrane proteins designed to activate T lymphocytes, resulting in tumour cell cytotoxicity independent of human leucocyte antigen (HLA). A CAR consists of three parts, an ectodomain responsible for antigen recognition, a transmembrane domain, and an intracellular domain responsible for intracellular signalling. An ectodomain is usually formed from a single chain variable fragment (scfv), which is a fusion protein of the variable region of the heavy and light chains of an antibody. While the intracellular domain of the first-generation CAR contains CD3-zeta for T lymphocyte activation, this signal alone is insufficient for proliferation, leading to short in vivo persistence of CAR-T. In the second and subsequent generations of CAR, co-stimulatory proteins are built together with CD3-zeta, which substantially improves CAR-T cell proliferation and persistence after infusion.

The manufacturing process of CAR-T cells is complex and labour-intensive (Fig. 1). T-lymphocytes are collected from the patient’s blood through leucopheresis. The harvested cells are then activated in vitro. Next, the CAR transgene will be introduced into the T-lymphocyte genome (typically through viral transduction). Further expansion of T-lymphocytes in vitro is performed before infusion to patients.
Guidelines of current good manufacturing practice (GMP) should be closely followed regarding the safety, purity and potency of the final product. Depending on the specific product, the manufacturing process takes two to four weeks to complete, during which the patient may need bridging chemotherapy/radiotherapy to control the disease before the infusion of CAR-T cells. The typical cell dose delivered is in the range of 10^6 CAR-T cells per kg body weight.

There are currently six CAR-T products approved by the United States Food and Drug Administration (FDA): Tisagenlecleucel (Tisa-cel, for treatment of relapsed or refractory (R/R) B-lineage lymphoblastic leukaemia (B-ALL), large B-cell lymphoma and follicular lymphoma), Axicabtagene Ciloleucel (Axil-cel, for treatment of R/R large B-cell lymphoma), Brexacabtagene Autoleucel (Brex-cel, for treatment of R/R B-ALL and mantle cell lymphoma (MCL)), Lisocabtagene Maraleucel (Liso-cel, for treatment of R/R large B-cell lymphoma and follicular lymphoma), Idecabtagene Vicleucel (Idel-cel, for treatment of R/R multiple myeloma) and Ciltacabtagene Autoleucel (Cilta-cel, for treatment of R/R multiple myeloma). The first four CAR-T cell products target CD19, a cell surface protein almost universally expressed on benign and malignant B-lymphocytes, while the latter two target B-cell maturation antigen (BCMA) expressed on mature plasma cells and myeloma cells.

Results from clinical trials for CAR-T treatment in different haematological malignancies are encouraging. For example, in R/R ALL, the complete remission (CR) rates after CAR-T cell infusion are 71% for Brex-cel and 81% for Tisa-cel. In Tisa-cel treated patients, around 50% are still in CR at 12 months post-infusion. These patients can be considered cured as relapse beyond 12 months is rare. In R/R large B-cell lymphoma, the complete response rates for Tisa-cel, Axil-cel and Liso-cel were 40%, 52% and 53%, respectively. A consistent finding among all three products in these pivotal trials for aggressive lymphoma is that roughly 30-40% of patients can achieve durable remission. In R/R myeloma, Ciltacabtagene Autoleucel induces a stringent complete response (sCR) in 67% of patients, and the median progression-free survival is not reached with a median follow-up time of 12.4 months. Taken together, CAR-T therapy has shown a remarkable success in the treatment of R/R blood cancers, which was unachievable by contemporary chemotherapeutic regimens.

The side-effect profile of CAR-T cell therapy is different from conventional chemotherapy. A few days before infusion of CAR-T cells, chemotherapy is generally given to deplete resident lymphocytes to optimise in vivo expansion of CAR-T cells after infusion. Neutropenia is, therefore, common, and patients could suffer from opportunistic infections. In addition, two important complications relatively unique to CAR-T cell therapy may occur: cytokine release syndrome (CRS) and immune effector cells associated neurotoxicity syndrome (ICANS). CRS results from massive cytokine release due to the activation and proliferation of CAR-T cells. Cytokines, including interleukin-6, interleukin-10 and interferon-gamma, are markedly elevated, leading to fever, vasodilatory shock, systemic capillary leak and multiple organ failure. Grade 3/4 CRS has a reported incidence of 10-40%. Treatment is aimed at dampening excessive inflammation with corticosteroid and interleukin-6 receptor antagonists (Tocilizumab). ICANS occurs because of a breakdown of the blood-brain barrier, leading to leakage of CAR-T cells and inflammatory cytokines into the central nervous system (CNS). The incidence ranges from 0-50% across different products. Manifestations of ICANS vary and can include tremors, headache, confusion, aphasia, convulsion or even coma. Management of low grade ICANS is supportive. If ICANS is severe, corticosteroids (dexamethasone) should be given to control excessive inflammation in the CNS.

Despite the high remission rate in clinical trials, some patients eventually have disease relapse. Clinical and molecular predictors may help to identify patients at a higher risk of relapse. Re-treatment with CAR-T infusion generally has a much lower rate of success, which is likely due to immunity against the CAR molecule.

CAR-T cell therapy was introduced to public hospitals in May 2021. Tisagenlecleucel is the only registered CAR-T cell product in Hong Kong and is licensed for treating R/R ALL under the age of 25 and R/R large B-cell lymphoma. At the time of writing this manuscript, Queen Mary Hospital and Hong Kong Children’s Hospital are the only public hospitals treating adult and pediatric CAR-T patients, respectively. After financial assessment, eligible patients will be offered a subsidy from the Community Care Fund.

Globally, the scale of CAR-T trials is growing at an unprecedented pace. The indications for CAR-T treatment are also expanding rapidly. China is currently running the largest number of CAR-T trials, followed by the US. Refinement of CAR-T manufacturing procedure, better preventive measures for complications and understanding of the pathogenesis of relapse after CAR-T will eventually make CAR-T a safer and more effective treatment strategy for haematological malignancies.

**CASE PRESENTATION**

A 67-year-old woman was referred for CAR-T cell therapy. She suffers from stage IV diffuse large B cell lymphoma with bone marrow involvement arising from pre-existing follicular lymphoma. She was treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone), R-GDP (rituximab, gemcitabine, dexamethasone and cisplatin), PRB (polatuzumab, rituximab and bendamustine) and BVP (bleomycin, vinblastine, cisplatin). None of these regimens resulted in a durable response. She was accepted into the CAR-T programme. She received bridging chemotherapy (R-DIME (rituximab, dexamethasone, ifosfamide, methotrexate and etoposide)) during CAR-T manufacturing. The CAR-T infusion was uneventful, and she was discharged on day 25. Figure 2 shows positron-emission-tomography/computerised tomography (PET/CT) images which were performed before (Fig. 2A) and one month after (Fig. 2B) CAR-T cells infusion, showing complete metabolic response. She is now six months post-treatment. Serial PET/CT scans showed no evidence of disease recurrence.
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FOR FIRST-LINE TREATMENT OF DLBCL

Reduced risk of disease progression, relapse, or death vs R-CHOP. That means more hope for the future, and more freedom from the threat of disease.

Indication
POLIVY® (polatuzumab vedotin) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).

References:
Working to take the “NO” out of “NO RESPONSE”

ICLUSIG® (ponatinib) gives appropriate patients a chance to achieve a response.¹

For patients with CML or Ph+ ALL when no other TKI is indicated, or who have the T315I mutation²

Abbreviated Prescribing Information

ICLUSIG® (ponatinib) 15 mg/45 mg tablets. Indication: In adult patients with (1) chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation; and (2) Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. Dosage: Recommended starting dose: 45 mg once daily. Assess the patient’s cardiovascular status before treatment initiation. Refer to the package insert for dose modification for management of toxicities. Contraindications: Hypersensitivity to the active substance or any of the excipients. Warnings and precautions: Risk of myelosuppression; a complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated. Monitoring for evidence of arterial occlusion and thromboembolism; interrupt treatment in such events. If decreased vision or blurred vision occurs, perform an ophthalmic examination (including fundoscopy). Reports of treatment-emergent hypertension; urgent clinical intervention required for hypertension associated with confusion, headache, chest pain, or shortness of breath. Discontinue treatment in patients developing serious heart failure. Caution recommended in patients with a history of pancreatitis or alcohol abuse. Patients with severe hypertriglyceridemia should be appropriately managed to avoid pancreatitis. Liver function tests should be performed prior to treatment initiation and monitored periodically, as clinically indicated. Interrupt treatment and evaluate patients for signs of severe hemorrhage. Monitor for active HBV infection in HBV carriers throughout therapy and for several months after treatment. Restart treatment in the event of post-treatment seroconversion. Caution recommended in patients with hepatic/renal impairment. Not advised in pregnancy; only used when clearly necessary. Stop breastfeeding during treatment & use effective contraception during treatment. Drug Interactions: Caution in concurrent use with CYP3A inhibitors/inducers. Transporter substrates (e.g. P-gp and BCRP) & anti-clogging agents in patients who may be at risk of bleeding events. Adverse reactions: Thrombocytopenia, pancreatitis, abdominal pain, atrial fibrillation, pneumonia, myocardial infarction, peripheral arterial occlusive disease, anemia, anginapectoris, decreases glomerular filtration rate, neutropenia, hypertension, coronary artery disease, congestive cardiac failure, cerebrovascular accident, sepsis, cellulitis, acute kidney injury, UTI and increased fever. Please see full Prescribing Information for details. Full prescribing information is available upon request.

Abbreviations:
CML: chronic myeloid leukemia; Ph+ ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; TKI: tyrosine kinase inhibitor

References:
2. Iclusig® (ponatinib) Hong Kong Prescribing Information revised Jan 2019.
A. Imatinib, Nilotinib, Dasatinib

Otsuka Pharmaceutical (H.K.) Ltd.
21/F, East Exchange Tower, 38 Leighton Road, Causeway Bay, Hong Kong. Tel: 2881 6299 Fax: 2577 5206
Which Type Of Watch Collector Are You?

Dr Herman SY LIU
MBBS(HK), MRCP (UK), FHKAM, FHKCP, FRCP(Glasgow), FRCP (Edinburgh)
Specialist in Hematology and Hematological Oncology

Collecting is a hobby of gathering things for fun. Common things that people collect include coins, stamps, photographs, vinyl records, musical instruments, pens, cameras, toys, drawings, art pieces, cameras, automobiles, wines, gems and watches...and Non-fungible tokens (NFT).

In recent years, younger generations are entering into the watch game, thanks to social media. I am also aware of many watch enthusiasts within the medical profession with a wide range of collections. I take this opportunity to share some of my humble timepieces. They can be divided into the following categories:

**ROLEX**

I started the discussion with the brand Rolex because it is the 'King' of watch brands to many collectors, in terms of popularity. For many years, Rolex remained the leader amongst Swiss watch brands, constituting 29% of market share and an estimated turnover of CHF 8 billion in 2021, an estimation of selling 1 million watches annually.

Since it was founded in 1908, the brand has made many innovations and introduced world renowned models like Daytona, Submariner, GMT, Day-Date, Datejust…

I have chosen four timepieces of different precious metals: Yellow Gold, Rose Gold, White Gold and Platinum (Fig. 1)

(a) Left upper quadrant: **Rolex Submariner 126619LB** in white gold, introduced in 2020, nicknamed Cookie Monster. The design is faithful to the original model launched in 1953. Wearing a yellow or rose gold watch can be a statement; white gold is definitely under the radar and can be a good alternative with the same elegance and classiness.

(b) Left lower quadrant: **Rolex GMT Master II 126715CHNR** in everose gold, introduced in 2018, nicknamed Root Beer. Rolex first introduced the everose gold in 2005; the gold used in Rolex watches is 18K, which means it is 75% gold by weight. The colour variation occurs as a result of the different materials used in composing the other 25% of the alloy (copper, platinum etc.). I did not ask for this particular model, but who will turn down an offer from the authorised dealer nowadays?

(c) Right upper quadrant: **Rolex Cosmograph Daytona 116506** in platinum, introduced in 2013, to celebrate the 50th anniversary of the original chronograph. It is the first Daytona in platinum with a heft of 286 grams. The dial is of ice-blue colour, and the bezel is brown, paying homage to Paul Newman’s famous blue eyes and brown hair. A keeper for sure!

(d) Right lower quadrant: **Rolex Submariner 126618LB** in yellow, introduced in 2020. I particularly like the combination of yellow gold and a royal blue dial which had been in production for many years in the submariner line. I had been in love with its predecessor since I was a medical student.

However, my daily wear is seldom precious metal Rolexes; you may see me wearing Milgauss and AirKing instead.

**THE HOLY TRINITY SPORTS WATCHES**

When I used the term ‘King’ to describe Rolex earlier, I knew some watch experts would disagree. The Big Three or the Holy Trinity should be Patek Philippe, founded in 1839; Vacheron Constantin, founded in 1755 and Audemars Piguet, founded in 1875. They are at the forefront of watchmaking, innovation, and luxury since...
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their founding. It was Gerald Genta who designed the first integrated bracelet luxury sports watches, Audemars Piguet Royal Oak and Patek Philippe Nautilus in 1972 and 1976 respectively (Fig. 2).

(a) Left: Patek Philippe Nautilus 5740G, introduced in 2018. It became the most complicated model of the Nautilus collection, yet the dimension is very similar to that of the base model 5711. To me, it is one the most good looking and functional sports watches and always reminds me of the slogan: You never actually own a Patek Philippe. You merely look after it for the next generation. It is also a very comfortable watch to wear.

(b) Middle: Vacheron Constantin 4500V/110A-B128, introduced in 2016. It is the third generation of the Overseas line, with an innovative quick-release functionality; the Maltese cross-inspired integrated bracelet can be swapped for either of the two straps provided with the watch within seconds. “Do better if possible, and that is always possible” is the vision of the company.

(c) Right: Audemars Piguet Royal Oak Jumbo Extra-Thin "50th Anniversary" 16202OR.OO.1240OR.0, introduced in 2022, to celebrate the first luxury sports watch, born in 1972. It looks exactly the same as its predecessor 15202 but with a new self-winding movement and the 50-year oscillating weight. The octagon design is a definite winner and matches the motto of the company: To break the rules, you must first master them.

Nowadays, these models are so iconic that one can recognise them from a distance. They become highly sought after and are difficult to acquire.

Fig. 2: The Holy Trinity Sports Watches (Personal Collection)

MY "DRESS WATCHES"

There is no definition for dress watches, usually they are simple, thin and elegant, to be worn with a suit. My interpretation of dress watches should be like these. (Fig. 3)

(a) Left upper quadrant: F.P. Journe Chronometre a Resonance, 4th generation, introduced in 2020, to celebrate the 20th anniversary of the first Resonance. It utilises the natural physical resonance without any mechanical transmission phenomenon, previously known as double balance or pendulum. I have to admit this is definitely one of my favourites.

(b) Left lower quadrant: A. Lange & Sohne Zeitwerk 140.032, introduced in 2009, displays the time in hours and minutes digitally, a controversial and polarised design. The unique time bridge is part of the movement that penetrates the dial, framing the displays of hours, minutes and seconds. I cannot remember how many times I watched the disc jumping minute by minute, and it felt like magic.

(c) Right upper quadrant: Patek Philippe 5270P, introduced in 2018, belongs to the family of perpetual calendars, which can be traced back since 1941 - from reference 1518, 2499, 3970, 5970 to the current reference 5270 - the entire line encompasses only five references. Reference 5270 was the first model of the line to be fitted with an in-house movement. I do not put it in a winder as setting the time, day, year and moon phase is the best way to communicate with the timepiece.

(d) Right lower quadrant: A. Lange & Sohne Datograph Up/Down 405.035, introduced in 2012, thirteen years after the first generation in 1999, a major challenge to the Swiss high-end watch manufacturers due to its technical and aesthetic development, raising the bar for in-house, high-end chronograph movements. I totally agree with what Lange CEO Wilhelm Schmid said, “It’s a watch people want to wear upside down.” And I am so lucky to have the autograph of the late Walter Lange on the accessories of this watch too.

They represent Haute Horology in the watch industry and give me tremendous joy in owning them.

Fig. 3: My “Dress Watches” (Personal Collection)
INDICATION
BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies, and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Important Safety Information for BLENREP (Belantamab mafodotin)

- The most commonly reported adverse reactions were keratitis, including keratopathy, and macular edema.
- Patients should be advised to use caution when driving or operating machinery as BLENREP may affect their vision.
- Patients should have an ophthalmic examination performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on BLENREP treatment.
- Physicians should advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment.

Applications for Summary of Product Characteristics (SPC) are pending in the following countries:

- Australia
- Canada
- France
- Germany
- Italy
- Japan
- Korea (Republic of)
- Mexico
- New Zealand
- Spain
- Switzerland
- United Kingdom
- United States

For adverse events reporting, please call GlaxoSmithKline Limited at (852) 3189 8989 (Hong Kong) or (853) 2871 5569 (Macau) or email to HK Adverse Event mailbox: HKAdverseEvent@gsk.com

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Level 10, 1-3 Pacific Place, 288 Canton Road, Kowloon
Telephone (852) 3189 8989
Fax (852) 3189 8931

A 30-minute infusion of BLENREP should be given over a minimum of 30 minutes. If a grade 2 or higher infusion-related reaction occurs during the infusion, the infusion should be continued at a reduced infusion rate and the dose reduced by 3 mg. Supportive therapy should be provided according to standard medical practice. If a grade 3 or higher infusion-related reaction occurs, the infusion should be discontinued and the dose reduced by 3 mg. Supportive therapy should be provided according to standard medical practice. If a severe infusion-related reaction occurs, the infusion should be discontinued, and the dose reduced by 3 mg. Supportive therapy should be provided according to standard medical practice. If a life-threatening infusion reaction occurs, the infusion should be discontinued, and the infusion should be reduced by 3 mg. Supportive therapy should be provided according to standard medical practice. If a grade 4 infusion-related reaction occurs, the infusion should be discontinued, and the infusion should be reduced by 3 mg. Supportive therapy should be provided according to standard medical practice. If a grade 5 infusion-related reaction occurs, the infusion should be discontinued, and the infusion should be reduced by 3 mg. Supportive therapy should be provided according to standard medical practice.

For appropriate patients faced with relapsed/refractory multiple myeloma

FORGE AHEAD
WITH A BOLD APPROACH

Target BCMA for RRMM

BLENREP is the first and only BCMA-targeted antibody-drug conjugate (ADC) monotherapy! So you can offer your RRMM patients a clear option.
THE INDEPENDENTS

Never before in the history of watchmaking have the independent watchmakers been so popular and influential. Their rise in recent years is directly related to the success of F.P. Journe and Philippe Dufour.

Like many talented watchmakers, François-Paul Journe started by restoring vintage clocks and then watches. Upon graduation in 1976, he was exposed to the works of Berthoud and Breguet, whose inventions included tourbillon, natural escapement and resonance. In 1989, Journe, together with Vianney Halter and Denis Flageollet, formed the THA (Techniques Horlogeres Appliquees), which created complications for brands like Audemars Piguet and Cartier. Journe began his own brand in 1999 with a set of Subscription Tourbillons, and the rest is history. He is acclaimed by the Grand Prix d’Horlogerie of Geneva (GPHG) for his horological creations of exception. It makes him the most awarded contemporary watchmaker of his generation. Since 2002, François-Paul Journe has received distinctions every year at the GPHG, except in 2007 and 2009 when he was a member of the Jury, (Fig. 4)

(a) Left: F.P. Journe, Chronometre Bleu, introduced in 2009. The simplistic “chrome blue” dial, the Journe’s signature hour and minute hands, white printed Arabic numerals, and a small seconds counter between 7 and 8 o’clock makes this watch just perfect in every angle. It is my first Journe watch from the boutique and a very important one!

(b) Middle: Kurono Tokyo Anniversary 2022 Grand Mori
The Japanese Hajime Asaoka started by creating custom timepieces. In 2019, he founded Kurono Tokyo to offer affordable watches; the Mori features the traditional Kyoto-style lacquer ‘urushi’ craftsmanship. Inspired by the canopies of the forest, this pattern on the dial mimics the unveiling of the sun rays seeping through the layers of the trees. There are no boutiques and every enthusiast has to try their luck at a specific time (usually HK time at 22:00) on the day of the global launch. You only have a few minutes.

(c) Right: Laurent Ferrier Classic Origin LCF036.T1.G1G, introduced in 2020, in a classic case with a smooth curving line to commemorate the 10th anniversary of the company. I am attracted by the fine finishing and futuristic case design.

Apart from being a technical director at the Patek Phillippe for 37 years, Laurent Ferrier was also a semi-professional car racer, finished third at the Le Mans in 1979, behind Paul Newman.

At the time of writing, I am waiting for the delivery of watches from Laurent Ferrier, the Gronefeld brothers, Kari Voutilainen and my favourite watchmaker F.P. Journe.

Going back to the title: Which type of watch collector am I? I do not have an answer as my taste changes along my journey. I only know that I meet a lot of new friends and I am learning something new and exciting every day. These timepieces are a great source of joy for me and I hope you find the same happiness as I do through watch collecting.

Looking forward to meeting and seeing your collections.
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<td>&lt; '*'Certificate Course on Mental Health 2022 (Video Lectures) *' &gt;</td>
<td>* Zoom Updates on LDL-C Management: Applying New Guidelines to Clinical Practice - Online *'</td>
<td>&lt; '*'Antiplatelet Management for Post PCI Patients - Online *' &gt;</td>
<td>&lt; '*'Certificate Course on Mental Health 2022 (Video Lectures) *' &gt;</td>
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<td><strong>1 THU</strong> 2:00 PM</td>
<td><strong>Zoom</strong> HKMA-HKSTP CME Lecture - AI-empowered local bone quality assessment system for osteoporotic bone fracture risk evaluation and surgical planning (Online) Organiser: The Hong Kong Medical Association and Hong Kong Science Park Speaker: Prof William Weija LU</td>
<td>Mr. Jeff CHENG Tel: 2527 8452 1 CME Point</td>
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<td><strong>2 FRI</strong> 2:00 PM</td>
<td><strong>Zoom</strong> Lipid Management for High CV Patients - Online Organiser: HKMA-Shatin Community Network Speaker: Dr Tsui Ping-tim</td>
<td>Ms. Candice TONG Tel: 3108 2513 1 CME Point</td>
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<td><strong>6 TUE</strong> 2:00 PM</td>
<td><strong>In-person / Zoom</strong> HKMA-HKSH CME Programme 2022-2023 (Physical Lecture + Online) Topic: Interventional Treatment For Metabolic Syndrome Organiser: The Hong Kong Medical Association and Hong Kong Sanatorium &amp; Hospital Speaker: Dr Daniel King-hung TONG Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong</td>
<td>HKMA CME Dept. Tel: 3108 2507 1 CME Point</td>
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<td><strong>7 WED</strong> 2:00 PM</td>
<td><strong>Zoom</strong> Common Surgical Conditions - Updates and Recent Advances - Online Organiser: HKMA-Central, Western &amp; Southern Community Network Speaker: Dr Cyrus Tak-yin TSE</td>
<td>Ms. Candice TONG Tel: 3108 2513 1 CME Point</td>
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<td><strong>8 THU</strong> 2:00 PM</td>
<td><strong>Zoom</strong> Practical Tips for Management in the Era of Disease - Specific Migraine Preventives - Online Organiser: HKMA-KLN East Community Network Speaker: Dr LEE Chi-nam</td>
<td>Ms. Candice TONG Tel: 3108 2513 1 CME Point</td>
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<td><strong>9 FRI</strong> 2:00 PM</td>
<td><strong>Zoom</strong> Antiplatelet Management for Post PCI Patients - Online Organiser: HKMA-KLN City Community Network Speaker: Dr Andrew Kei-yan NG</td>
<td>Ms. Candice TONG Tel: 3108 2513 1 CME Point</td>
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<td><strong>13 TUE</strong> 2:00 PM</td>
<td><strong>Zoom</strong> Counselling Aid: Diagnosis and Treatment Options for Heavy Menstrual Bleeding - Online Organiser: HKMA-KLN West Community Network Speaker: Dr Queenie Ho-yan WONG</td>
<td>Ms. Candice TONG Tel: 3108 2513 1 CME Point</td>
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<td><strong>14 WED</strong> 7:30 AM</td>
<td><strong>The Hong Kong Neurosurgical Society Monthly Academic Meeting - white matter tracts in the era of precision neurosurgery</strong> Organiser: Hong Kong Neurosurgical Society Speaker: Dr LAM Shek-ching Chairman: Dr POON Tak-lap Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting</td>
<td>1.5 points College of Surgeons of Hong Kong Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061</td>
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<td><strong>15 THU</strong> 2:00 PM</td>
<td><strong>Zoom</strong> Advances in Chronic Kidney Disease Management – Online Organiser: HKMA-New Territories West Community Network Speaker: Dr AU YEUNG Yick-cheung</td>
<td>Ms. Candice TONG Tel: 3108 2513 1 CME Point</td>
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<td><strong>20 TUE</strong> 7:00 PM</td>
<td><strong>Certificate Course on Mental Health 2022 (Video Lectures)</strong> Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr CHONG King-yee</td>
<td>Ms Vienna LAM Tel: 2527 8898</td>
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<td><strong>22 THU</strong> 2:00 PM</td>
<td><strong>Zoom</strong> Updates on LDL-C Management: Applying New Guidelines to Clinical Practice - Online Organiser: HKMA-HK East Community Network Speaker: Dr. Duncan Hung-kwong HO</td>
<td>Ms. Candice TONG Tel: 3108 2513 1 CME Point</td>
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Answers to Radiology Quiz

Answers:

1. A low-density pelvic lesion with a few tooth-like opacities is seen within. There was no dilated bowel, other radiopaque stone, nor pneumoperitoneum.

2. The radiographic features are most compatible with a mature ovarian teratoma (dermoid cyst). Related acute complications of dermoid cysts would be the top differential diagnoses in this clinical context, most commonly ovarian torsion. Other GI causes such as diverticulitis and appendicitis should also be considered.

3. Ultrasound pelvis or CT abdomen and pelvis. Imaging features of mature ovarian teratoma include tissues from different germ cell layers such as fat-fluid levels, teeth, tuft of hair, etc. Common radiological features of ovarian torsion include an enlarged ovary with peripherally displaced follicles, twisted vascular pedicle, and pelvic free fluid.
WE FORM THE Backbone of Regimens in Multiple Myeloma 1,2

**REVLIMID** is indicated:
- As monotherapy for the maintenance treatment of adult patients newly diagnosed MM who have undergone autologous stem cell transplantation.
- As combination therapy for the treatment of adult patients with previously untreated multiple myeloma.
- In combination with DEX for the treatment of MM in adult patients who have received at least one prior therapy.

**POMALYST** is indicated:
- In combination with BORT and DEX for the treatment of adult patients with MM who have received at least one prior treatment regimen including DEX.
- In combination with DEX for the treatment of adult patients with RRMM who have received at least two prior treatment regimens, including both **REVLIMID** and BORT, and have demonstrated disease progression on the last therapy.


References:

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Where there's ADCETRIS there's

Hope of life beyond

CD30+ lymphoma

Takeda Pharmaceuticals (HK) Ltd
23F & 24/F East Exchange Tower,
38 Leighton Road, Causeway Bay, Hong Kong
Tel: 2133 9800 Fax: 2866 2728

Oncology/Hematology Unit

Reception
Transplant Center
Pharmacy

Reference: 1* ADCETRIS Package Insert: EU-DEC18-HK-MA21

For reporting suspected side effects for Takeda products at All Hong Kong Takeda.com
For assuring medical information and other inquiries for Takeda products at medicalinfo@takeda.com