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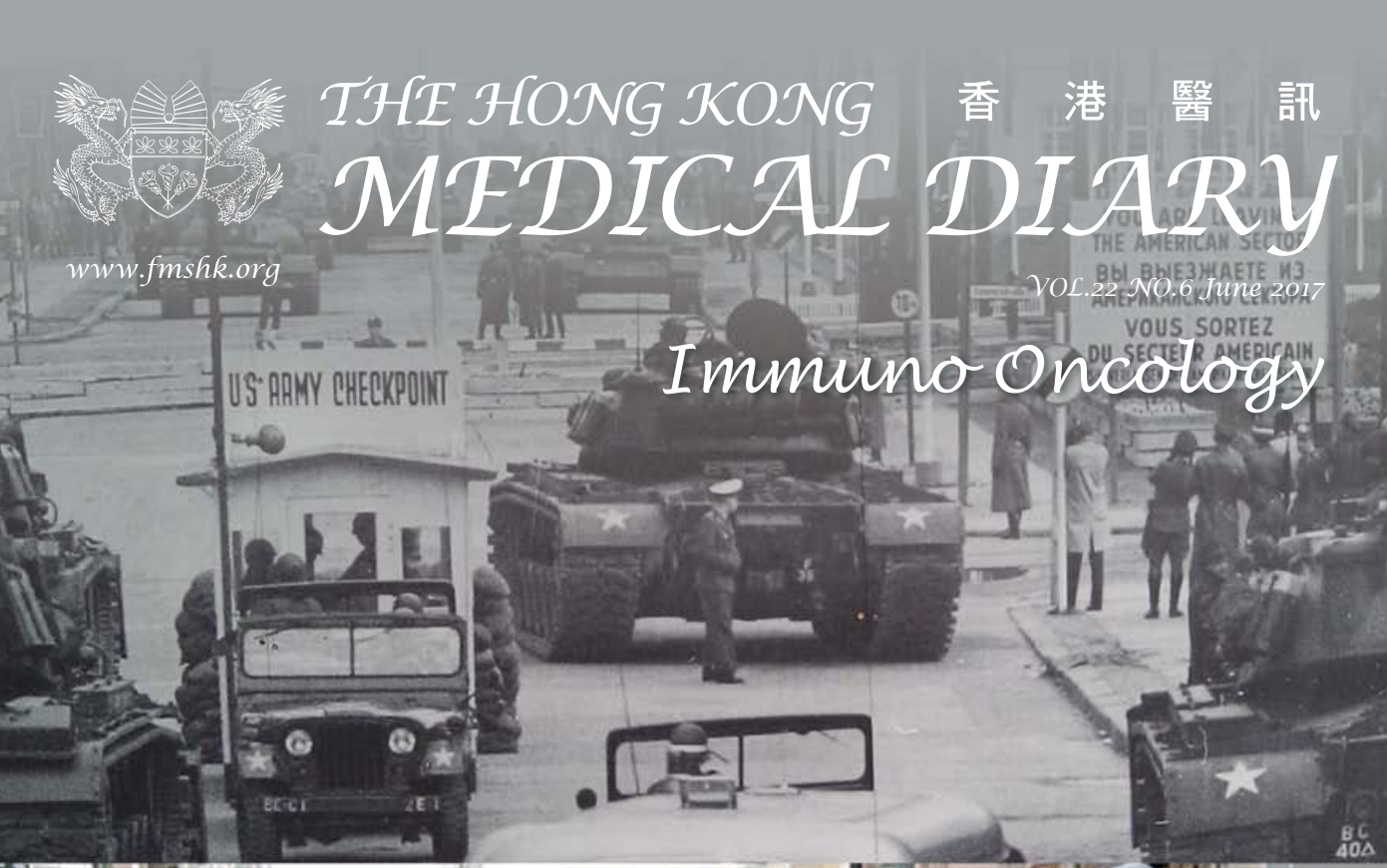

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PRIME

Vectibix® panitumumab | TARGETED PERSONALISED MEDICINE.

AGGRESSIVELY ACHIEVING **EARLY TUMOR SHRINKAGE** IN YOUR mCRC PATIENTS WITH WILDTYPE *RAS*

Adding Vectibix® to FOLFOX

≥30% TUMOR SHRINKAGE AT WEEK 8*†[1]

59% for Vectibix® + FOLFOX

VS

38% for FOLFOX alone

Difference: 21.8%†, 95%CI: 12.7-30.9; *p*<0.001

Enhancing the chance for surgical resection of tumors

CONSISTENT EFFICACY ACROSS ENDPOINTS:[1]

- **ORR** by radiological assessment: 60% vs 47%, *p*=0.003
- **Median PFS:** 11.7 m vs 8.7 m, HR=0.74, 95%CI: 0.61-0.89, *p*=0.0015
- **Median OS** 26.0 m vs 20.2 m, HR=0.76, 95%CI: 0.63-0.92, *p*=0.0057

*The results were based on pre-defined prospective-retrospective extended *RAS* mutation analysis of phase III PRIME RCT that was designed to compare the efficacy and safety of Vectibix®-FOLFOX4 with FOLFOX4 alone as first-line therapy in 1,183 patients with mCRC. 512 patients without *RAS* mutation, i.e., WT *RAS* were identified and subject to OS/ PFS analyses.

† 59.3 % of patient receiving Vectibix® + FOLFOX, and 37.5% of patients receiving FOLFOX alone had ≥30% tumor shrinkage at week 8.

mCRC = metastatic colorectal cancer, ORR = objective response rate, PFS = progression free survival, OS = overall survival, RCT = randomized clinical study, WT = wild-type

References:

1. Douillard JY, Siena S, Peeters M, Koukakis R, Terwey JH, Tabernero J. Impact of early tumour shrinkage and resection on outcomes in patients with wild-type *RAS* metastatic colorectal cancer. Eur J Cancer 2015;51:1231-1242.

Vectibix® (Panitumumab) Abbreviated Prescribing Information
Vectibix® Concentrate for Solution for Infusion 20 mg/mL

INDICATIONS: Vectibix is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC) as first-line in combination with FOLFOX or FOLFIRI, as second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan) and as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. **DOSAGE AND ADMINISTRATION:** The recommended dose of Vectibix is 6 mg/kg of bodyweight given once every two weeks. Prior to infusion, Vectibix should be diluted in sodium chloride 9 mg/mL (0.9%) solution for injection to a final concentration not to exceed 10 mg/mL. Modification of the dose of Vectibix may be necessary in cases of severe (≥ grade 3) dermatological reactions. There is no clinical data to support dose adjustments in the elderly. Vectibix must be administered as an intravenous (IV) infusion via an infusion pump, using a low protein binding 0.2 or 0.22 micrometer in-line filter, through a peripheral line or indwelling catheter. The recommended infusion time is approximately 60 minutes. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1000 mg should be infused over approximately 90 minutes. A reduction in the rate of infusion of Vectibix may be necessary in cases of infusion-related reactions. Vectibix must not administered as an intravenous push or bolus. **CONTRAINDICATIONS:** Vectibix is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to the active substance or to any of the excipients, and in patients with interstitial pneumonitis or pulmonary fibrosis. The combination of Vectibix with oxaliplatin-containing chemotherapy is contraindicated for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** *Dermatological reactions and soft tissue toxicity:* Dermatologic related reactions, a ph armacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients (approximately 90%) treated with Vectibix. Severe (NCI-CTC grade 3) skin reactions were reported in 34% an d life-threatening (NCICTC grade 4) skin reactions in < 1% of patients who received Vectibix in combination with chemotherapy. *Pulmonary complications:* Cases of interstitial lung disease (ILD), both fatal and non-fatal, have been reported, mainly from the Japanese population. *Electrolyte disturbances:* Progressively decreasing serum magnesium levels leading to severe (grade 4) hypomagnesaemia have been observed in some patients. Other electrolyte disturbances, including hypokalaemia, have also been observed. *Infusion related reactions:* Across monotherapy and combination mCRC clinical studies, infusion-related reactions (occurring within 24 hours of an infusion) were reported in approximately 4% of Vectibix-treated patients, of which < 1% were severe (NCI-CTC grade 3 and grade 4). Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema that occurred more than 24 hours after the infusion. *Acute renal failure:* Acute renal failure has been observed in patients who develop severe diarrhoea and dehydration. *Ocular toxicities:* Serious cases of keratitis and ulcerative keratitis have been rarely reported in the post-marketing setting. Vectibix should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration. *Patients with ECOG 2 performance status:* Assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC. A positive benefit-risk balance has not been documented in patients with ECOG 2 performance status. **INTERACTIONS:** The infusion line should be flushed with sodium chloride solution before and after Vectibix administration to avoid mixing with other medicinal products or Intravenous solutions. Vectibix should not be administered in combination with IFL chemotherapy or with bevacizumab-containing chemotherapy. **PREGNANCY, LACTATION AND FERTILITY:** *Pregnancy:* There are no adequate data from the use of Vectibix in pregnant women. *Breast-feeding:* It is unknown whether panitumumab is excreted in human breast milk. *Fertility:* Animal studies have shown reversible effects on the menstrual cycle and reduced female fertility in monkeys. Panitumumab may impact the ability of a woman to become pregnant. **UNDESIRABLE EFFECTS:** Very Commonly reported adverse reactions occurring in ≥ 20% of patients were gastrointestinal disorders [diarrhoea (50%), nausea (41%), vomiting (27%), constipation (23%) and abdominal pain (23%)]; general disorders [fatigue (37%), pyrexia (20%)]; metabolism and nutrition disorders [anorexia (27%)]; infections and infestations [paronychia (20%)]; and skin and subcutaneous disorders [rash (45%), dermatitis acneiform (39%), pruritus (35%), erythema (30%) and dry skin (22%)]. **OVERDOSE:** Doses up to 9 mg/kg have been tested in clinical trials. There have been reports of overdose at doses up to approximately twice the recommended therapeutic dose (12 mg/kg). Adverse events observed included skin toxicity, diarrhoea, dehydration and fatigue and were consistent with the safety profile at the recommended dose.

Abbreviated Prescribing Information Version: CDS24IPI08_EUSmPC042015API
Please read the full prescribing information prior to administration and full prescribing information is available on request.
Vectibix® is a registered trademark of Immunex Corporation.

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The Cover Shot

Checkpoint Charlie was once a crossing point in the Berlin Wall located at the junction of Friedrichstraße with Zimmerstraße and Mauerstraße. The name Charlie came from the letter C in the NATO phonetic alphabet. The Soviets called it the *Friedrichstraße Crossing Point* (КПП Фридрихштрассе, *KPP Fridrikhshtrasse*).

Checkpoint Charlie is frequently featured in spy movies and books. The two soldiers (one American and one Russian) represented at the Checkpoint Memorial were both stationed in Berlin during the early 1990s. The checkpoint booth was removed on June 22, 1990 while the checkpoint remained an official crossing for foreigners and diplomats until the German reunification during October 1990 when the guard house was removed. Developers also demolished the East German checkpoint watchtower in 2000, to make way for offices and shops. Checkpoint Charlie is nowadays one of Berlin's major tourist attractions.

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Immunotherapy: A New Era in Cancer Therapy at Dawn

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Immunotherapy, especially the development of immune checkpoint inhibitors has largely changed the algorithm of current cancer treatment. CTLA-4 prevents the co-stimulatory signal required for T cell activation. Programmed cell death protein 1 (PD-1) is another checkpoint that regulates the immune response. Ligation of PD-1 with its ligands PD-L1 and PD-L2 results in transduction of negative signals to T-cells. The expression of PD-1 on effector T-cells and PD-L1 on neoplastic cells enables tumour cells to evade anti-tumour immunity. Blockade of checkpoints such as CTLA-4 or/and PD-1 is thus an important immunotherapeutic strategy for cancer therapeutics.

Nowadays, various checkpoint inhibitors have been widely used both in the clinic and the clinical trials. The CTLA-4 inhibitor ipilimumab, PD-1 inhibitors such as nivolumab and pembrolizumab, and PD-L1 inhibitors such as atezolizumab and durvalumab have been approved for the treatment of various cancers, such as melanoma, non-small cell lung cancer and urothelial cancer as well. It is very likely that the indication for the use of these checkpoint inhibitors alone or in combinations will be extended to other solid or blood cancers soon. Therefore, it is important for the practising physicians to know about the basic principle, potential clinical application and the side effects of using these immunotherapy agents in the treatment of cancer patients.

In this issue, Dr Hilda Wong has nicely summarised the underlying science, clinical utility, potential biomarkers and the side effects associated with the use of immunotherapy. She also enlightens us with another article about her perspectives about the application of checkpoint inhibitors in treating ovarian cancer. Dr Gerry Kwok and Roland Leung have written an important article about the use of these checkpoint inhibitors in the management of non-small cell lung cancer. This is an important indication for checkpoint inhibitors given the high burden of non-small cell lung cancer globally. Another article is written by Dr Joanne Chiu about the potential use of immunotherapy in breast cancer. Although the checkpoint inhibitors are not yet formally approved for the treatment of breast cancer, the article does provide an insight about the future use of immunotherapy in treating the advanced breast cancer population, especially the patients with the triple negative subtype. Last but not least, Dr CL Chiang has nicely written an article about the potential combination of immunotherapy together with radiotherapy. Immunotherapy may indeed work synergistically with radiotherapy due to its immune-stimulatory effects.

We hope readers can enjoy and learn more about the application of immunotherapy in treating cancer patients after reading these articles.

Practical Use of Immune Checkpoint Inhibitors: Challenges and Opportunities

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 June 2017.

Abstract

The development of immune checkpoint inhibitors, including antibodies that block cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and the programmed death protein-1 (PD-1) pathway, has revolutionalised the management of cancer. Although our understanding of immunotherapy is still evolving, these agents are already almost in full swing in the clinic. This article aims to address several challenges associated with their overall use in the real-world practice, including selecting patients who may benefit, improving tumour response, assessing response and managing immune-related adverse events.

Introduction

The development of immune checkpoint inhibitors, including antibodies that block cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and the programmed death protein-1 (PD-1) pathway, has revolutionalised the management of cancer. Among therapeutic agents within our armamentarium, conventional chemotherapy is associated with lack of selectivity and tumour resistance. On the other hand, the adoption of a targeted strategy depends heavily on the presence of an actionable target in the tumour, clinical availability of a targeted drug and accurate predictive biomarkers, while the emergence of acquired resistance due to genetic and epigenetic instability of cancer remain problematic.[1] Immunotherapy takes advantage of the postulated ability of the immune system to recognise cancer cells as foreign and eliminates them effectively, potentially leading to better selectivity, durability of response and applicability across diverse tumour histological types.

Despite early disappointments in the field of cancer immunotherapy, the discovery of checkpoint regulation of T cells, linked to cancer's mechanism to evade the immune system, marks its renaissance. In brief, CTLA-4 prevents the co-stimulatory signal required for T cell activation, while the interaction between PD-1 on T cells and PD ligand-1 (PD-L1) on cancer cells also negatively regulate T cells. Blockade of CTLA-4 and/or the PD-1 pathway can therefore promote tumour-specific T cell expansion and activation, and revert the peripheral immune tolerance induced by cancer. Indeed, the CTLA-4 inhibitor ipilimumab, PD-1 inhibitors such as nivolumab and pembrolizumab, and PD-L1 inhibitors such as atezolizumab, have demonstrated promising clinical efficacy leading to their approval in various cancers, including melanoma,[2-5] non-small cell lung cancer (NSCLC)[6-8], renal cell carcinoma,[9] classical Hodgkin's lymphoma,[10] squamous cell carcinoma of the head and neck[11,12] and urothelial carcinoma.[13] In addition, other PD-1/PD-L1 checkpoint inhibitors are currently being investigated in multiple tumour types.

Although our understanding of immunotherapy is still evolving, these checkpoint inhibitors are already almost in full swing in the clinic. This article aims to address several challenges associated with their overall use in the real-world practice. The reader is referred to published reviews on detailed scientific basis of cancer immunotherapy,[14] and to other articles in the current issue of the journal on clinical trial data in specific tumour types.

Challenge 1: Selecting the right patient

While checkpoint inhibition can achieve complete and durable remissions in some patients, in the majority of others it fails to bring about any therapeutic effect at all. Except the more dramatic responses seen in the frontline setting, with the combination of ipilimumab and nivolumab in advanced melanoma[15] and perhaps with pembrolizumab in PD-L1 expressing NSCLC,[16] the reported overall response rate is only around 10-25% for many treatment-refractory tumours.[6-9] Such heterogeneous or nearly dichotomised responses imply that selecting the right patient who would derive benefit from checkpoint inhibitors is one of the biggest challenges in the clinic.

Tumour PD-L1 expression by immunohistochemistry is the most commonly used biomarker in clinical practice to predict response to PD-1 pathway inhibition. While higher PD-L1 scores are associated with increasing probability to benefit from PD-1/PD-L1 inhibitors, a small proportion of patients with PD-L1 negative tumours might still respond;[6-8,17] a similar trend is observed when assessing PD-L1 expression in tumour-infiltrating lymphocytes.[18] Indeed, nivolumab and atezolizumab are approved in certain tumour types regardless of PD-L1 expression. Nevertheless, subsequently emerging evidence, of variable strength, is in general supportive of its predictive role, and authorities have expanded their approval to include complementary PD-L1 assays. Notably, multiple

antibodies to detect PD-L1 with distinct cut-offs and scoring systems are available, and each was developed to complement a specific PD-1/PD-L1 inhibitor. In a comparison study, despite similar analytical performance of 3 out of 4 assays, interchanging assays and cut-offs led to different PD-L1 status results in some patients.[19] In addition to prominent inter-assay variability, another study suggested in NSCLC the presence of intra-tumoural heterogeneity and dynamic changes in PD-L1 expression,[20] complicating the interpretation of PD-L1 results and clinical trial data. To date, while awaiting further research and standardisation of assays, PD-L1 expression should assist the identification of patients who may best benefit, especially when prioritising other treatment options or particular concerns for toxicities exist, but by no means be regarded as absolute or exclusive.

High tumour mutational load, as determined by whole-exome sequencing, correlates with sensitivity to CTLA-4 blockade in melanoma, possibly via generating neoepitopes and increasing tumour neoantigen load.[21,22] Similarly, the durable clinical benefit rate with pembrolizumab was found to be significantly higher above a certain non-synonymous mutation rate cut-off in NSCLC,[23] and specific DNA mismatch repair gene defects associated with higher non-synonymous mutation burden predicted better ORR also to pembrolizumab in colon cancer.[24] On the other hand, genetic biomarkers are still under investigation and not yet routine in the clinic setting.

Extensive efforts are underway to evaluate other evolving biomarkers in the tumour microenvironment, such as intra-tumoural lymphoid infiltrate patterns, and activity of regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs) and indole 2,3-dioxygenase (IDO), as summarised in published reviews.[25,26] Some also advocate dynamic as opposed to static predictors of response.[27] Given the unravelling complexity of the immune system and multitude of its regulatory mechanisms, it is unlikely that we can simply rely on a single or few biomarkers to dictate response.

Furthermore, patient characteristics should be factored into treatment choice. Notably, ageing is associated with reduced number and function of antigen presenting cells and T cells but increased immunosuppressive cell populations such as Treg and MDSCs.[28,29] A meta-analysis of 9 randomised trials showed, with an age cut-off of 65-70 years, checkpoint inhibitors improved survival in both younger and older patients, except for the subgroup of older people treated in 4 trials of PD-1 blockade.[30] Notwithstanding these findings, the clinician should be aware of the potential impact of advanced immunosenescence on the response to immunotherapy.

Challenge 2: Tackling low and slow response

On the clinical benefit associated by checkpoint inhibitor monotherapy, the ORR is modest and the onset is variable and often delayed.[31,32] In contrast to chemotherapy which acts directly on tumour cells and leads to a response soon after treatment, immunotherapy produces an indirect anti-tumour effect by inducing cancer-specific immune responses which may take longer to appear. Moreover, stable disease, without clinically apparent reduction in the tumour bulk, is considered a form of clinical benefit in patients on immunotherapeutic agents.[32] The use of immunotherapy is therefore especially challenging in patients presenting with a large symptomatic tumour burden, an aggressive disease pace and a rapidly declining performance status.

While the above-mentioned predictive biomarkers are largely intrinsic and not modifiable, other factors involved in tumour sensitivity to checkpoint inhibitors may be amenable to intervention, representing opportunities to improve tumour response by combination approaches. The addition of chemotherapy, radiotherapy, other checkpoint inhibitors, cytokines, IDO inhibitors or cancer vaccines to currently used checkpoint inhibitors are being investigated in clinical trials.[33] In particular, the impact of cytotoxic chemotherapy or some small molecule targeted agents on the immunity is most intriguing. While conventionally these agents are considered always immunosuppressive, they may actually exert inhibitory, neutral or stimulatory effects depending on the dose and schedule being used.[34] Moreover, cytotoxic agents may elicit tumour cell apoptosis, termed immunogenic cell death, activating infiltrating myeloid and dendritic cells and thus inducing anti-tumour immune responses in the tumour microenvironment.[35] Similarly, radiotherapy may lead to tumour antigen release and T cell response, and an abscopal effect has been reported.[36] Other innovative measures, such as modulation of the intestinal microbiota,[37] to improve the efficacy of checkpoint inhibitors are also underway.

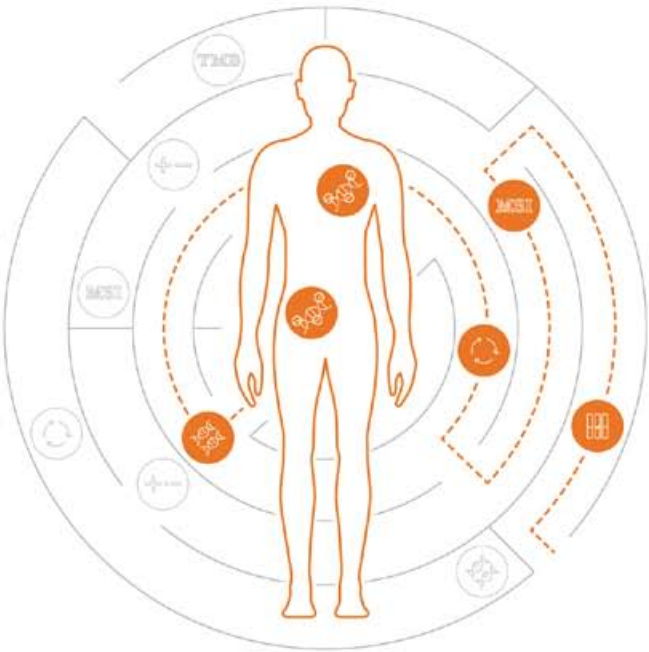
Meanwhile, as we only have the monotherapy indications, optimal sequencing of available options is important. In patients with bulky disease, modalities with a direct mechanism of action and faster onset of response could possibly be offered as induction before immunotherapy. This approach may potentially prevent the occurrence of imminent life- or organ-threatening complications, minimize cancer-related immunosuppression and reduce tumour burden to optimize the efficacy of immunotherapy.

Challenge 3: To continue or not to continue

Pseudoprogression, in which a clinical response is preceded by an initial increase in tumour burden, is a well described phenomenon with immunotherapy.[32] It may reflect either a transient infiltration by immune cells sometimes with oedema, or simply continued tumour growth before effective immune response takes place, both cases suggested by a study of tumour biopsies in patients on ipilimumab.[38] When a patient on immunotherapy has apparent disease progression, which would represent the majority of the times given the ORR, the clinician faces the dilemma whether to continue treatment or not. While allowing for pseudoprogression in the hope of ultimately prolonged tumour control, there are risks of further deterioration due to delayed replacement of a futile treatment, not to mention adverse events and costs.

Navigating the clinical complexities of cancer care

Exploring your patient's cancer allows you to discover more treatment possibilities.[1,2]
But because standard* cancer diagnostic techniques only test for a handful of possibilities, there are potentially many other classes of alterations, and treatment possibilities, that can be missed.[3]



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*FISH: Fluorescence in situ hybridisation; IHC: Immunohistochemistry; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; TMB: Tumour Mutational Burden; MSI: Microsatellite Instability

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Specific immune-related response criteria (irRC) have been developed from the conventionally used Response Evaluation Criteria in Solid Tumours or WHO criteria, to guide assessment and thus treatment decisions.[32] As the main novelty of the new criteria to capture additional responses beyond those described conventionally, measurable new lesions are now included into the "total tumour burden" and no longer necessarily define progressive disease. It is limited by the lack of prospective validation to support its generalisability to immunotherapeutic agents and cancer types other than CTLA-4 blockers in melanoma, from which it was developed.[32] There are also concerns that the irRC do not address non-measurable non-target lesions[39] and that it may overestimate treatment benefits.[40] On the other hand, in some patients with exceptional response kinetics and timeframes, the arbitrary cut-off of 25% increase in total tumour burden would still risk misclassification as progressive disease and inappropriate discontinuation of therapy. Practically, repeating imaging in 4 weeks to confirm the original assessment as recommended by the irRC is often not feasible.

In addition to the application of the irRC, clinical observations on the patient's performance status and symptoms would aid response assessments. In difficult cases, a tumour biopsy may differentiate histologically tumour growth from immune cells infiltration,[41] although this is invasive and often not possible in frail patients or those without an easily accessible tumour site. Amidst the scientific fascination of pseudoprogression and high hopes for immunotherapy, the clinician should bear in mind that the incidence of the former in solid tumours is only around 4%,[42] and consider the risk-to-benefit ratio whether to press on with immunotherapy on progression.

Challenge 4: Managing immune-related adverse events

Although checkpoint inhibitors are often described as well-tolerated especially with respect to chemotherapy, some degree of immune-related adverse events (irAEs) are common, potentially irreversible or fatal and thus not to be overlooked. These adverse events are thought to be related to the dysregulated immune system and cross-reactivity between tumour neoantigens and normal tissue antigens.[21] In individual studies, they were reported in up to 90% of patients on ipilimumab[43] and 70% in patients on PD-1 pathway blockade,[2,44] although the frequency of Grade 3 to 4 irAEs were 10-15%. More recently, a meta-analysis of 23 studies of checkpoint inhibitors showed that the incidence of irAE of any grade was significantly higher in CTLA-4 inhibitors (54%) than PD-1(26%) and PD-L1 blockers (13.7%); Grade 3 to 4 irAEs were also more common with CTLA-4 inhibitors (19%) and even more so with the combination of CTLA-4 and PD-1 pathway blockade.[45]

The spectrum of irAEs is diverse and may theoretically affect any organ system in the body. Skin rashes and vitiligo, colitis, hepatitis, pancreatitis, nephritis, pneumonitis, meningitis and neuropathies, endocrinopathies, arthritis and uveitis have all been reported with variable incidences.[46] They usually occur within 3-6 months, but sometimes up to a year, from the commencement of immunotherapy.[2,44,47] Typically, skin rashes are seen earlier on during weeks 3-10, followed by diarrhoea at weeks 5-10 and liver dysfunction at weeks 6-14, and endocrinopathies tend to be delayed in onset.[48] In particular, a high level of clinical suspicion and routine biochemical monitoring for a prolonged period are required to diagnose potentially life-threatening immune-related hypophysitis, hypothyroidism and adrenal insufficiency, as the patient may only present with vague symptoms such as fatigue. Endocrinopathies of any grade usually affect 5-10% of patients.[46] Other irAEs may lead to symptoms resembling those related to the underlying tumour, posing another diagnostic challenge. For example, interstitial pneumonitis may give rise to cough and shortness of breath similar to symptoms of the underlying lung cancer; immune hepatitis may cause deranged liver function which can be also related to the underlying liver cancer.

When irAEs are suspected, close liaison with respective organ specialists and prompt investigations to exclude alternative diagnoses and/or obtain histological confirmation are essential. Suspension or discontinuation of checkpoint inhibitors may be necessary. Most irAEs respond to steroids in 6-12 weeks,[47] and earlier initiation of steroids is associated with faster resolution of symptoms.[49] In general, low-dose steroid equivalent to prednisolone 0.5mg/kg/day is indicated for moderate symptoms, prednisolone 1-2mg/kg/day for more severe symptoms, and other immunosuppressive or immunomodulatory agents such as infliximab, mycophenolate mofetil and cyclophosphamide considered for steroid-refractory cases. After 2-4 weeks, full-dose steroid should be tapered off slowly over at least a month to avoid recurrence of irAEs. Guidelines and algorithms are available to guide the management of organ-specific irAEs according to severity.[46] Of note, although steroid administration is suspected to reduce anti-tumour immunity,[46] some clinical evidence showed no effects on overall survival or time to treatment failure.[50]

Conclusion

Checkpoint inhibitors represent a new hope for cancer patients and have been changing the treatment paradigm in clinical practice. Despite their widespread use, we have yet to fully understand the underlying immune mechanisms and their interplay with the plethora of host and environmental factors, nor do we have definitive biomarkers to predict treatment response. While awaiting insights from further research on immune pathways, biomarkers and combination strategies, given the modest response rate, variable onset of action, possibility of immune-related toxicities and high costs, rational use of these immunotherapeutic agents with individualised patient-centred assessment of risks and benefits is called for.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Practical Use of Immune Checkpoint Inhibitors: Challenges and Opportunities" by Dr Hilda WONG 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 30 June 2017. 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. CTLA-4 and PD-1 pathways negatively regulate T cells and represent mechanisms utilised by cancer cells to evade the host immune system.
2. Immune checkpoint inhibitors have been approved in the treatment of a number of tumour types, including malignant melanoma, lung cancer, renal cell carcinoma, classical Hodgkin's lymphoma and squamous cell carcinoma of the head and neck.
3. Immune checkpoint inhibitors harness the host protective immune response to destroy cancer cells and thus can achieve a response in all otherwise immunocompetent cancer patients.
4. Tumour PD-L1 expression can be determined by a standardised assay and is a definitive predictor of response to PD-1 pathway blockade.
5. Clinical benefits achieved by immune checkpoint inhibitors include stable but durable disease control and not necessarily tumour shrinkage.
6. Immunotherapy frequently leads to dramatic tumour responses and is the treatment modality of choice in patients presenting with large tumour burden and rapidly progressing disease.
7. A new set of immune-related response criteria has been developed to assess clinical benefit associated with immune checkpoint inhibition.
8. Immunotherapy is highly selective towards cancer cells thus associated with no side effects.
9. Immune-related adverse events include rash, hepatitis, colitis and endocrinopathies that usually occur a few weeks or months after the commencement of immune checkpoint inhibitors.
10. Immune-related adverse events are usually steroid responsive.

ANSWER SHEET FOR JUNE 2017

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2017 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Practical Use of Immune Checkpoint Inhibitors: Challenges and Opportunities

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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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Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to May 2017 Issue

Update in the Treatment of Overactive Bladder Syndrome (OAB)

1. T **2.** T **3.** F **4.** F **5.** T **6.** F **7.** T **8.** T **9.** T **10.** F

Treating metastatic non-small cell lung cancer (NSCLC) in the era of checkpoint inhibition, what's in, what's out?

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Patients with metastatic NSCLC have a guarded prognosis despite platinum based chemotherapy and targeted agents against tumours with driver EGFR mutations and ALK gene rearrangements. Recently, the USFDA approved anti-Programmed Death 1 Receptor (anti-PD-1) antibodies nivolumab and pembrolizumab and anti-Programmed Death Ligand 1 (anti-PD-L1) antibody atezolizumab for treatment of NSCLC. These agents changed the landscape of lung cancer treatment by harnessing the specificity and the durability of cellular immunity against tumour cells and their antigens. In the immune-editing theory of tumour development, early carcinogenesis activates the innate and adaptive immune system to eliminate cancer cells[1]. Adaptive tumour immunity begins with effective tumour antigen processing, followed by presentation and recognition by helper and cytotoxic T lymphocytes. In the presence of interleukin 2, T cell activation is triggered by the antigenic signal and a co-stimulatory signal that occurs when CD28 on T cells binds B7 ligands on Antigen Presenting Cells[2]. Inhibitory checkpoints such as the inducible PD-1 receptor on activated T cells fine tune this process by putting a break on T cell activation[3]. On ligating PD-L1 and PD-L2 on tumour cells and immune cells within the tumour microenvironment, T cells enter a state of anergy and apoptosis, abrogating cytotoxic T lymphocyte activation and effector response. Antibodies such as anti-PD-1 and anti-PD-L1 block the inhibitory checkpoints of T cell activation and restore anti-tumour immunity. They produce a unique spectrum of immune related adverse events (AE) which are predictable but non-specific.

Clinical evidence: efficacy and safety

At the time of writing, the FDA has approved 3 anti-PD-1/PD-L1 inhibitors for metastatic NSCLC pretreated with platinum doublet chemotherapy and EGFR or ALK inhibitors in tumours with appropriate genetic drivers. These agents have been extensively studied in randomised phase 3 trials, which have provided insight into predictive biomarkers.

Nivolumab

Nivolumab is a monoclonal IgG4 antibody against the PD-1 receptor which has shown efficacy in the Checkmate 017 trial[4]. 272 patients with squamous NSCLC were randomised to nivolumab at a dose of 3mg/kg every 2 weeks or docetaxel regardless of PD-L1 expression by immunohistochemistry. Patients on nivolumab showed a superior median overall survival (OS) of 9.2 months, compared with 6.0 months for docetaxel (HR= 0.59, 95% CI 0.44-0.79, P<0.001). Overall tumour response rate was 20% vs 9% (P=0.008) in favour of nivolumab and the median PFS was 3.5 months vs 2.8 months respectively (HR=0.62, 95% CI 0.47-0.81; P<0.001). Responses occurred early in both treatment arms but the duration of response was significantly longer for responders on nivolumab (median not reached vs 8.4 months). In subgroup analysis, there was consistent clinical benefit in both PD-L1 positive and negative tumours. Nivolumab was associated with fewer grade 3-4 AE (7% vs 55%), which included tubointerstitial nephritis, colitis, and pneumonitis (n=1 respectively). Most immune AE were grade 1-2 and included hypothyroidism (4% vs 0%), pneumonitis (5% vs 0%), rash (4% vs 6%), and diarrhoea (8% vs 20%). Treatment discontinuation was rare and was due to pneumonitis in 2% of patients on nivolumab.

In the Checkmate 057 trial, 582 patients with pretreated non-squamous NSCLC were randomised to nivolumab or docetaxel[5]. 79% of the population were current or former smokers, while 15% and 4% in the nivolumab arm, and 13% and 3% in the docetaxel arm respectively carried EGFR mutations and ALK translocations. The trial showed a 27% risk reduction for all causes mortality. Median OS was 12.2 months vs 9.4 months in favour of nivolumab (HR=0.73; 95% CI 0.59-0.89; P=0.002), and the ORR was 19% vs 12% for docetaxel (P=0.02). Median PFS was not significantly different, but those who benefited from nivolumab saw a higher proportion with progression free at 1 year (19% vs 8%). Duration of response was also longer (17.2 months vs 5.6 months). When tested for interaction, PD-L1 expression was strongly predictive of improved efficacy endpoints in favour of nivolumab, with statistical significance at >1%, >5%, and >10% cutoffs. At >10% cutoff, median PFS (5.0 months vs 3.7 months; HR=0.52, 95% CI 0.37-0.75) and OS (19.9 months vs 8.0 months; HR=0.40, 95% CI 0.27-0.58) strongly favoured nivolumab. The small number of patients who carried EGFR mutations did not show significant PFS or OSB benefit. Treatment related grade 3-4 AE occurred in 10% of patients on nivolumab, which was substantially lower than the docetaxel arm (54%). 1 patient on nivolumab died of encephalitis and 1% discontinued treatment due to pneumonitis. Immune related AE were mostly grade 1-2 and included rash (9%), pruritus (8%), diarrhoea (8%), hypothyroidism (7%), transaminitis (3%), infusion reactions (3%) and pneumonitis (3%).

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Pembrolizumab

In the Keynote 010 trial, 1034 pretreated NSCLC with 1% or greater PD-L1 expression were randomised to pembrolizumab 2mg/kg every 3 weeks, pembrolizumab 10mg/kg every 3 weeks, or docetaxel[6]. 70% of tumours were non-squamous, while 9% had EGFR mutations or ALK rearrangements. 80% of patients were current or former smokers. In the ITT population, median OS was 10.4 months, 12.7 months, and 8.5 months respectively. Pembrolizumab 2mg/kg and 10mg/kg respectively reduced risk of death by 29% (HR=0.71, 95% CI 0.58-0.88; P=0.0008) and 39% (HR=0.61, 95% CI 0.49-0.75; P=.004) compared with docetaxel. Median PFS was similar between the treatment arms. In the PD-L1 enriched cohort (50% or higher), median OS was significantly superior for pembrolizumb 2mg/kg (14.9 months vs 8.2 months; HR=0.54, 95% CI 0.38-0.77; P=.0002) and pembrolizumab 10mg/kg against docetaxel (17.3 months vs 8.2 months; HR=0.50, 95% CI 0.36-0.70; P<0.0001). Median PFS was 5.0 months, 5.2 months, and 4.1 months, giving a hazard ratio of 0.59 for pembrolizumab vs docetaxel. ORR was 30%, 29%, and 8% respectively. Subgroup analysis favoured pembrolizumab regardless of histology. Tumours with EGFR mutations however did not derive survival benefit, with PFS showing a trend for docetaxel. Treatment related grade 3-5 adverse events occurred in 13% and 16% in the low and high dose pembrolizumab cohorts and in 35% in the docetaxel cohort. Immune related AE occurred in 20% of patients on pembrolizumab and were mostly grade 1-2. Hypothyroidism (8%), pneumonitis (6.6%), hyperthyroidism (4.8%) and colitis (1.5%) were common, while grade 3-4 immune related AE in 1% or more patients included pneumonitis (2%) and skin reactions (1%) .

Keynote 024 randomised 305 patients with untreated NSCLC and PD-L1 expression on at least 50% of tumour cells and who were EGFR wild type and ALK rearrangement negative to pembrolizumab 200mg every 3 weeks or platinum based chemotherapy[7]. Most patients were current or former smokers. Patients on chemotherapy were allowed cross over at disease progression. At a median follow up of 11.2 months, the primary endpoint of PFS was met with 50% reduction in the risk of death and disease progression in favour of pembrolizumab (HR=0.5, 95% CI 0.37-0.68; P<0.001). Median PFS was 10.3 months and 6.0 months respectively. ORR was 44.8% compared with 27.8% for standard chemotherapy. Median duration of response was long and not reached at the time of analysis (NR vs 6.3 months). PD-L1 expression was analysed prospectively by fresh tissue biopsy, with 30% of tested patients having a 50% or higher proportion score. The 6 months survival rate was 80.2% vs 72.4%(HR=0.60, 95% CI 0.41-0.89; P=0.005). Notably, the hazard ratios were similar to that obtained in the PD-L1 enriched cohort in Keynote 010. Subgroup analysis showed consistent PFS superiority regardless of histology. Treatment related grade 3-5 AE occurred in 26.6% in the pembrolizumab arm vs 53.3% in the chemotherapy arm. This led to fewer discontinuations due to AE (7.1% vs 10.7%). Immune related AE occurred in 29.2% of patients on pembrolizumab, of which grade 3-4 skin reactions, pneumonitis, and colitis accounted for 3.9%, 2.6% and 1.3% respectively.

Atezolizumab

Atezolizumab is a humanised anti-PD-L1 targeting IgG1 antibody that was studied in pretreated NSCLC in the POPLAR and OAK study[8,9]. The antibody blocks PD-L1 and PD-1 ligation, but also PD-L1 and B7-1 interaction which may further enhance anti-tumour immunity. Unlike PD-1 inhibitors, the PD-L2 and PD-1 interaction is unaffected by atezolizumab, which may decrease unwanted AE. In the phase 2 POPLAR study, atezolizumab improved OS compared with docetaxel, and identified tumour cell (TC) and immune cell (IC) PD-L1 expression as independent predictors of survival. In the phase 3 OAK trial, 850 patients were randomised between atezolizumab 1200mg or docetaxel 75mg/m^2 every 3 weeks, stratified by PD-L1 expression. The primary endpoint of OS in the ITT and PD-L1 positive population (defined as 1% or higher in TC or IC) was met, with a 27% reduction in death in the ITT population (median OS 13.8 months vs 9.6 months; HR=0.73, 95% CI 0.62-0.87; P=0.0003) and 26% reduction in death in the PD-L1 positive population (median OS 15.7 months vs 10.3 months; HR=0.74, 95% CI 0.58-0.93; P=0.0102). Median PFS (2.8 months vs 4.0 months) and ORR (14% vs 13%) was not significantly different in the ITT population. Patients with tumour response were significantly longer for atezolizumab than docetaxel (median 16.3 months vs 6.2 months). Patients with highest PD-L1 expression (50% or more of TC or 10% or more of IC) showed greatest OS benefit (20.5 months vs 8.9 months; HR=0.41; 95% CI 0.27-0.64; P<0.0001) while patients with less than 1% PD-L1 expression in IC or TC showed survival benefit similar to the ITT and PD-L1 positive population (12.6 months vs 8.9 months; HR=0.75, 95% CI 0.59-0.96). Patients with intermediate PD-L1 expression (5% or greater in TC or IC) derived moderate benefit (HR=0.67, 95% CI 0.49-0.90; P=0.008). In subgroup analysis, atezolizumab benefits occurred regardless of histology (HR= 0.73 for both squamous and non-squamous) but not for EGFR mutations (HR=1.24, 95% CI 0.71-2.18).

Biomarkers for anti-PD-1/ PD-L1

In early lung cancer, PD-L1 expression is associated with poorly differentiated histology and inferior survival[10,11]. In advanced NSCLC, PD-L1 expression is a validated biomarker for anti-PD-1/PD-L1 checkpoint inhibitors. A meta-analysis of 9 studies involving pretreated NSCLC showed that anti-PD-1/ PD-L1 inhibitors demonstrated improved ORR (OR=1.83, 95% CI 1.41-2.36), PFS (HR=0.83, 95% CI 0.75-0.91), and OS (HR=0.68, 95% CI 0.61-0.75) over docetaxel in the ITT population[12]. In the nivolumab studies, squamous cell carcinoma regardless of PD-L1 expression and adenocarcinomas with 1% or higher PD-L1 expression derived PFS and OS benefits. In the pembrolizumab study, NSCLC with 50% or higher PD-L1 expression showed PFS and OS benefits, although the survival benefit was also apparent when PD-L1 was between 1-49%. Atezolizumab showed survival benefits proportional to PD-L1 expression and even in patients with less than 1% expression. Unfortunately PD-L1 staining and assessment methodologies varied between clinical trials, which is not only relevant to clinical practice, but also render cross trial comparisons difficult. The ongoing

Blueprint study aims to harmonise the different PD-L1 assays, with early data showing high concordance for tumour cell PD-L1 expression in 3 out of 4 commercially available assays (Ventana SP142, Dako 22C3, Dako 28-8, Ventana SP263) [13]. Since tumour PD-L1 expression is heterogenous and dynamic, the optimal strategy should be prospective testing on biopsy specimens. In a pooled analysis of EGFR mutated tumours, anti-PD-1/ PD-L1 inhibitors showed no survival benefit over docetaxel as second line therapy (N=186; HR=1.05, 95% CI 0.70-1.55; P<0.81) and cannot be recommended.

Conclusions

We currently suggest tumour PD-L1 staining by IHC in patients with untreated metastatic NSCLC who do not harbour EGFR mutations or ALK rearranged drivers. From Keynote 024, PD-L1 enriched tumours show significant benefit from treatment with pembrolizumab and should become the standard of care over platinum based chemotherapy. In pretreated NSCLC, anti-PD-1/ PD-L1 should be reserved for patients without EGFR or ALK drivers as growing evidence shows that these tumours may not benefit owing to the low mutation burden in the absence of smoking related carcinogenesis[14]. High PD-L1 expression on the other hand predicts and enriches clinical benefit from anti-PD-1/PD-L1 inhibitors. Since response and benefit are still confined to a selected group, other mechanisms of tumour immune escape should be harnessed and targeted in combination to enhance anti-tumour immunity beyond immune checkpoints. In the future, combination strategies are key to effective anti-tumour immunity, which should translate to better clinical outcomes.

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Immune Checkpoint Inhibitors for Breast Cancer

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Introduction

Immunotherapy is a new treatment for cancer. In fact, an immune response to cancer is not a new concept. Not only it is a general belief in our culture that the immune system plays a role in the combat of cancer, there were old medical evidences that patients' tumours regressed spontaneously after active infection due to an immunomodulatory effect[1]. It is long known that immunocompromised patients, such as patients who have received organ transplantation or with other acquired immunodeficiency, are prone to development of cancer. Today we know that the immune system is both tightly regulated and highly efficient. A normal immune response against cancer relies on recognition of the cancer cells and an efficient eradication of them. Tumour cells express tumour-associated antigens (TAAs). Antigen-presenting cells of our immune system process the TAA-related peptides, display the peptide via a pocket within the cell surface receptor major histocompatibility complex (MHC), which then present it to T-cells. The 2 most important types of T cells are CD4+ helper T cells and CD8+ cytotoxic T cells. Research efforts aim to design strategies to modulate immune regulation, either by up-regulation of immune activation or down-regulation of immune suppression or by direct immune response toward TAAs.

Immune Checkpoint Inhibitors

The development of immune checkpoint inhibitors has changed the landscape of current cancer management. Checkpoint inhibitors target checkpoints in the inhibitory pathway and unleash immune-mediated cancer clearance. The first checkpoint inhibitor approved by the US Food and Drug Administration is ipilimumab, an antibody against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). It was first approved for treatment of melanomas[2]. It is powerful and can induce long-term remissions in responders. Yet its potential toxicity hinders the development and today melanomas remain the only labelled use.

The second class of checkpoint inhibitors targets another domain of the inhibitory pathway, programmed death (PD-1) or its ligand PD-L1. The first 2 anti-PD-1 antibodies approved by FDA for clinical use are nivolumab and pembrolizumab. Other drugs of this class include anti-PD-L1 atezolizumab and avelumab. These checkpoint inhibitors are well tolerated in general and have quickly become the favourite candidate of immune-oncology research.

Early experience of anti-PD-1/PD-L1 and triple negative breast cancer

Research of early clinical trials suggested PD-L1 expression by immunohistochemistry (IHC) on tumour tissue might enrich for treatment response[3]. To increase the yield, some clinical trials of breast cancer require PD-L1 positivity to be one of the eligibility criteria. Breast cancers are divided into 3 subtypes - hormone receptor (HR) positive, HER2 receptor positive and if none of these 2 receptors are present, triple negative breast cancer (TNBC). Data from the Cancer Genome Atlas (TCGA) RNA sequencing showed significant greater PD-L1 gene expression in TNBC than non-TNBC[4]. Experience from clinical trials also showed that among the screened patients, 58% of TNBC patients and 19% of HR-positive HER2-negative tumours were PD-L1 positive by IHC[5, 6]. TNBC is believed to be the most promising breast cancer subtype to respond to immunotherapy.

The first data of pembrolizumab activity in TNBC derived from KEYNOTE-012, which is a nonrandomised phase Ib trial of single agent pembrolizumab at 10mg/kg once every 2 weeks given to PD-L1 positive patients with TNBC, gastric cancer, urothelial cancer or head and neck cancer[5]. The TNBC cohort recruited 111 patients. Patients were heavily pretreated with a median number of prior therapies being 2 and 25% of patients received 5 or more lines of prior therapies. Among the 27 patients evaluable for anti-tumour activity, the overall response rate was 18.5% and the median time to response was 17.9 weeks (range, 7.3 to 32.4 weeks). Common toxicities were mild in general and they included arthralgia, fatigue, myalgia and nausea. About 15% of patients experienced grade 3 or higher toxicities. The first anti-PD-L1 on stage for TNBC is atezolizumab (MPDL3280A). Twenty-seven eligible patients with PD-L1 expression were given this drug at 3 different doses of 15 mg/kg, 20 mg/kg or 1200 mg flat dose IV every 3 weeks[7]. Patients were also heavily pretreated with 80% having received ≥ 4 prior systemic regimens. Again, most toxicities were mild and 11% experienced more severe toxicities. The overall response rate (ORR) was 24% with 24-week progression-free survival (PFS) of 33%. Anti-PD-1 and anti-PD-L1 appeared to have similar spectrums of activity and toxicities in TNBC. KEYNOTE119 [NCT02555657] is a representation of phase III clinical trial comparing the efficacy of single agent pembrolizumab versus chemotherapy of the physicians' choice in later line treatment of TNBC.

Combination of anti-PD-1/PD-L1 with chemotherapy in TNBC

A major problem working with TNBC is its aggressive nature and patients might progress too quickly for the action of immunotherapy to take effect. Early experience also suggested immunotherapy alone might not provide sufficient benefits. As chemotherapy has been the mainstay of standard treatment for TNBC and there is the postulation that low dose chemotherapy might prime the immune system[8], the new generation of studies tends to adopt a combination approach. The preliminary experience was encouraging. In a phase I study combining atezolizumab (800 mg every 2 weeks) with weekly nab-paclitaxel (15mg/m^2 weekly for 3 weeks out of a 4 week cycle), the ORR was impressive ranging from 89% in the first line treatment to 43% in ≥ 3 line treatment[9]. There did not appear to be any additive toxicity. A phase III trial studying this combination in first line setting with similar regimen is ongoing [IMpassion130, NCT02425891]. Other anti-PD-L1 antibodies are also moving in a similar direction of chemotherapy combination in pursue of a better efficacy with immunotherapy. Pembrolizumab has been combined with eribulin in a phase Ib / 2 study [NCT02513472]. KEYNOTE355 is a phase III study comparing pembrolizumab with chemotherapy versus placebo with chemotherapy [NCT02819518].

Anti-PD-1/PD-L1 and other breast cancers

The early experience with anti-PD-1/PD-L1 in HR-positive HER2-negative breast cancer was discouraging. In KEYNOTE-028, treatment of pembrolizumab to heavily pretreated PD-L1 positive patients of this tumour subtype yielded an ORR of 12%. Similarly, in the JAVELIN study, 72 HR-positive HER2-negative patients unselected for PD-L1 status were given avelumab. The ORR was only 2.8%. There is not enough evidence to suggest an HR-positive HER2-negative breast cancer is an immunogenic cancer.

The potential role of immunotherapy in HER2-positive breast cancer is unknown. Anti-HER2 antibody trastuzumab is an effective targeted therapy with known antibody-dependent cellular cytotoxicity. There are a number of alternate anti-HER2 agents such as pertuzumab, lapatinib or T-DM1 (trastuzumab emtansine). When used alone or in combination, they yielded good disease control in metastatic settings. The action of checkpoint inhibitors relies on T-cell activation. Therefore, the presence of immune cells within the tumour has been regarded as a potential factor for immune response to TAA. Studies of early-stage breast cancer showed that the presence of tumour-infiltrating lymphocytes (TILs) was associated with a lower recurrence rate and an improved response to treatment[10,11]. A high TIL content in an early HER2-positive breast cancer was prognostic of a long term overall survival[12]. Therefore there is considerable evidence to suspect immunotherapy would be effective in this subtype of breast cancer. PANACEA is a phase Ib/II trial evaluating the combination of anti-PD-1 antibody MK3475 and trastuzumab in patients with trastuzumab-resistance HER2-positive metastatic breast cancers [NCT02129556]. The trial is ongoing and results are pending.

Biomarkers of response

The development of biomarkers for anti-PD-1/PD-L1 therapy has been a challenge[13]. Experience in other cancers suggested that the presence of PD-L1 expression tends to signify better treatment response, yet the absence of such signal did not preclude treatment response. PD-L1 IHC staining has variable outcomes depending on the protocol each company adopts for each clinical trial. First of all, different brands of antibody have different sensitivity. PD-L1 expression in tumours is not uniform and often there is only a limited amount of tissue to make decision. The definition of positive PD-L1 expression in each study varies as well. For instance, KEYNOTE-012 defined PD-L1 positivity as PD-L1 expression in ≥ 1% of tumour cells, yet in atezolizumab trial PD-L1 expression was defined as PD-L1 expression in ≥ 5% of infiltrating immune cells. We would see more unified definition of PD-L1 positivity in the future or more objective biomarkers to be developed.

Future directions

Although most of the experience for immunotherapy on breast cancer has been for advanced stage disease, there are ongoing efforts studying their effect in earlier stages of breast cancer. KEYNOTE-173 explores the combination of pembrolizumab with chemotherapy in TNBC for neoadjuvant use [NCT02622074]. The atezolizumab-nab-paclitaxel combination as neoadjuvant chemotherapy is also under evaluation in a phase II protocol [NCT02530489]. For patients with residual disease of ≥ 1 cm after neoadjuvant chemotherapy, there is now a phase III study comparing the use of adjuvant pembrolizumab versus observation [NCT02954874].

Many TNBCs are BRCA1-associated, or have the *p53* tumour suppressor gene mutations. These tumours have a defect in DNA repair and it might be a target for treatment. A poly (ADP-ribose) polymerase (PARP) inhibitor has been shown to benefit *BRCA*-mutated breast cancer in a phase III clinical trial (detailed results to be announced later this year). The PARP inhibitor might prime TNBC for the immune response of immunotherapy. Clinical trial of this combination is under investigation [NCT02657889].

Conclusion

Although there is no labelled use of immunotherapy in breast cancer today, immunotherapy is gaining its role in the management of this disease with the most promising subtype being TNBC. Most of the clinical experience available now is on anti-PD-1/PD-L1 alone in chemotherapy-pretreated disease. Phase III clinical trials are underway and the results are expected to be available in the next couple of years. There is a trend toward combining immunotherapy with chemotherapy especially in early line setting. There did not appear to have additive toxicities when the 2 classes of drugs were combined. Combining with other targeted agents, such as an PAPR inhibitor, might open new doors for treatment. We look forward to other immunotherapy strategies, such as other immune pathway modulators or tumour vaccines that would be available in the future.

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Radiology Quiz

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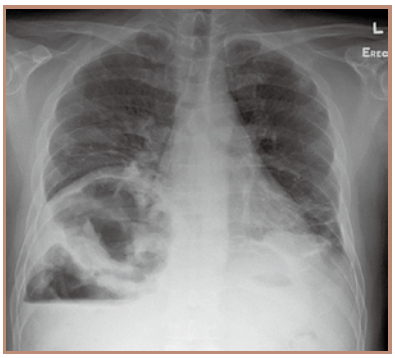

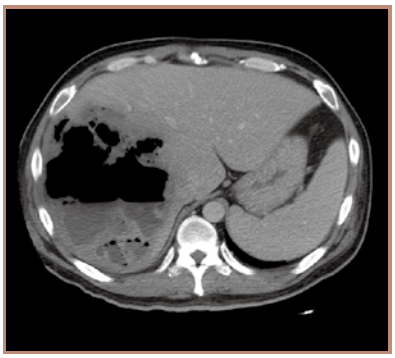

Questions

1. What are the CXR findings?
2. What are the CT findings?
3. What is the diagnosis?
4. What are the common causes?
5. What is the treatment?

(See P.36 for answers)

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References:
1. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure – Web Addenda.
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Towards Realising the Clinical Potential of Immunotherapy in Advanced Ovarian Cancer

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Abstract

The observation that ovarian cancer is an immunogenic tumour forms a compelling rationale for immunotherapy. While immunotherapy holds promise in diverse tumour types, it is currently considered largely investigational in ovarian cancer. This article provides an overview of the scientific basis and updated statuses of various immunotherapeutic agents in advanced epithelial ovarian cancer, thereby shedding light on the hopeful realisation of their clinical potential. Better understanding of cancer immunology will facilitate the development of predictive biomarkers, the design of combination strategies and the determination of the optimal clinical setting and route of administration.

Introduction

In our combat against cancer, the concepts of therapeutic strategies have much evolved over the past decades. However, despite improvements in surgery, chemotherapy and targeted therapy, ovarian cancer remains the leading cause of mortality from gynaecological cancers in Hong Kong[1] and in Western countries.[2] The majority of patients are first diagnosed at an advanced stage, with a 5-year survival of approximately 25%.[2]

The presence of tumour heterogeneity and lack of main oncogenic drivers identified limit the clinical use of targeted agents and personalised medicine in ovarian cancer, unlike the case in many other tumour types as exemplified by lung or breast cancers. To date, targeted agents have yet to be shown definitively to improve overall survival (OS) in the general epithelial ovarian cancer patient population. For example, the anti-angiogenic agent bevacizumab, in combination with chemotherapy, leads to only a modest improvement in progression-free survival (PFS) but not OS in the upfront[3,4] or recurrent settings,[5,6] although a subset of patients may derive an OS benefit.[4,7] The poly-ADP ribose polymerase (PARP) inhibitor olaparib is approved only in patients with germline *BRCA* gene mutation, constituting a minority (10-15%) of all ovarian cancer patients.[8,9] Niraparib, another PARP inhibitor, is more recently approved regardless of *BRCA* mutation status.[10] For both PARP inhibitors, a statistically significant OS improvement has not been shown. Mature data are still awaited for other targeted agents, such as pazopanib,[11] cediranib[12] and nintedanib.[13]

Given the relatively slow progress made in the development of targeted therapy, the time-honoured, tried-and-true regimen of taxane and platinum still remains the mainstay of treatment in advanced epithelial ovarian cancer, especially in the first line.[14] Although it is usually effective initially, and the intra-peritoneal administration of chemotherapy further improves survival compared with the conventional intravenous mode in eligible patients,[15] the majority of patients eventually relapse and develop resistance.

While immunotherapy holds promise in diverse tumour types, it is currently considered largely investigational in ovarian cancer. This article provides an overview of the scientific basis and updated statuses of various immunotherapeutic agents in advanced epithelial ovarian cancer, thereby shedding light on the hopeful realisation of their clinical potential.

The Role of the Immune System in Ovarian Cancer

Our current understanding of cancer immunology in general has been recently reviewed.[16] In ovarian cancer, tumour immunogenicity involving CD3+, CD4+ and/or CD8+ tumour-infiltrating lymphocytes (TILs) has long been established in a number of reports.[17-21] Indeed, the presence of CD8+ TILs is positively correlated with survival.[17,20,21] These observations are the first and foremost to suggest that immunotherapy may possibly be of therapeutic benefit in ovarian cancer.

On the other hand, ovarian cancer is also reported to recruit immunosuppressive cell types such as regulatory T cells (Tregs), counteracting CD8+ T cell-related immunity. High levels or proportion of Tregs, reflecting an immunosuppressive milieu, is associated with worse survival outcomes.[20,22] Concordantly, expression of the Treg-specific forkhead box transcription factor FoxP3 predicts poor prognosis.[23] Other immunosuppressive components such as myeloid derived suppressor cells[24] and tumour-associated macrophages (TAMs)[25] may also play a role in ovarian cancer. Strategies to overcome such immunosuppression are necessary to enhance host anti-tumour immunity or efficacy of any immunotherapies.

Moreover, the programmed death protein-1 (PD-1) pathway may represent an immune evasion mechanism in ovarian cancer. On the interaction between PD-1 receptors on T cells and programmed death ligand-1 (PD-L1) on cancer cells, T cell proliferation and activation are inhibited. PD-L1 expression in ovarian cancer

correlates with lower tumour CD8+ TIL infiltration[21] and higher Tregs,[26] and was also reported to predict poorer clinical outcomes independent of TILs in a study.[21] The negative prognostic significance was not confirmed in other studies,[27,28] although non-standardised PD-L1 assays and interpretation may explain discordant results. As for the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) checkpoint regulatory protein which is important in preventing T cell activation in other tumours, its role in ovarian cancer has not been definitely shown.[29] Meanwhile, another mechanism of ovarian cancer-related immunosuppression involves the enzyme indoleamine 2,3-dioxygenase (IDO), which, in response to increased levels of interferon gamma in ovarian cancer patients[30], causes depletion of tryptophan and T cell inactivation.[31] Expression of IDO negatively predicts survival in these patients.[32] Research is ongoing to delineate other mechanisms of immune evasion by ovarian cancer,[33, 34] as they may represent potential therapeutic targets.

Last but not least, the phenomenon of immunoediting can be observed in ovarian cancer, where T cell response can be elicited upon the occurrence of new mutations but not at subsequent recurrence,[35] demonstrating the selective outgrowth of cancer cells with immune escape. This suggests another limitation of the host immunity where immunotherapy may supplement.

Special Considerations in Ovarian Cancer Subtypes

Ovarian cancer is a heterogeneous entity comprising different clinical, histological and molecular characteristics and a spectrum of immunogenicity across individual tumours is expected. Immunohistochemical analyses of immune infiltrates have confirmed that the host immune response to ovarian cancer exhibits a wide variation according to histological subtypes.[36] Similarly, molecular studies have classified ovarian cancers into immunoreactive and non-immunoreactive subsets,[37] and the former is shown to be associated with increased TILs[38] and improved survival.[39] Therefore, the following subgroups warrant separate considerations.

BRCA-mutated ovarian cancer is postulated to be highly immunogenic, as the genetic aberration is associated with defective DNA repair, which may lead to enhanced neoantigen formation and immune cell activation. While *BRCA*-mutated ovarian cancer in general is thought to be associated with increased CD8+ TILs and expression of PD-L1,[40,41] other evidence showed that only *BRCA1* but not *BRCA2* mutations are characterised by the immunoreactive molecular subtype and intense TILs.[42] In summary, *BRCA* mutations cannot be regarded as a sole predictor of therapeutic benefit with immunotherapy.

Clear cell carcinoma of the ovary is a distinct histological subtype with chemoresistance and worse prognosis. The angiogenesis pathway, involving hypoxic inducible factor-1-alpha and vascular endothelial growth factor (VEGF), is particularly important in the pathogenesis of this subtype.[43] The finding that VEGF inhibits the development of dendritic cells to activate T cells[44] may imply diminished tumour immunogenicity. On the other hand, a recent report showed that clear cell ovarian cancers with microsatellite instability (MSI) exhibit a higher number of CD8+ TILs and PD-L1 expression in both tumour and immune cells, as compared with microsatellite stable clear cell ovarian tumours or other histological subtypes.[45] Taken together, careful patient selection with novel biomarkers and combination strategies of anti-VEGF and immunotherapy will likely be particularly important in this subgroup of aggressive tumours.

Ascites and peritoneal disease are common presentations in patients with advanced ovarian cancer. Interestingly, certain chemokines present in ascites of ovarian cancer patients affect the immune response, and the omentum has distinct immune functions.[29] For example, ascitic fluid tumour-induced leukaemia inhibitory factor and interleukin-6 activate TAMs which in turn are associated with Tregs and immunosuppression; these factors also predict poor prognosis.[25,46] Another study confirmed that Tregs in the malignant ascites were more activated and proliferative than in the blood.[47] Disease involvement in the peritoneal cavity may therefore impact on the therapeutic efficacy of systemic immunotherapy and the intra-peritoneal route of administration could be investigated.

Immune Checkpoint Inhibitors Under Clinical Development in Ovarian Cancer

Nivolumab, an anti-PD-1 monoclonal antibody, was the first checkpoint inhibitor to be investigated in ovarian cancer. In a phase II open-label trial, 20 patients with advanced or refractory, platinum-resistant ovarian cancer were treated with nivolumab at doses of 1 or 3mg/kg every 2 weeks till disease progression.[48] The primary endpoint was overall response (ORR), which was 15% in both cohorts, including 2 complete responses (CRs) in the 3mg/kg arm and 1 partial response (PR) in the 1mg/kg arm. Out of the 2 patients with CR, one had clear cell carcinoma. Disease control rate (DCR) was 45%. Among the 20 patients, 16 had moderate to strong PD-L1 expression, while 4 had weak expression; no correlation between PD-L1 expression and ORR was observed. A total of 8 patients (40%) developed grade 3 or 4 adverse events (AEs), while other common AEs included hypothyroidism, transaminitis, fever and rash.

Comparable results were reported in the interim analysis of a phase Ib trial evaluating pembrolizumab, another anti-PD-1 antibody, in patients with PD-L1 positive advanced solid tumours including 26 with ovarian cancer.[49] One patient with CR and 2 with PR were observed, yielding an ORR of 11.5%; DCR was 34.6%. One patient had grade 3 transaminitis, while others had milder AEs including arthralgia, diarrhoea, hypothyroidism and rash. A phase II study with pembrolizumab is recruiting (NCT02674061).

Two anti-PD-L1 antibodies have been studied in phase I trials. Avelumab 10mg/kg achieved an ORR of 9.7% and DCR of 54% in 124 patients with recurrent or refractory ovarian cancers, at the cost of grade 3 or 4 AEs in 6.5%.[50] BMS-936559, another anti-PD-L1 antibody, was given to 17 ovarian cancer patients among 207 with advanced

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solid tumours, leading to PR in 1 patient and stable disease in 3.[51] Common toxicities of these agents were similar to those with anti-PD-1 antibodies. A third anti-PD-L1 agent, durvalumab, is being investigated in a phase II study (NCT02764333).

Anti-CTLA-4 antibodies are also in early clinical development in ovarian cancer. Ipilimumab following vaccination with granulocyte-macrophage colony-stimulating factor-modified autologous tumour cells (GVAX) led to disease control in 4 out of 9 stage IV ovarian cancer patients, although grade 3 colitis occurred in 2 patients.[52] A phase II trial with ipilimumab for patients with recurrent, platinum-sensitive ovarian cancer has completed accrual (NCT01611558).

A significant period of time has lapsed since the last report of any preliminary results using immune checkpoint inhibitors in advanced ovarian cancer and updated findings are eagerly awaited. In addition, the combination of PD-1/PD-L1 pathway blockade with various chemotherapy or targeted agents are ongoing, pending results.

Other Immunotherapy Modalities in Ovarian Cancer

IDO inhibitors, such as indoximod, reverse immunosuppression mediated by the enzyme and are currently in clinical trials in a variety of solid tumours including ovarian cancer. Toll-like receptors (TLRs) may inhibit Tregs and activate antigen presenting cells, and represent another potential target for immunotherapy. The TLR agonist motolimod is being evaluated in combination with durvalumab and pegylated liposomal doxorubicin in advanced ovarian cancer (NCT02431559).

Therapeutic vaccines can theoretically prime naïve T cells and enhance immune responses against ovarian cancer, although their clinical results are disappointing. In two large phase III trials, anti-idiotypic cancer vaccines as maintenance therapy failed to improve progression-free survival or overall survival in advanced ovarian cancer.[53,54] More recently, combination approaches, such as p53-targeted peptide vaccination in conjunction with gemcitabine and interferon-alpha,[55] or peptide vaccination targeting survivin in addition to metronomic cyclophosphamide,[56] have shown promise in generating T cell response in advanced ovarian cancer patients.

Alternatively, adoptive cell transfer where tumour-associated antigen-specific T cells are passively infused to the patient, is actively pursued in early clinical studies. In particular, therapy with genetically engineered T cells to express a chimeric antigen receptor (CAR-T) against ovarian cancer-specific antigens, such as mesothelin[57] and MUC16,[58] have been reported.

Conclusion

The observation that ovarian cancer is an immunogenic tumour forms a compelling rationale for immunotherapy. Various immunotherapeutic agents are still investigational, although some have shown early promise. Better understanding of cancer immunology will facilitate the development of predictive biomarkers, the design of combination strategies and the determination of the optimal clinical setting and route of administration.

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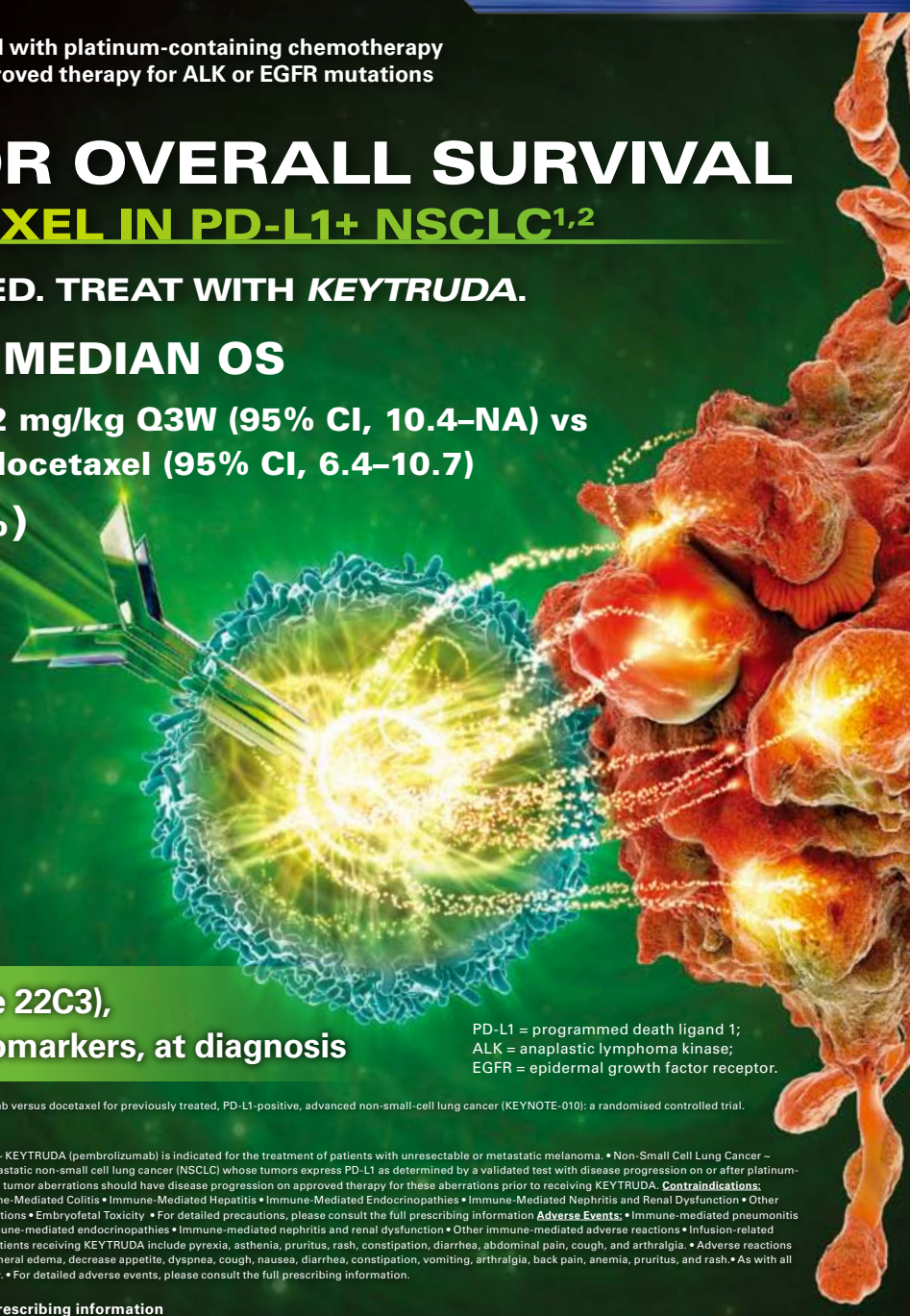

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Combination of immunotherapy and radiotherapy

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Introduction

Radiotherapy (RT) is an efficacious and cost-effective treatment that is received by up to 50% of all patients with cancer. It is estimated to be responsible for 40% of all cancer cures and also plays an important role to improve the quality of life in late-stage cancer patients. Traditional teaching has emphasised the local tumouricidal effect of radiation to kill the cancer cells directly by inducing irreparable DNA damage that leads to irreversible damage of the tumour cells. Recently, growing evidence suggested that RT could also elicit an immune response that can manifest as an immune-mediated tumour regression outside of the targeted site (abscopal effect).[1] The potential of RT to induce an immunogenic cell death and efficiently convert the irradiated tumour into an in-situ vaccine has implications for both local and systemic control. It provides a strong rationale to combine the novel immunotherapy and radiation.

Immune-modulatory effect of radiation

Historically, RT has been considered to be immunosuppressive based on conventional treatment techniques with a large irradiation field including a considerable volume of bone marrow and circulating blood volume, which resulted in reduced blood cell counts.[2] Also, to minimise the side effects to normal tissue, conventional RT needs to be delivered over several weeks in multiple small daily doses (typically 1.8-2Gy per fraction). Nowadays, advancement of technology has enabled us to deliver high-dose radiation precisely to the target with stereotactic body radiotherapy (SBRT). SBRT typically involves treatment of the tumour with radiation dose >5Gy per fraction with perfect target conformity under image guidance. It has been widely practised in both curative and oligo-metastatic settings.[3] Studies have shown that SBRT was associated with less myelo-suppression than conventional RT[4] given the smaller field and shorter period of treatment. Moreover, preliminary data suggested the radiation-induced immune response is dose dependent,[5] a higher dose of radiation is more effective in encouraging the destroyed cancer cells to act as an anti-tumour vaccine in-situ.[6]

The microenvironment created by cancer cells is characterised by immunosuppression and evasion of immune surveillance. SBRT resets the equilibrium by activating the immune system through several mechanisms. First of all, following cell death, there is a surge of tumour-associated antigens (TAAs) in the form of necrotic cell debris that encourages the antigen presenting cells (APC) and dendritic cells to stimulate the tumour-specific immune response.[7] Secondly, the release of death signal and cytokines after cell death will further enhance the process of TAAs presentation.[8] Thirdly, radiation induces a series of molecular phenotypic alteration of cancer cells, includes down-regulation of anti-apoptotic genes and modulation of antigen-processing machinery components, which render the cancer cells more amendable to cytotoxic T cell mediated destruction.[9] Collectively, SBRT encourages steps of antigen presentation to the immune system and recruitment of cytotoxic T cells to attack tumour cells and virtually helps in shifting the balance away from tumour-promoting immunosuppression towards anti-tumour immunity.

Immunotherapy and SBRT

The balance between immune response and self-tolerance is maintained by the co-stimulatory and inhibitory effect of immune checkpoint molecules, which can either create a local immunogenic or immunosuppressive environment. Immune checkpoint molecules thus are crucial in maintaining self-tolerance and protecting against normal tissue damage by autoimmunity. However, cancer cells also hijack these mechanisms to tip the balance towards an immunosuppressive one in favour of them to escape from the immune attack.[10] Two most widely studied and relevant classes of immune checkpoint molecules are PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic-T lymphocyte-associated-antigen 4). By targeted inhibition of these molecules, immunotherapies work by activating the immune system and amplifying the tumour antigen-specific T cell response.

The PD-1 receptor is present within the tumour microenvironment to limit the activity of infiltrating cytotoxic T lymphocytes, thus damping the effective immune responses.[11] The action of PD-1 receptor was triggered by binding of its ligands PD-L1 (programmed cell death ligand 1) that is often overexpressed on the surface of tumour cells. Similarly, CTLA-4 is a receptor overexpressed on the surface of CD4 + T cells, inhibiting their activation upon binding of TAAs presented by APC creates an immunosuppressive effect.[12] Therefore, the immunotherapies blocking the activation of PD-1 and CTLA-4 pathways can stimulate the anti-tumour immune response. It represents the breakthrough of treatments in melanoma, non-small cell lung cancer and various kinds of cancers.[13-14]

Therefore it is no surprise that SBRT and immunotherapy is a perfect couple based on their complementary immune-stimulatory effects. The property of high dose per fraction in SBRT promotes antigen presentation, recruitment of cytotoxic T cells and renders cancer cells more susceptible to immune-mediated damage, while immune-checkpoint inhibitors could augment each step of these immune activation processes.[15]

Pre-clinical evidence

Data from several pre-clinical studies have proved this concept. A study has demonstrated regression of the primary irradiated tumour and distant metastases following radiotherapy (12Gy x 2 fractions) combined with CTLA-4 blockade and the benefit of tumour shrinkage has translated into better overall survival. Further analyses confirmed that these effects were elicited by CD8+ T cell-dependent anti-tumour immunity.[16] Another study by the same group showed that the use of different SBRT regimens (20Gy x 1, 8Gy x 3, or 6Gy x 5) in combination with anti-CTLA-4 antibody therapy again resulted in enhanced regression of the primary tumour compared with the use of either SBRT or immunotherapy alone. Again, the amount of CD8+ T cells demonstrating tumour-specific IFNγ production was proportional to the inhibition of the secondary tumour. Interestingly, substantial inhibition of tumour growth outside of the radiation field was seen only when immunotherapy was added to the fractionated SBRT schedule and not the single-dose regimen.[17] Treatment of other types of immunotherapy, for example, anti-CD137, anti-CD40, has also been shown to enhance the anti-tumour effect of high dose radiotherapy. Based on the currently published data, we know that combined SBRT and immunotherapy improved the outcome compared with either single modality alone. The promising result provided a strong rationale to test the combination in clinical settings.

Clinical evidence

There are some publications on this bimodal treatment of high dose radiation and immunotherapy, mainly in the form of case reports. Postow et al. were the first to describe an abscopal effect of the SBRT and anti-CTLA-4 antibody. A female with metastatic melanoma received SBRT (9.5Gy x 3 fractions) to the painful para-spinal metastasis, in conjunction with ipilimumab, an anti-CTLA-4 monoclonal antibody. Computed tomography scans revealed not only a local response but also a substantial regression of lesions outside the radiation field.[18] In another similar case report, the author reported a remarkable improvement in the outcome of a metastatic melanoma patient who progressed while on ipilimumab alone but reported a complete systemic response after SBRT (18Gy x 3 fractions) treatment of two out of seven liver metastases.[19] A third case report of the abscopal effect of ipilimumab was in a metastatic non-small cell lung cancer patient who received SBRT of liver metastases (5Gy x 6 fractions), significant regression of both in-field and out-of-field lesions occurred and biopsy of the nodal metastasis revealed a pattern of enhanced T cell infiltration of the tumour nests.[20] Stamel et al. also reported a patient with metastatic melanoma with brain metastasis, who was treated with the combination of stereotactic radiosurgery (SRS) and ipilimumab. The patient experienced a complete remission including resolution of skin and nodal metastases and a concomitant increase in MAGEA3 titres – suggesting an underlying systemic immune mechanism.[21] Multiple studies with similar outcome have also been published as in Table 1.[22-23] Also, based on the current published reports, the combination is safe without undue toxicity. The encouraging results have set the stage for conducting prospective clinical trials investigating the combination of immunotherapy and SBRT.

Table 1 Selected published studies of immunotherapy and RT combination reporting abscopal (out-of-field) effect

Study details	SBRT dose	SBRT target	Immunotherapy agent	Sequence of treatment
Postow et al (2012)	9.5Gy x 3	Para-spinal	Ipilimumab	Immunotherapy then SBRT, then immunotherapy
Hiniker et al (2012)	18Gy x 3	Liver	Ipilimumab	Immunotherapy then SBRT, then immunotherapy
Golden et al (2013)	6Gy x 5	Liver	Ipilimumab	Concurrent
Stamell et al (2013)	Not reported	Brain	Ipilimumab	Concurrent
Karbach et al (2014)	45Gy x 1	Brain	Autologous tumour-lysate-loaded dendritic cells	SBRT then immunotherapy
Seung et al (2012)	20Gy x 1	Any	Interlukin-2	SBRT then immunotherapy

Table 2 Selected ongoing trials investigating the combination of immunotherapy and SBRT

Study details	SBRT dose	SBRT target	Immunotherapy agent	Sequence of treatment	Phase
MD Anderson Cancer Center (NCT02239900)	12.5Gy x 4 6Gy x 10	Liver, lung, adrenal	Ipilimumab	Concurrent, or immunotherapy then SBRT	I/II
Chiles Research Institute (NCT01862900)	15Gy x 1 20Gy x 1	Lung, liver	Anti-OX40	Concurrent	I/II
Stanford University (NCT01769222)	10Gy x 2	Any	Ipilimumab	Concurrent	I/II
NIH/ NCI (NCT22988946)	8Gy x 1 8Gy x 3	Liver	PD-1 inhibitor	SBRT then immunotherapy	I
Thomas Jafferson University (NCT01703507)	15Gy x 1 18Gy x 1 21Gy x 1 24Gy x 1	Brain	Ipilimumab	Concurrent	I
MD Anderson Cancer Center (NCT02444741)	12.5Gy x 4	Lung, liver	PD-1 inhibitor	Concurrent	I/II

Future direction

The partnering of SBRT and immunotherapy is still experimental at this stage. However, there are sufficient data in supporting the on-going studies. Indeed, the number of clinical trials (mainly phase I/II) exploring this combination is rapidly expanding in the past couple of years, mostly in metastatic solid cancer (See Table 2). Several considerations need to be carefully addressed in designing the clinical trials to evaluate this combination. First of all, radiotherapy parameters, the appropriate selection of dose fractionation regime of radiation is of critical importance in generating the immune response. Pre-clinical studies in breast and colon cancers

suggested that 3 fractions of 8Gy or 5 fractions of 6Gy are superior to one single fraction ablative dose of 20Gy in the combination of CTLA-4 blockage to produce an abscopal response.[17] While pre-clinical data seem to support that a fractionated approach is superior to a single dose regime, however, we still lack prospective clinical data, and whether it holds true in combined with other kinds of immune checkpoint inhibitors remains unknown. Apart from this, the sizes of the radiation field and target site of radiation are also crucial in determining the immune response. Second is the sequencing of therapies, all reported cases of abscopal response in CTLA-4 blockage have occurred in patients who received RT concurrent with or immediately after the immunotherapy. The pre-clinical model showed RT first followed by delayed CTLA-4 inhibitors resulted in inferior response.[17-18, 20] This strategy has theoretical advantages of stimulating antigen-presenting cells and effector T cells before SBRT, which will allow these cells to be readily available to respond to the efflux of tumour antigens generated by the radiation treatment. However, emerging data suggested the choice of the immunotherapeutic agent is more important in dictating the appropriate sequence on how to merge these two treatment modalities. Thirdly, trial endpoints selection, traditional clinical trial endpoints like RECIST response, progression-free survival and overall survival may fall short in identifying the responder of this approach, given the distinct response pattern of immunotherapy and SBRT. New immune-related response criteria and biomarkers of immunological readouts have been proposed to overcome the current limitations.[24-25] Finally, patient selection, appropriate choice of candidates is of paramount importance, the degree of myelo-suppression, overall tumour burden, prior exposure to RT and chemotherapy, which affect the amount of immune response, all should be taken into consideration.[26]

Conclusion

Technological advancement in past decades has revolutionised the radiotherapy treatment, in which nowadays can allow precise delivery of radiation to the target with great conformity while keeping the adjacent normal tissue with acceptable risk and treatment completed within a few days. SBRT has been widely utilised in the early stage as well as advanced stage cancer patients with limited metastases. Despite the fact that pro-immunogenic nature of SBRT has been proven in pre-clinical studies, its potential in the clinic has not been fully realised at the moment. With the synergistic effect in merging SBRT with immunotherapy, there is clear potential of this combination to substantially increase the local control as well as the abscopal effect in controlling the systemic micro- and marco-metastases. Multiple prospective clinical trials testing this approach are underway and the results are eagerly awaited.

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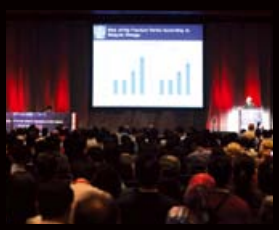

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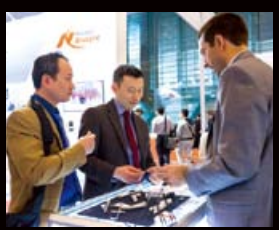

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The Federation Presidents' and Issue Editors' Dinner 2017

The Presidents' and Issue Editors' Dinner 2017 of the Federation was successfully held at the Aberdeen Marina Club on 25 April 2017. It was a great occasion for reunion and fraternity among the Presidents of member societies and the Editors of the Hong Kong Medical Diary.

During the Dinner, Executive Committee members of the Federation gave an update on our work and activities throughout the year. The Presidents of our member societies were also invited to give us comments and suggestions on the secretarial services offered by the Federation. Souvenirs were presented to Editors of the Medical Diary in appreciation of their dedication and support in ensuring the continuing success of the Diary. We were honoured by the presence of Prof. Sophia Chan, Undersecretary for Food and Health and Dr. Constance Chan, Director of Health, at our Dinner and their speeches on the collaboration between the Government and the Federation.

Our special thanks go to Meetings & Exhibitions Hong Kong of the Hong Kong Tourism Board as the supporting organization and Audi Hong Kong as the sponsor. The evening was made more memorable by the delightful vocal performance by Mr. Samuel Chan, Chairperson of Hong Kong Occupational Therapy Association and the talk on Prevention of Sports Injuries by Dr. Lobo Louie, President of the Hong Kong Association of Sports Medicine.


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* HKMAPS 2nd Photo Competition and Sharing Session 2017 **4**	**5**	* HKMA Kowloon West Community Network – Prescription of Insulin Therapy in a Primary Clinic * HKMA Tai Po Community Network - Option of Oral Anti-diabetic Agent for a Better CV Outcome * FMSHK Officers' Meeting * HKMA Council Meeting **6**	* HKMA Shatin Doctors Network - Update in Joint Pain Management **7**	* HKMA Kowloon East Community Network - Managing Chronic Heart Failure – The Reality in Practice **8**	**9**	* Refresher Course for Health Care Providers 2016/2017 **10**
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18	**19**	* HKMA Kowloon West Community Network – Current Management Strategies in GERD * HKMA Tai Po Community Network - Update in Joint Pain Management **20**	**21**	* HKMA Kowloon East Community Network - Total Diabetes Management: ABC + M * HKMA New Territories West Community Network - Biomarker Testing in Non-Small Cell Lung Cancer Type * FMSHK Executive Committee Meeting **22**	**23**	**24**
25	**26**	* HKMA Tai Po Community Network - From Evidence to Practice: Managing Heart Failure Patients in Hong Kong **27**	* HKMA Central, Western & Southern Community Network - Certificate Course on Geriatrics (Session 3) - Understand Sarcopenia **28**	**29**	**30**	

Date / Time	Function	Enquiry / Remarks
1 THU 1:00 PM	**HKMA New Territories West Community Network – Would New Type of Insulin Make Initiation of Insulin Easier?** Organiser: HKMA New Territories West Community Network; Chairman: Dr. TSUI Fung; Speaker: Dr. WONG Lai Sze, Alice; Venue: Red Royalty Banquet Restaurant (紅爵御宴), 1/F, Manhattan Plaza, No. 23, Sai Ching Street, Yuen Long, N.T.	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
4 SUN 2:00 PM	**HKMAPS 2nd Photo Competition and Sharing Session 2017** Organiser: The Hong Kong Medical Association; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Miss Ada SIU/ Miss Heiman CHAN Tel: 2527 8285
6 TUE 1:00 PM	**HKMA Kowloon West Community Network – Prescription of Insulin Therapy in a Primary Clinic** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. MOK Kwan Yeung, Matthew; Speaker: Dr. MA Pui Shan; Venue: Crystal Room IV-V, 3/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
1:45 PM	**HKMA Tai Po Community Network - Option of Oral Anti-diabetic Agent for a Better CV Outcome** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. WU, Enoch; Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No.9 Nam Wan Road, Tai Po, N.T.	Ms. Candice TONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
7 WED 1:00 PM	**HKMA Shatin Doctors Network - Update in Joint Pain Management** Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. WONG Tsz Cheung; Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin, N.T.	Ms. Candice TONG Tel: 2527 8285 1 CME Point
8 THU 1:00 PM	**HKMA Kowloon East Community Network - Managing Chronic Heart Failure – The Reality in Practice** Organiser: HKMA Kowloon East Community Network; Chairman: Dr. TING Ka Chu; Speaker: Dr. Adrian CHEONG; Venue: Lei Garden Restaurant, Shop No. L5-8, APM, No. 418 Kwun Tong Road, Kwun Tong, Kln	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
10 SAT 2:15 PM	**Refresher Course for Health Care Providers 2016/2017** Organiser: Hong Kong Medical Association; HK College of Family Physicians; HA-Our Lady of Maryknoll Hospital; Speaker: Dr. Lam Wing Wo; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
13 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network - Diabesity Management** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. HO Fung; Speaker: Dr. FUNG Lai Ming; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:45 PM	**HKMA Tai Po Community Network - Factors to Consider when Choosing MMRV Vaccines** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. WAN Ching Yu; Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No.9 Nam Wan Road, Tai Po	Mr. Vincent NG Tel: 9738 2998 1 CME Point
14 WED 7:30 AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Transfusion in Neurosurgery** Organiser: Hong Kong Neurosurgical Society; Chairman: Dr TSANG Chun Pong; Speaker: Dr LAU Sau Ning, Sarah; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 Fax. : 2965 4061 1.5 CME points (College of Surgeons of Hong Kong)
1:00 PM	**HKMA Central, Western & Southern Community Network - Certificate Course on Geriatrics (Session 2) - Mobility Problems in Elderly** Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. TSANG Kin Lun; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
20 TUE 1:00 PM	**HKMA Kowloon West Community Network – Current Management Strategies in GERD** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. WONG Wai Hong; Speaker: Dr. LEE Ming Kai, Derek; Venue: Crystal Room IV-V, 3/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
1:45 PM	**HKMA Tai Po Community Network - Update in Joint Pain Management** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwun, John; Speaker: Dr. WONG Tsz Cheung; Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No.9 Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
22 THU 1:00 PM	**HKMA Kowloon East Community Network - Total Diabetes Management: ABC + M** Organiser: HKMA Kowloon East Community Network; Chairman: Dr. SHIU Ka Lok, Ivan; Speaker: Dr. YIP Wai Man; Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O, Kln	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA New Territories West Community Network - Biomarker Testing in Non-Small Cell Lung Cancer Type** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHAN Lam Fung, Lambert; Speaker: Dr. CHEUNG Ming Chee, Michael; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong	Mr. Ziv WONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: HKMA New Territories West Community Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
27 TUE 1:45 PM	**HKMA Tai Po Community Network - From Evidence to Practice: Managing Heart Failure Patients in Hong Kong** Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwun, John; Speaker: Dr. YU Cheuk Man;Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No.9 Nam Wan Road, Tai Po	Ms. Candice TONG Tel: 2527 8285 1 CME Point
28 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Certificate Course on Geriatrics (Session 3) - Understand Sarcopenia** Organiser: HKMA Central, Western & Southern Community Network; Speaker: Dr. CHAN Chun Chung, Ray; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Mr. Ziv WONG Tel: 2527 8285 1 CME Point

Answers to Radiology Quiz

Answer:

1. There is a lobulated radiolucent lesion noted at the right subdiaphragmatic region
2. There is a hypodense lesion with internal air fluid level noted at the R lobe of the liver. This is associated with peripheral contrast enhancement.
3. Liver abscess
4. Bacterial, Parasitic or Fungal
5. Image guided aspiration or drainage + antimicrobial therapy

Dr Andrew CHENG
MBBS (HK)
Resident, Department of Radiology, Queen Mary Hospital

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5 Jul	Principles and Concepts of Quality of Life (QoL)	Dr Wendy Wong Assistant Professor, Hong Kong Institute of Integrative Medicine, School of Chinese Medicine The Chinese University of Hong Kong
12 Jul	Linguistic Validation and Basic Psychometric Evaluation of QoL Measures	Dr Daniel Fong Associate Professor, School of Nursing The University of Hong Kong
19 Jul	Further Psychometric Evaluation of QoL measures	Dr Daniel Fong Associate Professor, School of Nursing The University of Hong Kong
26 Jul	Interpreting QoL in Practice	Dr Daniel Fong Associate Professor, School of Nursing The University of Hong Kong
2 Aug	Using QoL in Chinese Medicine	Dr Zhao Li Chief of Chinese Medicine Service The Hong Kong Tuberculosis Association Chinese Medicine Clinic cum Training Centre The University of Hong Kong
9 Aug	Using QoL in Health Economic Evaluation	Dr Carlos Wong Research Assistant Professor, Department of Family Medicine and Primary Care The University of Hong Kong

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Officiating Guests:

- **Dr KO Wing Man, BBS , JP**
- **Dr LEI Chin Ion** *Director of Health Bureau, Macau*

Speakers: (in alphabetical order)

- **Ms Elaine CHAN**
  Chief Health Officer, Zurich Insurance Company Limited
- **Ms Eleanor KAM**
  Head of Ageing Innovation,
  New World Development Company Limited
- **Mr Alex LAM**
  Chairman, Hong Kong Patients' Voices
- **Dr Walton LI**
  Medical Superintendent, Hong Kong Sanatorium & Hospital
- **Mr Albert Wong**
  Chief Executive Officer,
  Hong Kong Science and Technology Parks Corporation
- **Mr John WONG**
  Regional President, Boston Consulting Group

Moderator

- **Mr Stephen LEUNG**
  Country Manager, Pfizer Corporation Hong Kong Limited

Programme Rundown

1:30pm	Registration (Shanghai Room, Level 8)
2:00pm	Opening Ceremony
2:15pm	Annual Conference
5:15pm	AGM & Fellowship Conferment
6:00pm	Dinner Reception (Star Room, Level 42)
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