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INSTRUCTIONS FOR AUTHORS

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Comments on any aspects of the profession are also welcome as Letter to the Editor.

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Editorial

News & Short Communications

Drugs & Therapeutics

Pharmaceutical Techniques & Technology

Society Activities

New year, new development

The beginning of 2020 marks a new chapter of development for Hong Kong Pharmaceutical Journal (*HKPJ*). Starting this year, three issues of *HKPJ* will be published. This will give the Editorial Committee more time to prepare up-to-date articles that serve the interests of members, authors and readers better. In addition, funding for the development of electronic version of *HKPJ* has been secured. Taskforce members are looking into the process of digitization now. We hope the electronic version can be rolled out in 2021.

The theme for this issue is oncology. According to World Health Organization, cancer is the second leading cause of death worldwide.[1] In Hong Kong, the Hong Kong Cancer Registry reported that there were over 30,000 new cancer cases and over 14,000 cancer deaths in 2016.[2] Treatment modalities may include surgery, radiation therapy and chemotherapy. Advances and innovations in the treatment of cancer have created a variety of new options, such as targeted therapy and immunotherapy. Regardless of the cancer drug chosen, systemic therapy remains the mainstay of treatment.

Chemotherapeutic agents interfere with the DNA synthesis or function. They directly or indirectly inhibit the proliferation of tumor cells. Because they act primarily on rapidly dividing and growing cells, chemotherapy is associated with range of adverse effects including bone marrow suppression or gastrointestinal complications such as nausea and vomiting. Chemo-induced nausea and vomiting (CINV) is a distressing acute side effect of cancer treatment and can happen in up to 80% of patients.[3] The introduction of neurokinin-1 receptor antagonists (NK-1 RA) into the management of CINV has significantly improved in the prevention of both acute and delayed CINV. Article by Tenney et al (p. 127) featured the use of NK-1 RA in the management of CINV.

Lung cancer is the second most common cancer in Hong Kong in 2017, after colorectal cancer[2] and non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer. Before the era of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) and immunotherapy, chemotherapy was the only option available for patients with advanced-stage disease. With an improved understanding of the molecular and genetic components in cancer development, novel agents that target specific pathways in NSCLC emerged. The review written by Mr. Kemo Lam discussed the use of EGFR-TKIs and the place in therapy for different generations of EGFR-TKIs in patients with NSCLC EGFR mutation (p. 121). Durvalumab, a programmed cell death protein (PD-L1) inhibitor, is a new revelation for patients with unresectable stage III NSCLC. The article by Ms. Chanel Tsui provided an overview of this drug with clinical efficacy and safety data (p. 124).

I hope that you enjoy this special issue. As always, your suggestions on any part of the Journal is valuable and can send the comments to me or other members of the Editorial Committee. Moreover, if you would like to know more about the digitization of *HKPJ*, please contact me for more details.

May PS Lam
Editor-in-Chief
9 February 2020

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Prepared by Howard Chan, Chiu TS Ching

Palbociclib plus Exemestane with Leuprolide Shows Prolonged Progression-free Survival Over Capecitabine in Premenopausal Women with Hormone-receptor Positive, HER2-negative Metastatic Breast Cancer

Date: October 24, 2019

The KCSG-BR15-10 randomized controlled phase 2 trial, conducted between June 2016 and December 2018, proposed significantly improved progression-free survival (PFS) by palbociclib plus exemestane with leuprolide over capecitabine in premenopausal women with hormone-receptor positive, HER2-negative metastatic breast cancer.

The trial recruited premenopausal women aged 19 years or above with hormone receptor-positive, HER2-negative recurrent or metastatic breast cancer; 86% were tamoxifen-resistant, and those previously received radiotherapy to less than 25% of bone marrow, or one endocrine treatment or chemotherapy for advanced disease, were also eligible. 184 patients were randomly assigned in 1:1 ratio to receive either combination therapy (oral palbociclib 125mg once daily for 3 weeks, oral exemestane 25mg once daily for 4 weeks plus subcutaneous leuprolide 3.75mg every 4 weeks) or oral capecitabine 1250mg/m^2 twice daily for 2 weeks, repeated every 3 weeks until intolerable toxicity or progression. Palbociclib was discontinued if re-initiation cannot be done after 3-week delay or over two dose reductions.

Primary endpoint was investigator-assessed PFS, while notable secondary endpoints included overall survival (OS) and toxicity. 178 patients were included in the final modified intention-to-treat population analyses. Median PFS was significantly higher in the combination therapy arm (20.1 months vs 14.4 months; hazard ratio [HR] 0.659 [95% confidence interval (CI), 0.437 to 0.994], p=0.0235). Both dosing interruptions and dose reductions were more frequent in the combination therapy arm (88 [96%] vs 65 [76%], 44 [48%] vs 41 [48%] respectively). Median OS of all patients was not reached since 12 patients died of progression at the time of data cut-off.

Trial results suggested higher effectiveness of combination therapy over capecitabine in prolonging PFS. However, later response observed in the combination therapy arm also implied necessity of careful assessment for optimal response, particularly in patients with recurrent disease within 24 months of adjuvant endocrine therapy.

Source: www.thelancet.com

Overall Survival Significantly Prolonged with Osimertinib over Standard Treatment in Untreated, EGFR-mutated Advanced NSCLC

Date: November 21, 2019

A recent study suggested the superior effect of osimertinib, a third-generation oral irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI).over standard EGFR-TKIs in prolonging progression-free survival (PFS) in patients with untreated EGFR-mutated advanced non-small-cell lung cancer (NSCLC).

FLAURA is a two-year, double-blind phase 3 randomized controlled trial in which patients with untreated metastatic or locally advance NSCLC were screened for eligibility of receiving first-line treatment with standard EGFR-TKIs. After EGFR mutation screening, 556 were stratified by tumour mutation status (Ex19del or L858R) and race (Asian or non-Asian), further assigned to receive either oral osimertinib 80mg once daily (n=279) or standard oral EGFR-TKI (gefitinib 250mg once daily or erlotinib 150mg once daily, n=277) in 1:1 ratio. The primary endpoint was duration of investigator-assessed progression-free survival, with overall survival, objective response rate, response duration, disease-control rate, response depth and safety as secondary endpoints.

Investigator-assessed PFS was significantly longer in the osimertinib group than in the standard EGFR-TKI group (HR for disease progression or death, 0.46; 95% CI, 0.37 to 0.57; p<0.001), which corresponds to conclusions made by blinded independent central review. Consistent benefits were also observed across predefined subgroups, including race, EGFR mutation type and presence of known or treated CNS metastases at trial entry. With regards to secondary endpoints, safety profile was similar between the two arms, with osimertinib group associated with a slightly lower rate of adverse events leading to permanent treatment discontinuation than standard EGFR-TKI group (37 [13%] vs 49 [18%] respectively).

Trial results showed potential of osimertinib being used as first-line treatment for treating EGFR-mutated NSCLC. Further research is warranted to fully characterized possible resistance when used as frontline therapy, as well as any mechanisms involved.

Source: www.nejm.org

Use of Anastrozole for Breast Cancer Prevention (IBIS-II): Long-term Results of A Randomized Controlled Trial

Date: December 12, 2019

Two large clinical trials have shown a reduced rate of breast cancer development in high-risk women within 5 years of follow-up by using aromatase inhibitors (MAP.3 and International Breast Cancer Intervention Study II [IBIS-II]). Blinded long-term follow-up results for IBIS-II, with the objective of determining anastrozole efficacy in preventing breast cancer (both invasive and ductal carcinoma in situ) post-treatment, were recently reported.

IBIS-II is an international, randomized, double-blind, placebo-controlled trial. 3864 postmenopausal women at increased risk of developing breast cancer were recruited between Feb 2003 and Jan 2012 and were randomly assigned to receive either oral anastrozole 1mg daily or matching placebo for 5 years. After treatment completion, women were followed yearly to collect data on breast cancer incidence, death, other cancers, cardiovascular events and fractures. Primary outcome was all breast cancer.

1920 were assigned to anastrozole and 1944 to placebo. After a median follow-up of 131 months (Inter-quartile range 105 to 156), 49% reduction in breast cancer was observed for anastrozole (85 vs 165 cases; HR, 0.51, 95% CI, 0.39 to 0.66; p<0.0001). Reduction was larger in the first 5 years (35 vs 89; HR, 0.39; 95% CI, 0.27 to 0.58; p<0.0001), but still significant after 5 years (p=0.014) without significant difference from previous 5 years (p=0.087). Invasive oestrogen receptor-positive breast cancer was reduced by 54% (HR 0.46; 95% CI 0.33 to 0.65; p<0.0001), with significant continued post-treatment effect. 59% reduction in ductal carcinoma in situ was observed (HR, 0.41; 95% CI, 0.22 to 0.79, p=0.0081), especially in participants known to be oestrogen receptor-positive (HR, 0.22; 95% CI, 0.07 to 0.65; p<0.0001). No significant difference in deaths was observed overall (69 vs 70; HR, 0.96; 95% CI, 0.69 to 1.34; p=0.82) or for breast cancer. Significant decrease in non-breast cancers was observed for anastrozole (147 vs 200, odds ratio 0.72, 95% CI 0.57 to 0.91, p=0.0042); no excess of fractures or cardiovascular disease was observed.

Analysis has identified a significant continuing reduction in breast cancer with anastrozole in the post-treatment follow-up period, without evidence of new late side-effects. Further follow-up is needed to assess the effect on breast cancer mortality.

Source: www.thelancet.com

Use of EGFR-TKI treatments in Non-Small Cell Lung Cancer

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ABSTRACT

Tyrosine kinase inhibitor (TKI) monotherapy has become the standard of care for patients with epidermal growth factor receptor (EGFR) mutation positive advanced non-small cell lung cancer (NSCLC). Currently, five TKIs are available for the treatment of EGFR-mutated lung cancer. Patients with NSCLC EGFR mutation show a pronounced response after the use of EGFR-TKI treatment but may acquire resistance after ~9 to 14 months of such therapy. In this review, different generations of EGFR-TKI regimen will be discussed.

Keywords: *tyrosine kinase inhibitor, gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, non-small cell lung cancer*

INTRODUCTION

Tyrosine kinase inhibitor (TKI) monotherapy has become the standard of care for patients with epidermal growth factor receptor (EGFR) mutation positive advanced non-small cell lung cancer (NSCLC). Five TKIs namely gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib are currently available for the treatment of EGFR-mutated lung cancer. Evidence-based median progression-free survival (PFS) in clinical trials for different EGFR-TKIs treatment regimens are show below:

Table 1. Median PFS in clinical trials for patients with EGFR mutation–positive advanced NSCLC treated with EGFR-TKIs

Regimen	Trials	Median PFS (Months)
Gefitinib	WJTOG3405, NEJ002, LUX-Lung 7, ARCHER 1050	9.2-10.9
Erlotinib	EURTAC, OPTIMAL, NEJ026	10.4-13.3
Afatinib	LUX-Lung 3, LUX-Lung 6 LUX-Lung 7	11.0-11.1
Dacomitinib	ARCHER 1050	14.7
Erlotinib + Bevacizumab	NEJ026	16.9
Osimertinib (Second line)	AURA3	10.1
Osimertinib (first line)	FLAURA	18.9

NSCLC EGFR mutation patients show an initial pronounced response since the use of first generation EGFR-TKI treatment. They may acquire a resistance to these drugs after ~9 to 14 months of such therapy. In this review, we try to discuss different generations of EGFR-TKI regimen and maximize the overall survival of the EGFR-TKI treatments.

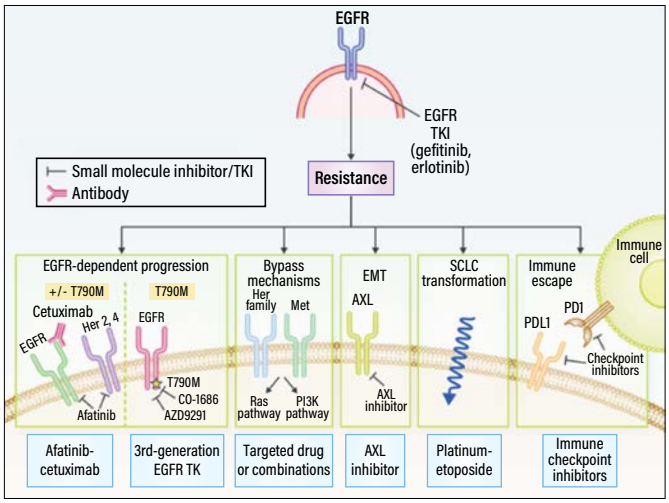

Figure 1: *Mechanisms of TKIs–resistance and choice of alternative agents*

First-Generation EGFR-TKIs: Erlotinib or Gefitinib

In May 2003, US Food and Drug Administration (FDA) has granted accelerated approval of gefitinib for the second-line treatment of advanced non-small cell lung cancer (NSCLC), based upon data from Phase II trials showing 13.6% US patients achieved tumour shrinkage of at least 50%. In November 2004, erlotinib also received FDA approval for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In May 2013 and July 2015, erlotinib and gefitinib have further received their first-line approval from FDA respectively. In September 2016 a multicenter, randomized phase III trial (WJOG 5108L) directly compared erlotinib with gefitinib for the first-line treatment of advanced lung adenocarcinoma.[1] The median PFS was 8.3 and 10.0 months for gefitinib and erlotinib respectively (p = 0.424). The study did not demonstrate non-inferiority of gefitinib compared to erlotinib in terms of PFS. The two arms of Kaplan–Meier survival **(Figure 2)** were almost identical, and therefore these two first-generation EGFR-

TKIs were considered almost equivalent in clinical practice.

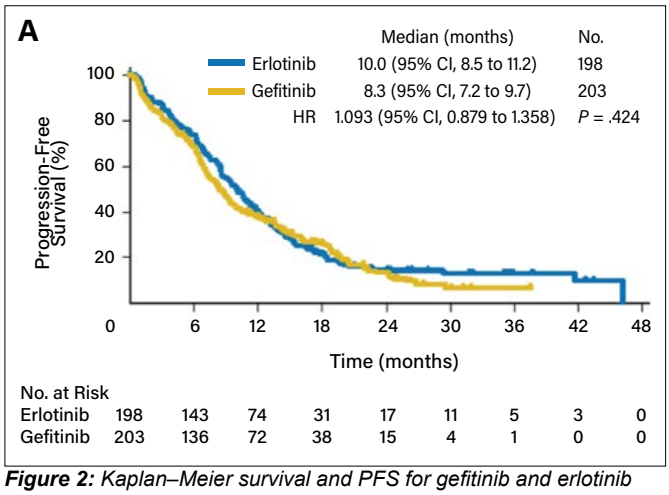

Figure 2: *Kaplan–Meier survival and PFS for gefitinib and erlotinib*

Second-Generation EGFR-TKIs: Afatinib or Dacomitinib

Afatinib or dacomitinib are second generation EGFR–TKIs which irreversible block tyrosine kinase activity. They have higher affinity for the EGFR kinase domain and might be expected to result in a more persistent suppression of EGFR signaling compared with erlotinib or gefitinib.[2] A Phase IIb, randomized trial (LUX-Lung 7) comparing afatinib with gefitinib for the first-line advanced lung adenocarcinoma with EGFR positive activating mutations (exon-19 deletions or the L858R point mutation) was conducted.[3] The primary endpoints were PFS, overall survival (OS) and time to treatment failure. Results showed statistically significant improvement in afatinib with PFS (median of 11.0 versus 10.9 months; hazard ratio (HR) = 0.73 [95% confidence level (CI) 0.57-0.95], p = 0.017) and time to treatment failure (median of 13.7 versus 11.5 months; HR = 0.73[95% CI 0.58-0.92], p = 0.0073) when compared to gefitinib.

Dacomitinib not only bind to EGFR, but also related to proteins ErbB2 and ErbB4.[4] An open-label phase III, randomized study (ARCHER 1050) comparing dacomitinib with gefitinib, for treatment-naive patients with EGFR mutation–positive advanced NSCLC was performed. The primary endpoint of ARCHER 1050 was PFS. Dacomitinib cohort demonstrated a significant PFS improvement with a median value of 14.7 months compared to 9.2 months in the gefitinib arm (HR = 0.59 [95% CI 0.47-0.74], p < 0.0001).[5] In contrast to LUX-Lung 7, the ARCHER 1050 study excluded patients with brain metastases. The OS analysis of dacomitinib for the intention-to-treat population also show a significant improvement, with a median of 34.1 months compared to 26.8 months for gefitinib (HR = 0.76 [95% CI 0.582-0.993], p = 0.044).[6] In conclusion, this second-generation EGFR-TKI is superior to first-generation EGFR-TKI, at least in terms of PFS.

Third-Generation EGFR-TKI: Osimertinib

In November 2015, the U.S. FDA approved osimertinib for metastatic NSCLC positive for EGFR T790M who had progressed during or after prior EGFR-TKI therapy. Osimertinib is an irreversible T790M mutant–specific EGFR-TKI. It has been used in second line setting for advanced NSCLC in order to overcome T790M-mediated acquired resistance to first- or second-generation EGFR-TKIs.[7] An open-label, phase III randomized trial (AURA3) compared osimertinib versus platinum-based doublet chemotherapy in patients with T790M mutation of EGFR that had progressed from previous EGFR-TKI therapy.[8] The primary endpoint of this trial was PFS. Results have shown that osimertinib was associated with a statistically improvement in PFS compared to the standard of care platinum-doublet chemotherapy (median of 10.1 versus 4.4 months; HR = 0.30, p < 0.001) **(Table 1)**. In patients with central nervous system (CNS) metastases at the baseline, PFS was also conferred a significantly improvement with osimertinib than with platinum-based doublet chemotherapy (8.5 versus 4.2 months; HR = 0.32, with a 95% confidence interval of 0.21–0.49)

Recently, osimertinib has obtained an additional FDA indication for first-line treatment of metastatic NSCLC EGFR mutation at exon-19 deletions or the L858R point. A phase III, randomized trial (FLAURA) has evaluated the efficacy and safety of osimertinib in comparison to the standard treatment first-generation EGFR-TKI (gefitinib at 250 mg daily or erlotinib at 150 mg daily), for treatment-naive patients with EGFR-mutated metastatic NSCLC. The results revealed osimertinib was associated with a longer PFS compared to the standard of care (median of 18.9 versus 10.2 months; HR = 0.46 [95% CI 0.37-0.57], p < 0.001).[9] This positive result also applied to patients with CNS metastases at study entry in subgroup analysis.

Combination of EGFR-TKIs with Antiangiogenic Agents

Given that addition of bevacizumab (antiangiogenic agents) to chemotherapy show clinical activity for NSCLC.[10,11] The vascular endothelial growth factor (VEGF) is one of the key regulators that likely contributes to the pathogenesis and progression of NSCLC. A phase II study (JO25567) for first-line therapy in patients with advanced non-squamous NSCLC harboring EGFR mutations was undertaken in Japan, comparing erlotinib plus bevacizumab with erlotinib alone. The study demonstrated that the primary endpoint PFS of the combination treatment was longer than erlotinib monotherapy (HR = 0.54 [95% CI 0.36-0.79], p = 0.0015).[12] After that, a phase III study has compared erlotinib plus bevacizumab with erlotinib alone, in patients with untreated EGFR mutation–positive NSCLC. The result showed a significant median PFS improvement with 16.9 months compared to 13.3 months (HR = 0.605 [95% CI 0.417-0.877], p = 0.016) respectively[13] **(Table 1)**.

Given that ramucirumab (a monoclonal immunoglobulin G1 antibody) binds to the extracellular domain of the VEGF receptor VEGFR-2 with high specificity, a randomized phase Ib/III study (RELAY) investigating the safety and efficacy of the combined use of ramucirumab and erlotinib for NSCLC patients with activating EGFR mutation is now undergoing.[14]

EGFR-TKI treatment sequence and future directions

Refer to **table 1**, for first line EGFR mutation metastatic NSCLC, osimertinib (first line) FLAURA offers the best median PFS 18.9 months.[10] Erlotinib + bevacizumab offers the second best median PFS 16.9 months.[13] To maximize OS, these two choices in combination with other treatment options, may need to be considered by oncologists and further investigated by studies.

In real-world clinical practice, a retrospective observational study for TKI-naive patients with first-line treatment of afatinib, acquired the T790M mutation of EGFR, and then received osimertinib has been studied. The median time on treatment for sequential afatinib and osimertinib was 27.6 months.[15] However, some oncologists may be hesitant in using this approach, given that patients may not detect T790M mutation after prior EGFR-TKI therapy. Tumor mutation burden (TMB) in pre–EGFR-TKI tumor specimens is a potential biomarker for the prediction of T790M-mediated resistance. A recent study assessed the impact of TMB on the outcome T790M mutation.[16] Among patients detected T790M mutation, the median TMB was 3.77 mutations/Megabase (mutations/Mb) versus 4.72 mutations/Mb for those patients who did not acquired T790M mutation. The results suggested that on the basis of TMB if an optimal cut-off value can be determined, it may be possible to select patients likely to develop the T790M mutation.

On the other hand, the mechanisms of resistance to osimertinib in the first-line setting have not been fully elucidated. Recently a retrospective analysis of the FLAURA trial looking at the mechanisms of acquired resistance to first-line osimertinib, found that the MET amplification was present at low frequency (15%), followed by the C797S mutation (7%), PIK3CA (7%), KRAS (3%) mutations and HER2 amplification (2%).[17] This findings weaken support for the treatment strategy of osimertinib as first line setting, given the lack of targeted treatment options after osimertinib failure.

For future directions in maximizing the duration of PSF and OS, further investigation is required. The combination of atezolizumab and bevacizumab plus chemotherapy (carboplatin and paclitaxel) (IMpower150) has showed improvement in progression-free survival in advanced non-squamous non-small cell lung cancer (NSCLC) and the safety profile was consistent with those individual medicines.[18] It will be interesting to see a clinical trial with the addition of erlotinib or osimertinib to this combination. The combination of antiangiogenic agents with osimertinib may also give a better response. Comprehensive characterization of resistance mechanisms for osimertinib will also contribute to the development of more effective strategies and new targeted agents.

Author's background

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Durvalumab: a new revelation for patients with unresectable stage III Non-Small Cell Lung Cancer

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ABSTRACT

Durvalumab is a programmed cell death ligand 1 (PD-L1) inhibitor that has been approved by US FDA for the treatment of unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. In the PACIFIC study, higher progression free survival rate and better survival benefit were observed in the durvalumab arm. Diarrhoea, pneumonitis, rash and pruritis were the most commonly adverse events occurred with durvalumab.

Keywords: *durvalumab, programmed cell death ligand 1 inhibitor, non-small cell lung cancer*

INTRODUCTION

Lung cancer is the most common cancer in men and third most common cancer in women; approximately 2 million new cases were diagnosed in 2018.[1] Generally speaking, there are two main types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer. Around 85% of lung cancers are NSCLC, which are further categorised into three major histological types: adenocarcinoma (35%-40%), squamous cell carcinoma (25%-30%) and large cell carcinoma (10%-15%).[2-3] Around one third of patients with NSCLC present with stage III, locally advanced disease, and the majority have unresectable tumours.

Current practice for those with stage III unresectable NSCLC is platinum-based chemotherapy with concurrent radiotherapy; although this can achieve initial disease control, the majority of these patients will eventually progress.[4] The mean progression-free survival amongst these patients is poor and the five-year survival rate is as low as 15%, corresponding to a median survival of no longer than 28 months. Poor prognostic factors for survival in these patients may due to advanced stage of disease at time of diagnosis, poor performance status, and potential diagnosis with metastatic disease.

Durvalumab (IMFINZI®) is a selective, high affinity, human IgG1 monoclonal antibody which blocks programmed cell death ligand 1 (PD-L1) binding to programmed cell death protein (PD-1) and CD80. PD-L1 blockade leads to increased T-cell activation, leading to T-cells killing tumour cells. It was first approved in mid 2017 by the Food and Drug Administration (FDA) for treatment with locally advanced or metastatic urothelial carcinoma who has previously received platinum-based chemotherapy; and in 2018, it was approved for patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.[3,7]

Pharmacology

PD-L1 is a transmembrane protein that plays an important role in suppressing the adaptive arm of immune system in particular events. Normally the adaptive immune system responds to antigens that are associated with immune system activated by danger signals, endogenous or exogenous. This, in turn, propagates clonal expansion of antigen specific T cells and/or helper cells. PD-L1 is an immune checkpoint protein expressed on tumour cells and tumour infiltrating cells. PD-L1 blocks T-cell function and activation through interaction with PD-1

and CD80. Binding of PD-L1 to the inhibitory checkpoint molecules transmits an inhibitory signal that reduces proliferation, cytotoxic T-cell activity and cytokine production.[3]

Durvalumab acts by blocking and interrupting the interaction of PD-L1 with PD-1 and CD80. The blockade releases the inhibition of immune response without inducing antibody dependent cell-mediated cytotoxicity. This enhances anti-tumour immune responses and increases T-cell activation.[7,8]

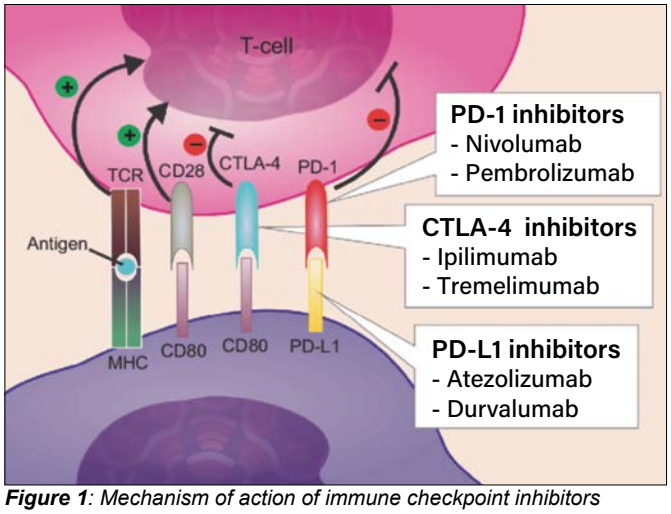

***Figure 1**: Mechanism of action of immune checkpoint inhibitors*

Clinical efficacy

The efficacy of durvalumab was evaluated in the PACIFIC study - a randomised, double blind, placebo controlled, multicentre study evaluating the immune checkpoint inhibitor in patients with stage III unresectable NSCLC who did not have disease progression after concurrent chemoradiotherapy.[6,7]

In the study, 713 patients were enrolled and were assigned, in 2:1 ratio, to receive durvalumab (intravenously at 10mg/kg) or placebo every 2 weeks for up to 12 months. Patients were recruited in regardless to their PD-L1 expression level. The co-primary endpoints were progression free survival (PFS) and overall survival (OS).

The median PFS from randomisation with durvalumab was 16.8 months (95% confidence interval (CI), 13.0-18.1) versus 5.6 months (95% CI, 4.6-7.8) with placebo. PFS rates were further analysed at 12-month period and 18-month period - durvalumab group delivered higher PFS rates at both time periods comparing to placebo group **(figure 2)**. In terms of overall survival, durvalumab group achieved a higher percentage of OS than the placebo group at 12 months and 24 months, 83.1% vs 75.3% and 66.3% vs 55.6% respectively. The overall survival benefit with durvalumab was observed across all predefined subgroups (according to patients' demographics, response to previous treatment and baseline clinicopathologic features). **Figure 2** and **figure 3** showed Kaplan-Meier curves for progression free survival and overall survival respectively.

Safety

Adverse events of any cause and grade were assessed in both durvalumab and placebo group. 96.8% of the patients who received durvalumab experienced adverse events of any grade, and 94.9% in the placebo group;

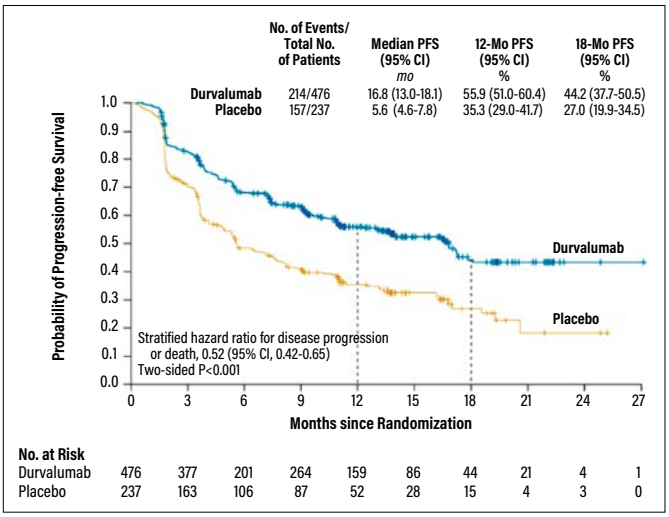

***Figure 2**: Kaplan-Meier curves for progression free survival in the Intention-to-Treat population*

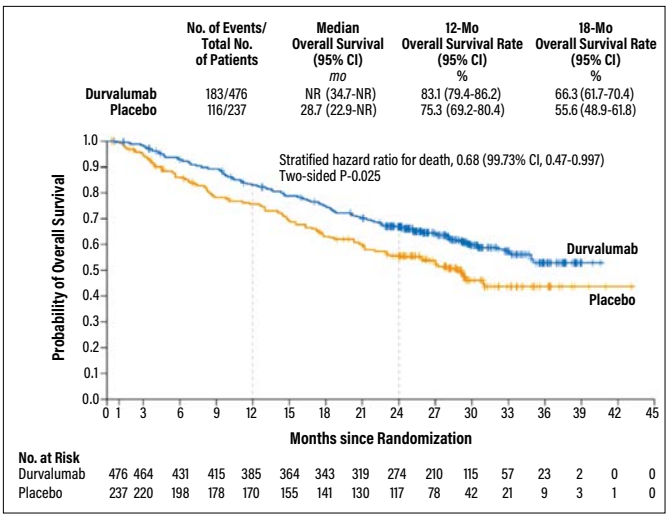

***Figure 3**: Kaplan-Meier curves for overall survival in the Intention-to-Treat population*

grade 3 or above adverse events occurred in 29.9% and 26.1% of the patients, respectively. 15.4% of patients in durvalumab group discontinued due to adverse events and 9.8% in the placebo group; however death due to adverse events were fairly similar in both groups, 4.4% and 5.6% respectively. Most commonly occurred adverse events of any grades with durvalumab versus placebo were diarrhoea (18.3% and 18.8%), pneumonitis (12.6% and 7.7%), rash (12.2% and 7.3%) and pruritis (12.2% and 4.7%).

Immune-mediated adverse events of any grade were also of special interest - this was defined as adverse events that required the use of corticosteroids, immunosuppressants or endocrine therapy. Regardless of cause, immune-mediated adverse events were reported in 24.2% of patients in durvalumab group and 8.1% in placebo group; and grade 3 or above immune mediated adverse events were reported in 3.4% and 2.6% of patients, respectively.

Dosage and Administration

Durvalumab is given via intravenous infusion over 60 minutes, and the standard dose for NSCLC is 10mg/kg every two weeks.[8,9] No capping of dose has been suggested at this point. Temporary withhold or permanent discontinuation should be considered for tolerability and/or patient safety, however dose modification is not recommended.

Special warnings and precautions

Durvalumab can cause serious, potentially fatal adverse events including immune mediated pneumonitis, hepatitis, colitis or diarrhoea, nephritis, dermatitis, infections and infusion-related reactions. Depending on severity of events, dose should be temporary withheld and corticosteroid treatment (and if necessary additional immunosuppressive therapy) should be initiated, or permanently discontinued.[3,7]

No dose adjustment is recommended in patients with mild or moderate renal impairment. Unfortunately, data from patients with severe renal impairment are too limited to draw conclusions on this population.[9]

Mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) had no clinically significant effect on the pharmacokinetics of durvalumab. The effect of moderate liver function impairment (bilirubin > 1.5 to 3 x ULN and any AST) or severe liver function impairment (bilirubin > 3.0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown; however, as IgG monoclonal antibodies are not primarily cleared by the liver, a change in hepatic function is not expected to influence durvalumab exposure).[9]

CONCLUSION

Durvalumab lengthens progression free and overall survival compared to placebo, with a manageable adverse events profile. In conclusion, durvalumab treatment offers a valuable option for patients with unresectable stage III NSCLC in delaying disease progression and prolonging survival.

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Review of Neurokinin-1 Receptor Antagonists in Chemotherapy-Induced Nausea and Vomiting

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ABSTRACT

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse effect of cytotoxic chemotherapy agents that can compromise patients' adherence, and ultimately have a negative impact on therapeutic outcomes. The neurokinin-1 receptor antagonists (the *"-pitants"*, NK-1 RA) have been the latest emerging class of anti-emetic agents used for CINV prophylaxis. These agents have proven benefit, in combination with other antiemetics, in the prevention of CINV, especially with moderate and high emetic risk chemotherapy. The NK-1 RAs are commonly utilized in combination with a serotonin receptor antagonist and corticosteroids for prophylaxis of both acute and delayed phases of CINV. The ultimate goal in managing CINV is to prevent nausea and vomiting with no adverse effects, rather than treating the nausea and vomiting once it has occurred. All major oncology treatment guidelines recommend an NK-1 RA for the prevention of emesis from high emetic risk chemotherapy; however, the guidelines are not all in agreement when using NK-1 RAs for moderate emetic risk chemotherapy. This review covers the key clinical findings for the efficacy of four commonly used NK-1 RAs: *aprepitant*, *fosaprepitant*, *netupitant* and *rolapitant*. To aid selection among NK-1 RAs by healthcare professionals, an intra-class comparison of the four NK-1 RAs is discussed to highlight differences including half-life, metabolism and formulation among these medications. The dosing regimen, adverse effects, drug interactions and international clinical guideline recommendations of each NK-1 RA will be discussed in this review as well.

Keywords: *aprepitant; fosaprepitant; netupitant; rolapitant; nausea and vomiting; chemotherapy-induced nausea and vomiting*

INTRODUCTION

Nausea and vomiting are the most common side effects of chemotherapy that may lead to patients delaying or refusing treatment. Approximately 80% of patients receiving cytotoxic therapy will face chemotherapy induced nausea and vomiting (CINV), which could compromise their adherence to therapy and adversely affect treatment outcomes.[1] Patients are at increased risk of CINV if they have risk factors such as nausea and vomiting with the previous cycle, history of morning sickness, age less than 60 years, female gender, expecting to have nausea and vomiting, use of non-prescribed antiemetics at home, or less than 7 hours of sleep the previous night.[2] These risk factors are in addition to the emetogenicity profile of the chemotherapy regimen being utilized. The mainstay of current guidelines for prophylaxis of CINV of high emetic risk chemotherapy (HEC) is to provide a corticosteroid, a serotonin receptor antagonist (5-HT3 RA) and a neurokinin-1 receptor antagonist (NK-1 RA) for the acute and delayed phases of CINV.[3-5] The prophylaxis of CINV of moderately emetic risk chemotherapy (MEC) might also involve an NK-1 RA for the high-risk population. [3-5] Although slight differences among all the major guidelines exist, including (National Comprehensive Cancer Network) (NCCN), Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO), and American Society of Clinical Oncology (ASCO), the usage of NK-1 RAs for adult patients receiving MEC or HEC are encouraged universally. Where the guidelines may differ is among the selection of a particular NK-1 RA over the other NK-1 RAs. In the past five years, there have been two new NK-1 RAs developed. As the role of NK-1 RAs in CINV expands, this paper serves to provide a comprehensive review on the existing NK-1 RAs and seeks to equip healthcare providers with useful information for selecting the most appropriate agent.

PATHOPHYSIOLOGY AND CLASSIFICATION OF CINV

While the complex pathophysiology of CINV has yet to be fully understood, some critical parts of the hypothesis were tested and proven. CINV is believed to involve both the peripheral (vagal afferents and glossopharyngeal nerves) and central nervous systems (nucleus tractus solitarius (NTS), area postrema (AP) and dorsal motor

nucleus) while having numerous neurotransmitters involved.[6,7] The NTS is responsible for integrating afferent emetic signals and coordinating autonomic responses such as abdominal muscle contraction and relaxation.[6]

NK-1 RAs affect the delayed phase of CINV. The delayed phase of CINV is caused by the binding of substance P to NK-1 receptors located in the NTS and the AP, thereby inducing an emetic response.[7] Substance P is also suggested to play an auxiliary role in the acute phase of CINV due to the presence of NK-1 receptors in the vagal afferent terminals.[8] NK-1 RAs exert the greatest effect on the inhibition of NK-1 receptors located in the NTS, thereby disrupting the signal transduction pathway of emesis. Additionally, NK-1 RAs increase the bioavailability of dexamethasone that is used for both acute and delayed phases of CINV resulting in a needed dose change for dexamethasone.[9]

Three different types of CINV have been categorized and defined **(Table 1)**. Acute emesis is defined as emesis occurring within 24 hours of chemotherapy. It commonly starts within one to two hours of chemotherapy treatment and usually peaks at four to six hours. Delayed emesis occurs 24 hours after chemotherapy and usually peaks at 48 to 72 hours. Lastly, there is anticipatory emesis that happens prior to chemotherapy as a conditioned response in patients who have had significant nausea and vomiting during previous treatments with chemotherapy. Some may also consider refractory emesis as another classification. The MASCC/ESMO and the ASCO guidelines all define HEC as that which produces a greater than 90% risk of emesis and MEC as that which produces a 30% to 90% risk of emesis.[1,3,10,11]

Table 1. Categories of CINV[6]

Type of Nausea and Vomiting	Onset	Maximum Intensity	Duration
Acute	1.5 – 3 hour	5 – 6 hour	12 – 24 hour
Delayed	24 hours	2 – 3 days	5 – 7 days
Anticipatory	Before chemotherapy	Variable	

APREPITANT ANDFOSAPREPITANT

Drug Background and Indication

Aprepitant, the first NK-1 RA approved by the Food and Drug Administration (FDA) in the United States, was marketed in Hong Kong in 2004 under the brand name EMEND®.[12] Aprepitant is available as an oral capsule in Hong Kong, however, the oral suspension formulation has not been registered.[13] Fosaprepitant is a prodrug of aprepitant used for intravenous injection and was approved in Hong Kong in 2012. Both aprepitant and fosaprepitant are indicated for the prophylaxis of CINV due to MEC or HEC.[13] Aprepitant and fosaprepitant are classified as $P_1S_1S_3$.[14] In the local setting, aprepitant and fosaprepitant are listed as special drugs in the Hospital Authority Drug Formulary.[15]

Dosing Regimen

For adults and pediatric patients, aged 12 years or above, aprepitant is suggested to be administered at an oral dose of 125 mg daily on the first day and 80 mg daily on the second and third days of each MEC and HEC cycle in combination with other antiemetics (summarized in **Table 2**).[13] Similarly, fosaprepitant is administered as an intravenous infusion of 150 mg on the first day, over 20-30 minutes, of each MEC and HEC cycle in combination with other antiemetics (summarized in **Table 2**).[16] No dosage adjustments are suggested for renal impairment or mild to moderate hepatic impairment.[13] Weight-based dosing for aprepitant and fosaprepitant should be utilized for patients less than 12 years of age.

Clinical Evidence

A phase III randomized, double blind, active-controlled study conducted in 27 countries from 2008 to 2009 demonstrated the non-inferiority of a single dose 150 mg fosaprepitant to multiple dose aprepitant for patients receiving cisplatin therapy. The study detected no significant difference between the two arms in the proportions with complete response in the overall phase (95% CI: -4.1 to 3.3) and in the delayed phase (95% CI: -3.5 to 3.7) and in the proportion without vomiting (95% CI: -5.3 to 2.0).[17] In addition, a bioequivalence study showed that single-dose oral administration of 165 mg and 185 mg aprepitant capsules, in both fed and fasted state, is similar to the approved dosing of a single IV infusion of 150 mg fosaprepitant (1 mg/mL) over 30 minutes.[18] The infusion of fosaprepitant should be completed 30 minutes prior to the infusion of chemotherapy as it takes 30 minutes for fosaprepitant to be converted to aprepitant. The bioavailability of oral aprepitant is 60-65%.

Apart from the clinical trials used for approval of aprepitant/fosaprepitant, multiple clinical trials were continuously conducted to expand the role of aprepitant in various kinds of nausea and vomiting, including the expansion to the pediatric population and hematologic malignancies in adults. In general, corticosteroids and 5-HT3 RAs have been used in CINV therapy with an efficacy rate of approximately 60-70%. The addition of NK-1 RAs increases the efficacy rate to 80-90%.

A randomized controlled trial was conducted in 2015 on 41 adult patients with HEC or MEC in hematologic malignancies. The trial demonstrated a significantly higher complete response rate in the aprepitant plus 5-HT3 RA arm than the 5-HT3 RA monotherapy arm (82 vs 47%, p = 0.026) with a similar incidence of adverse effects. However, it also identified that the superiority

Table 2. Dosing regimen of aprepitant for the prevention of nausea and vomiting[13,16,48]

Medication	Emetogenic risk category	Population	Day 1	Day 2	Day 3	Day 4
Aprepitant capsules*	High	Adults and pediatric patients (≥ 12 years of age)	125 mg orally	80 mg orally	80 mg orally	None
	Moderate					
Dexamethasone	High	Adults	12 mg orally	8 mg orally	8 mg orally	8 mg orally
	Moderate			None		
	High	Pediatric patients (12-17 years)	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1-4†			
	Moderate					
5-HT3 RA	High	Adults	**Palonosetron:** 0.25 mg administered 30 minutes prior to the start of chemotherapy	None		
	Moderate		**Palonosetron:** 0.5 mg administered approximately one hour prior to the start of chemotherapy OR **Ondansetron:** 8 mg administered 30 minutes before the start of chemotherapy, then 8 mg dose 8 hours after the first dose. 8 mg Q12h for 1-2 days after completion of chemotherapy			
	High	Pediatric patients (12-17 Years)	**Palonosetron:** 20 mg/kg (max 1.5 mg) administered 30 minutes prior to chemotherapy	None		
	Moderate		**Ondansetron:** Same as adult dosing			

** Administer aprepitant capsules 1 hour prior to chemotherapy treatment on days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, administer aprepitant capsules in the morning.*

† Administer dexamethasone 30 minutes prior to chemotherapy treatment on day 1 and in the morning on days 2-4. A 50% dosage reduction of dexamethasone is recommended to account for a drug interaction with aprepitant.

in efficacy depends on the treatment regimens and the effect on nausea was not significant.[19]

Additional randomized, placebo-controlled, double-blind, multi-center clinical trials researching aprepitant efficacy in adult populations demonstrated similar findings for patients receiving carboplatin and paclitaxel with gynecologic cancers[19] and those on cisplatin-based regimens with germ cell tumors.[20]

A phase III trial conducted in 2015 showed that the addition of aprepitant to ondansetron with or without dexamethasone might also be effective in the prevention of CINV in pediatric patients aged 6 months to 17 years.[21] Dosing for patients between 6 months to 12 years of age was 3 mg/kg up to 125 mg of aprepitant oral suspension on day 1 and 2 mg/kg up to 80 mg on days 2-3. The complete response rate, the proportion of patients without vomiting and the proportion of patients without use of rescue medication were higher in the aprepitant group in acute, delayed and both phases combined.[21]

Aprepitant is considered safe in pediatric patients since adverse events were similar between study and control groups, as well as between pediatric and adult patients.[21] In another similar randomized, double blind, placebo-controlled trial in which the pediatric population received HEC, the aprepitant arm had less acute moderate and severe vomiting (38% vs 72%; p=0.001) and a higher complete response rate (48% vs 12%; p<0.001).[22]

Adverse Effects, Interactions and Monitoring

The incidence of adverse reactions was reported to be slightly higher in the aprepitant, 5-HT3 RA and corticosteroid group compared to the 5-HT3 RA and corticosteroid group. Common adverse reactions as compared to the control group include fatigue (13% vs 12%), diarrhea (9% vs 8%), asthenia (7% vs 6%), dyspepsia (7% vs 5%), hiccups (5% vs 3%) and neutropenia (4% vs 3%).[13]

Aprepitant is known to be a substrate and weak inhibitor of CYP3A4 and a weak CYP2C9 inducer. The inducing effect peaks around day 8 and resolves or nearly resolves on day 15.[13,23] Drugs which are substrates of CYP3A4 and CYP2C9 may result in a lower concentration of aprepitant. For most drugs, the degree of induction is not likely to be of clinical importance. However, for CYP3A4 and CYP2C9 substrates with a narrow therapeutic index, such as warfarin and phenytoin, the effect could be clinically important and should be monitored cautiously. The FDA prescribing information recommends avoiding the use of aprepitant with strong CYP3A4 inducers as they may decrease the serum concentration of aprepitant.[13,23] Aprepitant should also be used in caution along with chemotherapeutic CYP3A4 substrates including grapefruit juice.[18] Monitoring of aprepitant and fosaprepitant should be for signs of a hypersensitivity reaction and INR/PT values in patients concomitantly taking warfarin therapy. Obtaining liver function tests may also be warranted due a 3% risk

of increased serum alanine transaminase (ALT) and no significant data in patients with Child-Pugh class C hepatic impairment.

Clinical Practice Guidelines

The MASCC/ESMO guidelines do routinely recommend NK-1 RAs in the adult population for HEC and MEC CINV. However, the guidelines do not consider or recommend aprepitant or fosaprepitant over other NK-1 RAs. The primary situation where the guidelines preferentially recommend aprepitant is in the pediatric population as aprepitant currently has the most supporting data in this population.[3] Aprepitant and fosaprepitant may be used for acute and delayed nausea and vomiting, but should not be used for anticipatory emesis as behavioral therapy and benzodiazepines are preferred treatments for this subtype of CINV. For high-dose chemotherapy used in stem cell transplant, aprepitant should be used in combination with a 5-HT3 RA and dexamethasone.

NETUPITANT

Drug Background and Indication

NEPA is a fixed oral combination therapy that consists of a 5-HT3 RA, palonosetron, and netupitant that is indicated for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of chemotherapy. Its use includes controlling HEC and MEC CINV. Both oral palonosetron and netupitant prevent nausea and vomiting during acute and delayed phases after chemotherapy.[24] In Hong Kong, NEPA is marketed under the brand name of Akynzeo® oral capsules, in which each capsule contains netupitant 300 mg and palonosetron 0.5 mg, and is legally classified as $P_1S_1S_3$.[25] It was registered on 31st July, 2017 in Hong Kong,[26] but is not included in the Hospital Authority Drug Formulary as of August 2018.[27] Fosnetupitant is a prodrug form of netupitant used for intravenous injection. It is initially approved in April 2018 in the United States, but is not yet available in Hong Kong as of August 2018.

Table 3. Proportion of patients achieving efficacy endpoints (intention-to-treat population)[19]

Phases	Aprepitant group* (n=152)	Placebo group* (n=150)	*p*-value
Complete response			
Acute	101 (66%)	78 (52%)	0.01
Delayed	77 (51%)	39 (26%)	<0.01
Overall	61 (40%)	30 (20%)	<0.01
No vomiting			
Acute	108 (71%)	80 (53%)	<0.01
Delayed	84 (55%)	42 (28%)	<0.01
Overall	71 (47%)	32 (21%)	<0.01
No use of rescue medication			
Acute	133 (88%)	115 (77%)	
Delayed	110 (72%)	81 (54%)	
Overall	101 (66%)	73 (49%)	

** Both groups receive a 5-HT3 RA plus dexamethasone prior to chemotherapy in addition to aprepitant or placebo*

Dosing Regimen

HEC (including Cisplatin-Based Chemotherapy):
The dosing regimen in adults is to administer one capsule of NEPA an hour before the start of chemotherapy with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1 as one single dose treatment. Remaining days in the cycle will only involve dexamethasone 8 mg orally once daily on days 2-4.[26]

Anthracyclines and Cyclophosphamide-Based Chemotherapy and Chemotherapy Not Considered High Emetic Risk:
The dosing regimen in adults is to administer one capsule of NEPA about an hour before the start of chemotherapy with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on day 1 as one single dose treatment. It is not necessary to administer dexamethasone on days 2-4.[24]

NEPA can be taken with or without food. No dosage adjustment is necessary for patients with mild to moderate hepatic or renal impairment. However, use of NEPA in patients with severe hepatic impairment or creatinine clearance lower than 30 mL/min should be avoided.[24]

Clinical Evidence

Cisplatin Regimen:
The efficacy and safety of NEPA in the prevention of acute and delayed nausea and vomiting in cancer patients receiving a chemotherapy regimen that included cisplatin was compared with a single oral dose of palonosetron 0.5 mg in a multicenter, randomized, parallel, double-blind, controlled phase III clinical trial. [28] The results summarized in **Table 4** reflect that NEPA showed superior complete response rates compared with palonosetron 0.5 mg alone.[29]

Table 4. Proportion of patients responding by treatment group and phase[27]

CINV phase	NEPA (n=135) complete response	Palonosetron 0.5 mg (n=136) complete response	p-value*
Delayed phase (1)	90.4%	80.1%	0.030
Acute phase (2)	98.5%	89.7%	0.002
Overall phase (3)	89.6%	76.5%	0.003

** Adjusted p-values for multiple comparisons using Cochran-Mantel-Haenszel test, stratified by gender.*
(1) Delayed phase: 25 to 120 hours post-cisplatin treatment.
(2) Acute phase: 0 to 24 hours post-cisplatin treatment.
(3) Overall: 0 to 120 hours post-cisplatin treatment.

Anthracycline and Cyclophosphamide (AC) Regimen:
In another multicenter, randomized, parallel, double-blind, active controlled, superiority trial, the efficacy and safety of NEPA in the prevention of acute and delayed

nausea and vomiting in cancer patients during the first cycle of an AC regimen for treating solid malignant tumors was compared with a single oral dose of palonosetron 0.5 mg. All patients received a single oral dose of dexamethasone. A total of 1455 patients were randomized to the NEPA arm or palonosetron arm. A total of 1450 patients (NEPA n=725; palonosetron n=725) received the study medication, in which 1438 patients (98.8%) completed cycle 1.[29]

The results summarized in **Table 5** show that NEPA was superior to palonosetron 0.5 mg during the delayed phase. Complete response rates were also significantly higher for NEPA compared with palonosetron 0.5 mg during acute and overall phases.[29]

Table 5.: Proportion of patients responding by treatment group and phase -- Cycle 1[28]

	NEPA (n=724)	Palonosetron 0.5 mg (n=725)	p-value*
Primary Endpoint: Complete response			
Delayed phase(1)	76.9 %	69.5 %	0.001
Major Secondary Endpoints: Complete response			
Acute phase(2)	88.4 %	85.0 %	0.047
Overall phase(3)	74.3 %	66.6 %	0.001

** p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.*
(1) Delayed phase: 25 to 120 hours after AC treatment.
(2) Acute phase: 0 to 24 hours after AC treatment.
(3) Overall: 0 to 120 hours after AC treatment.

Adverse Effects, Interactions and Monitoring

Adverse reactions with comparison to control occurring in cancer patients receiving NEPA and cisplatin-based HEC (cycle 1) include dyspepsia (4% vs 2%), fatigue (4% vs 2%), constipation (3% vs 1%) and erythema (3% vs 2%). For patients receiving NEPA and AC-based chemotherapy (cycle 1), adverse reactions include headache (9% vs 7%), asthenia (8% vs 7%) and fatigue (7% vs 5%) when compared to active control. Hepatic adverse effects of increasing liver aminotransferase levels have been reported (0.1-0.3% vs 0.1-0.6%).[24] Serotonin syndrome has also been reported with 5-HT3 RAs, in which most reports have been associated with concomitant use of serotonergic drugs.[24]

Netupitant is a substrate and moderate inhibitor of CYP3A4. Therefore, NEPA should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. The inhibitory effect on CYP3A4 can last for multiple days.[30,31] It can significantly increase systemic exposure to chemotherapeutic agents that are metabolized by CYP3A4.[31] No additional laboratory monitoring is required for patients on NEPA. Only signs and symptoms of hypersensitivity and serotonin syndrome should be monitored in patients on NEPA.

Clinical Practice Guidelines

ASCO 2017 Guideline:
ASCO 2017 Guideline suggests that adult patients who are treated with cisplatin and other single agents with high emetogenic risk should be offered a four-drug combination of an NK-1 RA, such as netupitant, a 5-HT3 RA, dexamethasone and olanzapine, in which dexamethasone and olanzapine should be continued on days 2-4.[3] Adult patients receiving AC should be administered a four-drug combination of an NK-1 RA, such as netupitant, a 5-HT3 RA, dexamethasone and olanzapine, in which olanzapine should be continued on days 2-4.[3] For adult patients who are treated with carboplatin of an area under the curve (AUC) ≥ 4 mg/mL per minute, a three-drug combination of an NK-1 RA, such as netupitant, a 5-HT3 RA and dexamethasone should be provided.[3]

MASCC/ESMO 2016 Guideline:
MASCC/ESMO 2016 Guideline suggests that for preventing acute nausea and vomiting following non-AC HEC, it is recommended to give a three-drug regimen which involves single doses of a 5-HT3 RA, dexamethasone and an NK-1 RA, such as netupitant, before chemotherapy, followed by dexamethasone on days 2-4 to prevent delayed nausea and vomiting.[32] For the prevention of acute nausea and vomiting in women with breast cancer receiving AC chemotherapy, a three-drug regimen including single doses of a 5-HT3 RA, dexamethasone and an NK-1 RA, such as netupitant, given before chemotherapy is recommended. If netupitant has been used on day 1, administration of dexamethasone on days 2 and 3 is not necessary for preventing delayed nausea and vomiting.[32] A combination of a 5-HT3 RA, dexamethasone and an NK-1 RA, such as netupitant, for preventing acute nausea and vomiting in patients receiving carboplatin-based chemotherapy is also recommended. If netupitant is used on day 1, no additional prophylaxis for delayed nausea and vomiting prevention is suggested.[32]

ROLAPITANT

Drug Background and Indication

Rolapitant is the latest candidate developed amongst the class of NK-1 RAs and approved by the FDA as a 90 mg oral tablet in September 2015. Rolapitant, as of August 2018, is unavailable on the Hong Kong market [26] Rolapitant is a prescription drug indicated for the "prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, high emetic risk chemotherapy".[33,34]

Dosing Regimen

The recommended dosing regimens of rolapitant are summarized in **Table 6**. Rolapitant should be initiated in each cycle concomitantly with a steroid and a 5-HT3 RA for the prevention of CINV. According to the manufacturer, the use of rolapitant should not be more frequent than

Table 6. Dosing regimen of rolapitant[16, 33, 47]

Prevention of nausea and vomiting associated with cancer chemotherapy					
Medication	Emetogenic risk category	Day 1	Day 2	Day 3	Day 4
Rolapitant	High	Administer 2 hours prior to initiation of chemotherapy Oral: 180 mg as a single dose Injectable emulsion: Infuse 166.5 mg over 30 minutes	None		
	Moderate				
Dexamethasone	High	30 minutes prior to initiation of chemotherapy Oral: 20 mg	8 mg twice daily	8 mg twice daily	8 mg twice daily
	Moderate		None		
5-HT3 antagonist	High	**Palonosetron:** 0.25 mg administered 30 minutes prior to chemotherapy	None		
	Moderate	**Palonosetron:** 0.25 mg administered 30 minutes prior to chemotherapy OR **Ondansetron:** 8 mg administered 30 minutes before the start of chemotherapy, then 8 mg dose 8 hours after the first dose. 8mg Q12h for 1-2 day after completion of chemotherapy			

every 2 weeks due to its extended half-life. Moreover, the administration of rolapitant tablets is unaffected by food intake.[34] While data is lacking for severe hepatic and renal impairment, the manufacturer advises to take extra caution when prescribing rolapitant to patients with decreased renal or liver function.[34]

Clinical Evidence

The approval of rolapitant was based on three phase III clinical trials investigating the use of rolapitant in cisplatin based and AC-based regimens.

Cisplatin Regimen:
The efficacy of rolapitant in prophylaxis of CINV after administration of cisplatin-based HEC was demonstrated in two randomized, active-controlled, double-blind phase III trials, namely HEC-1 and HEC-2. There were 526 patients in HEC-1 and 544 patients in HEC-2 being randomized into the 180 mg rolapitant group or the active control placebo group.[35] There were a significantly greater proportion of patients in the rolapitant group than in the control group achieving a complete response (no emesis or use of rescue medication) in the delayed phase (HEC-1: 192 [73%] vs 153 [58%], p=0.0006; HEC-2: 190 [70%] vs 169 [62%], p=0.0426; pooled studies: 382 [71%] vs 322 [60%], p= 0.0001).[35]

AC Regimen:
Another randomized, double-blind, active-controlled phase III clinical trial demonstrated efficacy of rolapitant for the prevention of CINV after administration of an MEC or AC regimen. In this study, 1369 patients from 170 cancer centers in 23 countries were randomized into the 180 mg oral rolapitant group or th active control group.[36] The proportion of patients receiving rolapitant who had complete responses in the delayed phase was significantly greater than those receiving active control therapy (475 [71%] vs 410 [62%], p = 0.0002).[36]

Adverse Effects, Interactions and Monitoring

Patients on rolapitant are found to exhibit classical adverse effects of NK-1 RAs. The most common adverse reactions reported in studies on rolapitant are hiccups (5% vs 4%), decrease in appetite (9% vs 7%), neutropenia (7-9% vs 6-8%), dizziness (6% vs 4%), dyspepsia (4% vs 2%) and urinary tract infection (4% vs 3%).[34]

The FDA issued a safety alert on rolapitant injectable emulsion regarding anaphylaxis and other serious hypersensitivity reaction in early 2018.[37] Signs of anaphylaxis (both during and after administration), including rash, in patients receiving rolapitant injectable emulsion should be closely monitored. Patients with an allergy history to legumes including soybean oil should not receive rolapitant regardless due to possible cross sensitivity. Other choices in the same class can be considered if the patient has a confirmed or suspected allergy to legumes.

Rolapitant is a CYP3A4 substrate and thus the use of CYP3A4 inducers can reduce the efficacy of rolapitant. Rolapitant is also a p-glycoprotein and BCRP inhibitor and thus the choice of chemotherapy might affect the applicability of rolapitant.[34]

Rolapitant is found to be a moderate CYP2D6 inhibitor with activity that can last for more than 7 days.[34] Healthcare professionals should be cautious about concurrent CYP2D6 substrates with a narrow therapeutic index. The concomitant use of thioridazine and rolapitant will significantly increase the plasma concentration of thioridazine, which may lead to QT prolongation and Torsades de Pointes.[34] Attention should also be drawn to chemotherapeutic agents metabolized by CYP2D6 such as tamoxifen. The efficacy of tamoxifen can be largely reduced by CYP2D6 inhibition due to the decreased biotransformation into active metabolite.[38]

Adverse effects should be monitored regularly if the use of CYP2D6 substrates with a narrow therapeutic index is inevitable including signs of a hypersensitivity reaction and INR/PT values in patients concomitantly taking warfarin.

Clinical Practice Guidelines

Although rolapitant and NEPA were developed only recently, the NCCN guidelines do not imply a preference in the class of NK-1 receptor antagonists for prevention of emesis in high emetic and moderate risk intravenous chemotherapy.[39] Therefore, the efficacy of emesis prevention of each agent should not differ from others in the same class. The primary factors affecting the choice of NK-1 RA for CINV should be the price, availability, interactions and dosing convenience.

TREATMENT COMPARISONS

Navari et al. performed two studies on the role of NK-1 RA on CINV. In the first study, they compared aprepitant + palonosetron + dexamethasone (APR regimen) to olanzapine + palonosetron + dexamethasone (OLZ regimen) in patients receiving HEC like cisplatin or AC. The percentage of patients without nausea was significantly higher in the OLZ group (38% in APR vs 69% in OLZ).[40] The result is similar in the second study, where they compared fosaprepitant + palonosetron + dexamethasone (FOS regimen) to olanzapine + palonosetron + dexamethasone (OLZ regimen) in patients receiving HEC plus local radiation. The percentage of patients without nausea was also significantly higher in the OLZ group (41% in FOS vs 71% in OLZ).[41]

Aprepitant was also compared to dexamethasone and metoclopramide for the prevention of delayed emesis. In a study conducted in 2014, 580 breast cancer patients receiving AC were given an aprepitant-palonosetron-dexamethasone regimen before chemotherapy, and then randomized to receive oral dexamethasone or aprepitant on days 2-3. No significant difference in nausea was observed.[42] In another study in 2015, patients were randomly assigned to treatment with aprepitant on days 2-3 or metoclopramide on days 2-4, plus dexamethasone on days 2-4 in both groups. No significant difference in nausea or other side effects was seen between the groups.[43]

NK-1 RAs show similar efficacy in reducing CINV compared to dexamethasone and metoclopramide, but may be less effective than olanzapine. However, given its favorable tolerability and side effect profile, it is preferred as the most common adverse effects are mild.[44] The NK-1 RAs are very well tolerated as shown by the similar adverse effect incidence between the active NK-1 RA group and the active control group.

Currently, there are insufficient studies comparing NK-1 RA agents, so no statements regarding the comparative safety or efficacy can be made at this time. There are two studies that compared netupitant with palonosetron against aprepitant with ondansetron that showed improved efficacy in the netupitant and palonosetron arm. However, neither of these studies were designed to assess the comparative efficacy, so further studies are needed.[28,39] A notable difference with rolapitant compared with other NK-1 RAs is that it is not a CYP3A4 inhibitor. Therefore, it is not required to decrease the dose of dexamethasone (from 20 mg to 12 mg on day 1 and from 8 mg twice daily to once daily on days 2-3) as it would with other NK-1 RAs. When selecting between NK-1 RAs, the decision will ultimately come down to convenience and cost. Aprepitant is used as a 3-day regimen whereas all the other NK-1 RA's have a 1-day single dose option. Lastly, all the NK-1 RAs are only available as branded products in Hong Kong.[14]

According to the NCCN guideline, the preferred intravenous NK1-RA option is fosaprepitant (in combination with a 5-HT3 RA and dexamethasone). Other key differences between NK-1 RAs are summarized in **Table 8.**

FUTURE DEVELOPMENT

Pediatrics

According to the World Health Organization, though childhood cancers are rare, they still affect 50 to 200 per million children and over 200,000 children are diagnosed with new cancers each year.[45,46] Therefore, CINV prophylaxis in the pediatric population will be a new direction for drug development. As of yet, only aprepitant among the NK-1 RA class is approved for this purpose.[14] An ongoing phase II clinical study is evaluating the use of netupitant + palonosetron (NEPA) in pediatric patients, which may bring a new option with fewer drug interactions for the control of CINV in childhood cancer patients in the foreseeable future.

Nausea

Recommendations for CINV prophylaxis in guidelines such as MASCC/ESMO, ASCO and NCCN guidelines

Table 7. Summary of two clinical trials comparing olanzapine and NK-1 RAs[38,40]

Patients randomized	Chemotherapy regimen	Antiemetic prophylaxis	Proportion of patients with no nausea (%)		
			Acute	Delayed	Overall
251	HEC (AC/non-AC)	APR vs OLZ	87 vs. 87	38 vs. 69	38 vs. 69
109	HEC (+ radiotherapy)	FOS vs OLZ	77 vs. 86	41 vs. 71	41 vs. 71

Table 8. Comparison of orally administered NK-1 RA[44]			
	Rolapitant	**Aprepitant**	**Netupitant/Palonosetron**
Indications	Prevention of delayed nausea and vomiting associated with the use of cancer chemotherapy agents, used in combination with other antiemetic agents	1. Prevention of acute and delayed CINV, used in combination with other antiemetic agents 2. Prevention of postoperative nausea and vomiting	Prevention of acute and delayed nausea and vomiting associated with emetogenic cancer chemotherapy agents
Dosing for CINV	180 mg administered 1 to 2 hours prior to chemotherapy	125 mg on day 1 administered 1 hour prior to chemotherapy, followed by 80 mg on days 2 and 3	Netupitant 300 mg/palonosetron 0.5 mg fixed-dose combination capsule administered 1 hour prior to chemotherapy
Half-life	169-183 hours	9-13 hours	96 hours
Pediatric patients	Not established	Safety and effectiveness established for patients 6 months of age and older	Not established
Contraindications			
	Rolapitant	**Aprepitant**	**Netupitant/Palonosetron**
History of hypersensitivity to drug or other ingredients	X	X	X
Co-administration with thioridazine	X		

are based on studies in which the primary efficacy endpoint was most commonly complete response in vomiting, but not nausea-related outcome. Therefore, the control of nausea as part of a complete response (i.e. no nausea and vomiting) should be the final goal of nausea and vomiting control. Clinical trials with nausea as the primary efficacy endpoint will help determine the most effective antiemetic combination for nausea prevention, as trials on vomiting control are much more established compared to nausea control.[10]

Other agents

A study evaluating the safety and efficacy of intravenous fosnetupitant/palonosetron (260 mg/0.25 mg) combination compared to oral netupitant/palonosetron (300 mg/0.5 mg) in AC chemotherapy is currently recruiting.

CONCLUSION

CINV prevention is important in cancer treatment because of its critical role in improving quality of life, patient tolerance and adherence to chemotherapy. With the gradual understanding of the mechanisms of CINV, we are closer to effectively addressing the problem. There are some minor differences among these NK-1 RAs and each drug has different characteristics such as route of administration, elimination half-life, interactions and contraindications that can further restrict their usage in certain patients or make certain NK-1 RAs more preferred in specific patient populations. In addition to a well-tolerated side effect profile, the proven efficacy of NK-1 RA in combination with other anti-emetic agents in the prophylaxis of CINV makes it an important class of drug to be used in cancer patients.

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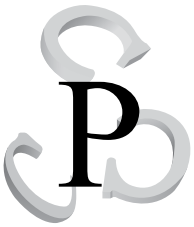
Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)



2 CE Units

Review of Neurokinin-1 Receptor Antagonists in Chemotherapy-Induced Nausea and Vomiting

1. ***Which of the following is a risk factor for developing chemotherapy-induced nausea and vomiting?***
   A. Female gender
   B. Age > 65
   C. Migraine history
   D. Smoker

2. ***Which of the following laboratory tests should a clinical pharmacist review prior to dispensing aprepitant?***
   A. Thyroid stimulating hormone (TSH) and T4 levels
   B. Liver function tests (LFT)
   C. Creatinine clearance (CrCl)
   D. White blood cell (WBC) count

3. ***For the prevention of CINV in a patient receiving a HEC regimen, which of the following regimens does the MASCC/ESMO guideline recommend?***
   A. Palonsetron-olanzapine
   B. Ondansetron-dexamethasone
   C. Ondansetron-dexamethasone-fosaprepitant
   D. None of the above

4. ***In comparison to palonsetron alone, the combination of netupitant-palonsetron was shown to be _____ in terms of efficacy.***
   A. Superior
   B. Equivalent
   C. Inferior
   D. Equivalent with a trend towards superiority

5. ***Which of the following antiemetics has the longest half-life and least frequent dosing regimen?***
   A. Rolapitant
   B. Aprepitant
   C. Netupitant-Palonsetron
   D. Fosaprepitant

6. ***When educating nursing staff on the new addition of rolapitant to a private clinic formulary, which of the following pieces of information is CORRECT regarding rolapitant?***
   A. Rolapitant requires 3 doses given once daily.
   B. Rolapitant has fewer drug interactions than aprepitant or netupitant.
   C. Rolapitant can cause hypersensitivity in those allergic to legumes as it contains soybean oil.
   D. Rolapitant does not require adjustment in those with severe renal or hepatic impairment.

7. ***When should you administer the NK-1 RAs with respect to chemotherapy?***
   A. 1-2 hours prior to starting chemotherapy
   B. Up to 3 hours after completing chemotherapy
   C. The night before starting chemotherapy
   D. They are compatible with platinnum-based and anthracycline-containing regimens and may be infused concomitantly with chemotherapy

8. ***Which of the following medications for CINV prevention is NOT a CYP3A4 substrate?***
   A. Aprepitant
   B. Rolapitant
   C. Netupitant
   D. Palonsetron

9. ***Which of the following medications is NOT commonly given as an antiemetic for highly emetogenic chemotherapy?***
   A. Dexamethasone
   B. Olanzapine
   C. Metoclopramide
   D. Diphenhydramine

10. ***CLE is a 48 year old Chinese female (71 kg, 164 cm) who will start AC chemotherapy today for breast cancer. She has no other past medical history other than a 12-year history of smoking, history of morning sickness with each of her three children and her current breast cancer. Which of the following pieces of information should the patient and the care provider consider when deciding if the patient should take an NK-1RA?***
    A. The patient's most recent QTc interval recording
    B. The emetogenicity risk of the chemotherapy agents being used
    C. The patient's ethnicity and weight
    D. All of the above

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 263(D&T)

Spinal Muscular Atrophy: A Treatment Update

1. B 2. B 3. A 4. C 5. C 6. D 7. D 8. A 9. D 10. A

Combined Cytotoxicity of Bioactive Components from Scutellaria Barbata Herba and Hedyotis Diffusa Herba on the Differentiation of Acute Promyelocytic Leukemia Cell

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ABSTRACT

The combined cytotoxic effects of various bioactive agents from *Scutellaria barbata* and *Hedyotis diffusa* were studied by MTT assay, DNA fragmentation analysis and morphological monitoring using an acute myeloid leukemia cell line HL-60. Median effect analysis and zero interaction response surface analysis were adopted to determine the combined effects of various compounds. The zero interaction response surface analysis, which is a 3-dimensional (3-D) model, was found to be more reliable in comparison to other methods. Synergistic effects were observed for p-coumaric acid in combination with scutellarein. However, antagonistic effects were observed whenever p-coumaric acid was combined with ursolic acid and oleanolic acid. It was noted that drug interactions were ratio dependent. These results suggest that the efficacy of anti-cancer activity using mixed phyto-compounds depends not only on chemical profiles but also their combination ratio. Among the bioactive compounds screened, combination of scutellarein and p-coumaric acid was found to have a better cytotoxic effect against HL-60 cells.

Keywords: *Scutellaria Barbata Herba, Hedyotis Diffusa Herba, Ursolic acid, Oleanolic Acid, HL-60, Combined Cytotoxic activity, Cancer Prevention, Cytotoxic Methods*

INTRODUCTION

In recent years, investigators found that by isolation of active components from Chinese herbs, some components could be used for cancer prevention or chemotherapy.[1-5] A typical example is the investigation of constituents in Ginseng and its actions.[6] The application of Chinese herbs for curing cancer always combines 2 to 20 herbs together. The application of combined herbs may contribute to its diversity and wellbeing for cancer prevention and chemotherapy. However, there is lack of scientific evidences or explanation on their combined use.

Scutellaria barbata (SB) and *Heydotis diffusa* (HD) are two common Chinese herbs used in the treatment of leukemia. The combination of SB and HD are found in over 20 Chinese herbal formulas for treatment of leukemia.[7-9] Several reports by Wong *et al* suggested that the combination of crude extracts of SB and HD had synergistic effects in modulation of mutagenesis, inhibition of tumor growth and augmentation of macrophage oxidative burst.[10-15] Further studies were carried and successfully isolated and purified bioactive compounds from SB and HD such as scutellarein (SC),[16-18] ursolic acid (UA), oleanolic acid (OA),[19-22] stearic acid (ST),[17] p-coumaric acid (PCA),[23] sitosterol and stigmasterol[17,20-22] were employed for studying their combined effects on the cytotoxicity of acute promyelocytic leukemia cell line HL-60.

To evaluate the effects of drug combination *in vitro,* two 2-dimensional models, median effect analysis[24] and isobolgram[25] and zero interaction response surface, a 3-dimensional model,[26-27] were employed. A number of reviews have mentioned advantages and disadvantages of these methods.[28-31]

The purpose of this study is to provide more data about the scientific background of herb formulas by evaluation of the combined effects of various bioactive compounds. We have also made a comparison between the common methods used in studying the effect of drug combination.

MATERIALS AND METHODS

Cell Line

Human acute promyelocytic leukemia HL-60 was purchased from American Type Culture Collection (Rockville, MD). The cells were grown in suspension

and propagated in RPMI-1640 medium supplemented with 10% heat-inactivated bovine serum, 100 units/ml penicillin, 100 µg/ml streptomycin and 2 mM L-glutamine, all of which were obtained from Gibco, Grand island, NY, USA. To ensure the cells grew exponentially, the culture was divided once per three days to a concentration of 2 x 10^5 cells/ml. Cells were maintained in a humidified atmosphere saturated with 5% CO_2 at 37ºC.

Drugs

Bioactive components of SB and HD, namely, Oleanolic acid (OA), p-coumaric acid (PCA), stigmasterol and 3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma Chemical Co. (St. Louis, MO). Ursolic acid (UA), stearic acid (SA) and beta-sitosterol were purchased from ACROS Chemical Ltd. Scutellarein was obtained from Apin Chemical Ltd. (Milton Park, Abingdon, UK). The purity of all chemicals used was more than 95%.

MTT Assay

Inhibition of the growth of HL-60 cell lines was determined according to the method described by Mosmann[32] and subsequently modified by Shimura *et al*.[33] Briefly, 1 x 10^4 logarithmic growing cells were plated in each well of 96-well plates containing various concentrations of drugs. The cells were incubated for 4 days and then the activity of mitochondrial succinic dehydrogenase was measured by incubation for 4 hours in the presence of MTT (0.5 mg/ml) followed by the adding of 200 µl stop solution (50% w/v SDS, 50% v/v 0.1N HCl and 50% v/v isobutanol). After 20 hrs incubation, the absorbance was measured at 570 nm. The relative viability was expressed by the following formula:

$$\text{Relative viability} = \frac{\text{absorbance of treated cells - absorbance blank}}{\text{absorbance of untreated control - absorbance blank}} \times 100$$

The IC_{50} value was defined as the dose of drug required causing a 50% of relative viability. At least 3 experiments were carried out for each drug concentration. In this experiment, the ratios of 2 drugs were from 1:64, 1:32, 1:16, 1:8, 1:4, 1:2, 1:1, 2:1, 4:1, 8:1, 16:1, 32:1 and 64:1.

Visualization of DNA Fragmentation

DNA fragmentation was analysed by agarose gel electrophoresis as described by Mollinedo *et al* (1993).

Morphological Monitoring of Cells by Laser Confocal Microscopy

HL-60 cells were centrifuged at 750xg and the pellet was resuspended in 25 µl dye mixture of acridine orange and ethidium bromide. The morphologies of HL-60 cells were evaluated according to the following observations: cells uptake of acridine orange (green fluorescence) and exclusion of ethidium bromide (red fluorescence) are regarded live normal cells; wherever cells contain neutrophilic characteristics are treated as differentiating cells; if chromatin condensation stained by acridine orange or ethidium bromide but appearance of apoptotic bodies, they are regarded as apoptotic cells; and if orange nucleus with intact structure is observed, the cells are regarded necrotic cells.

Combination Effect Analysis

Median effect analysis

From the method described by Chou and Talalay[24] the dose-response curves can be plotted for single drug and two drugs in a fix-ratio combination using the median effect equation:

$$f_a/f_u = (D/D_m)^m \qquad \textbf{(Equation 1)}$$

In **equation 1**, D is the dose and Dm is the median effect dose required for a 50% inhibition of growth, fa is the fraction affected by dose D, fu is the unaffected fraction and m is the Hill-type coefficient signifying the sigmoidicity of the dose-effect curve. Using the principles of the mass action law, the summation effects of 2 drugs can be described by

$$\frac{(fa)_{A,B}}{(fu)_{A,B}} = \frac{(fa)_A}{(fu)_A} + \frac{(fa)_B}{(fu)_B} + \alpha \frac{(fa)_A(fa)_B}{(fu)_A(fu)_B} = \frac{(D)_A}{(Dm)_A} + \frac{(D)_B}{(Dm)_B} + \alpha \frac{(D)_A(D)_B}{(Dm)_A(Dm)_B}$$

(Equation 2)

where $(D)_A$ and $(fa)_A$ are the dose and the effect of drug A respectively. $(D)_{A,B}$ and $(fa)_{A,B}$ are the dose and the effect of drug A and B in a particular dose ratio respectively. In **equation 2**, in which α = 0 is for the mutually exclusive drugs and α = 1 is for the mutually non-exclusive drugs. Interaction of the two drugs is quantitatively determined by the Combination index (CI) which is defined by,

$$CI = \frac{(D)_1}{(Dx)} + \frac{(D)_2}{(Dx)_2} + \alpha \frac{(D)_1(D)_2}{(Dx)_1(Dx)_2}$$

(Equation 3)

where Dx is the dose that is required to produce x% cytotoxic effect and both are determined by m, Dm and **equation 1**. This analysis generates the combination effect as below:

When CI = 1, additive effect is showed
CI < 1, synergistic effect is showed
CI > 1, antagonistic effect is showed

All data analysis was done by the Microsoft Excel program based on the above equations.

Improved IC_{50} isobolgram analysis

The effects of combination of biological active compounds at the IC_{50} point were analyzed by the isobolgram method described by Steel and Peckham.[25] Three isoeffect curves were plotted under the principle of isobolgram method to construct the envelope of additivity on an isobolgram **(Figure 1)** :

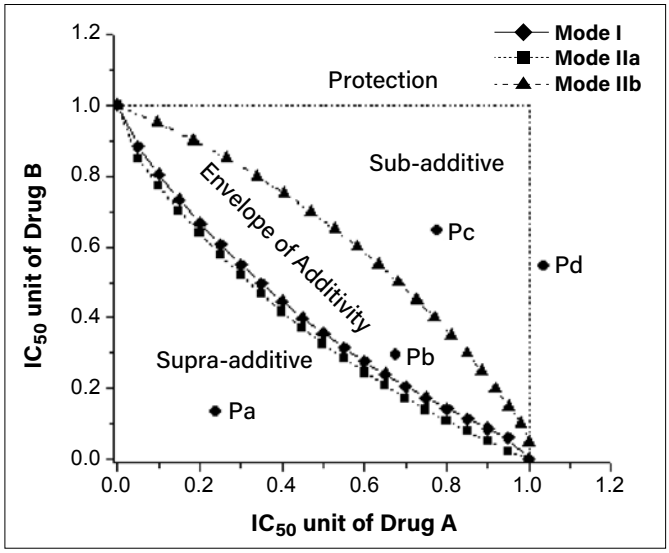

Figure 1. IC_{50} isobolgram in the combination of drug A and drug B. *An envelope of additivity is constructed from the dose-response curve of 2 drugs (drug A and B). The data points Pa, Pb, Pc and Pd indicate synergism, additive, antagonism and protection.*

Mode I line: When the dose of drug A was chosen, an increment in effect to be provided by drug B. The calculation of addition was performed by taking the increment in doses, starting from zero, that produced log survival which added up to IC_{50} (heteroaddition).

Mode IIa line: When the dose of drug A is chosen, an increment of effect remained to be produced by drug B. The calculation of addition was performed by taking the increment in doses, starting from the point on the dose-response curve of drug A where the effect of dose of drug A had ended, that produced log survival that added up to IC_{50} (isoaddition).

Mode IIb line: When the dose of drug B is chosen, an increment of effect remained to be produced by drug A. The calculation of addition was performed by taking the increment in doses, starting from the point on the dose-response curve of drug B where the effect of dose of drug B had ended, that produced log survival that added up to IC_{50} (isoaddition).

Generally, two methods are used to construct the isoeffect curves. According to the method from Kano *et al*,[34-35] a French curve model was fitted to the data and used to make the dose-response curves and the isobolgrams. From the method of Aoe *et al*,[36] only the m value in median effect plot analysis was used for the construction of isobolgram. For comparison, the IC_{50} isobolgrams were plotted according to these two methods. In the present study, method from Kano *et al* [34-35] was employed because of its accuracy in representing the shape of isoeffect curves in the isobolgram. In light of this, the IC_{50} unit and all the IC_{50} values used in the isobolgram analysis were determined by the sigmoid fit curves from the Windows computer program Microcal Origin 6.0.

In the isobolgram, concentrations of the drug combination that give point to the left of the envelope of additivity can be regarded as supra-additive (synergism) **(Figure 1 , Pa)**. A combination of drugs that data points falls within the envelope of additive can be described as additive **(Figure 1, Pb)**. A combination of drugs that data points falls to the right of envelope of additive can be described as sub-additive (antagonism) **(Figure 1, Pc)**. A combination of drugs that data points falls outside the square area can be described as protection **(Figure 1, Pd)**.

Zero interaction response surface analysis

The zero interaction response surface analysis was performed according to a method described by Dressler, Muller and Suhnel.[26] The zero interaction response surface is constructed by a computer program, namely Combitool (IMB Group) which is kindly provided by Dr. Jurgen Suhnel. In this study, the calculation of response surfaces is based on Loewe additivity principal. When a drug combination data point lines above the zero interaction response surfaces, the 2 drugs have supra-additive interaction (synergism). When a drug combination data point falls below the zero interaction response surfaces, the 2 drugs have sub-additive interaction (antagonism). When a drug combination data point falls into the zero interaction response surface, the 2 drugs have non-interaction effect (additive) **(Figure 2)**.

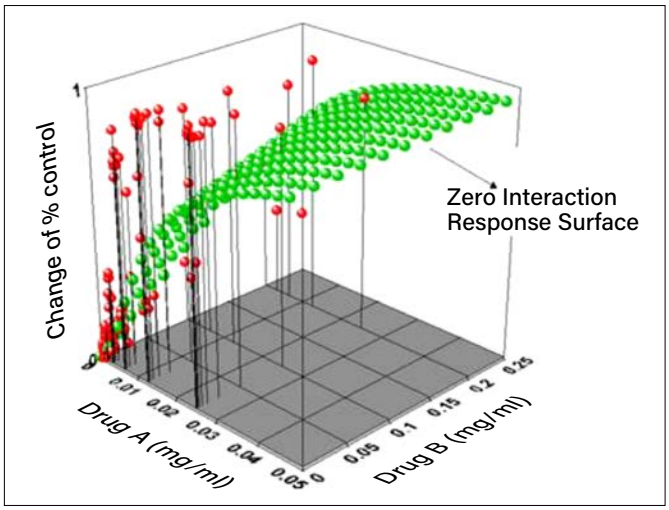

Figure 2. Comparison of the Loewe additivity surface and of experimental combination effects for the cytotoxic effect of drug A and B. *When a drug combination data point lines above the zero interaction response surfaces, the 2 drugs have supra-additive interaction (synergism). When a drug combination data point falls below the zero interaction response surfaces, the 2 drugs have sub-additive interaction (antagonism). When a drug combination data point falls into the zero interaction response surface, the 2 drugs have non-interaction effect (additive).*

RESULTS

Cytotoxicity of Various Bioactive Compounds of SB and HD on HL-60 Cells

The results of cytotoxicity assay of various drugs are shown in **Figure 3**. Drugs were added to HL-60 cells in culture for a 4 days incubation. Scutellarein showed the lowest IC_{50} value with a concentration of 11.96 µg/ml. Two related structural compounds, Ursolic acid and oleanolic acid, gave a similar IC_{50} values 13.51 µg/ml and 14.11 µg/ml respectively. In contrast, stearic acid needed an about three-fold higher concentration (43.45 µg/ml) to achieve the same effect. An IC_{50} value was obtained with a concentration of 203.32 µg/ml of p-coumaric acid. Sitosterol and stigmasterol showed a mild effect against HL-60 cells with IC_{50} values larger than 200 µg/ml.

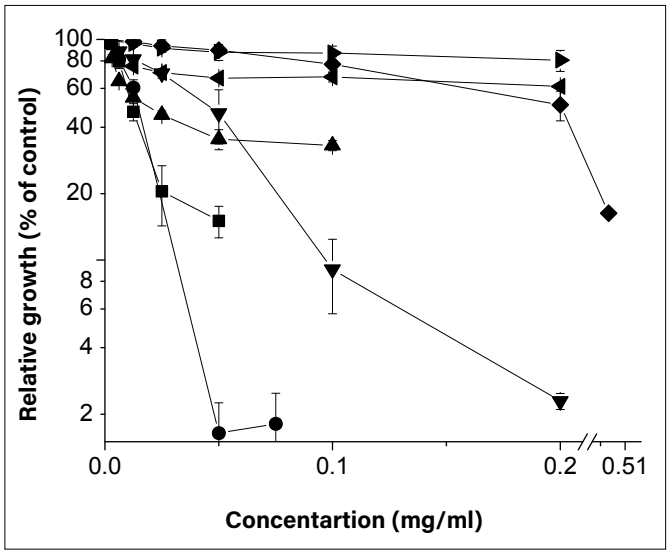

Figure 3. Dose response curves for biological active compounds alone. *Cell were incubated with scutellarein (■), ursolic acid (●), Oleanolic acid (▲), Stearic acid (▼), p-coumaric acid (◆), sitosterol (◂) and stigmasterol (▸) for 4 days. Each point represents the mean value ± SE (bars) of 4 independent experiments performed in triplicate.*

SB and HD Extracts induced Apoptosis and Death of HL-60 Cells

To investigate the apoptotic effects of the ethanol extracts of SB and HD on HL-60 cells, inter-nucleosomal DNA cleavage, a typical event in apoptosis was performed. DNA was isolated from cells 24 hrs after addition of the ethanol extracts of SB or HD. Treatment with the ethanol extracts of SD and HD at concentrations of 50-150 µg/ml resulted in the pattern of a typical DNA ladder from the DNA samples of HL-60 cell by gel electrophoresis **(Figure 4)**. No obvious discrete DNA band was observed in sample treated with SB or HD crude ethanol extracts less than 10 µg/ml.

The laser confocal microscopy pictures present in **Figure 5** show that the EtOH extracts of both herbs caused typical chromatin condensations, cell shrinkage, and membrane blebbing in treated HL-60 cells after exposure to extracts for 72 hrs. Similar observation was

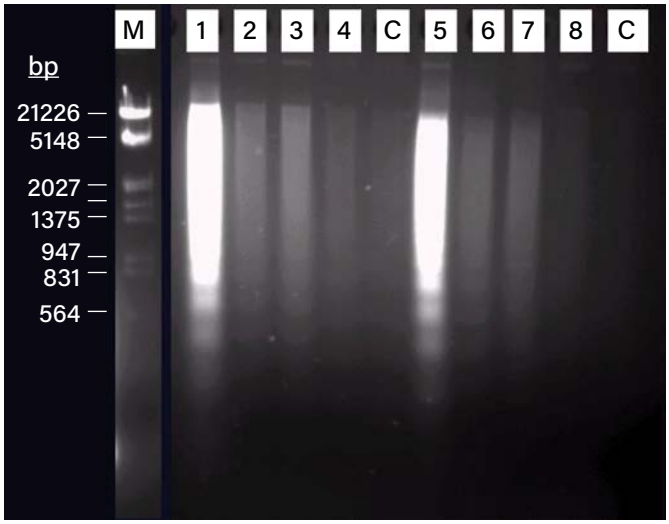

Figure 4. DNA fragmentation after treatment of HL-60 cells with ethanol extracts of SB or HD. *M = DNA ladder marker and C = untreated cells. HL-60 cells were incubated with (1) 150, (2) 100, (3) 50 and (4) 10µg/ml ethanol extracts of HD for 1 day. Cells were also treated with (5) 150, (6) 100, (7) 50 and (8) 10µg/ml ethanol extracts of SB for 1 day.*

noted in scutellarein-treated cells **(Figure 5a)**. Monocytes were shown in the HD ethanol extract-treated cells (data not shown), which suggested that compounds from the ethanol extracts if HD might induce differentiation of HL-60 cells. In light of this, HL-60 cells were incubated with lower concentration of UA and OA (7.5 µg/ml) to observe the morphological changes of cells. Monocytic and granulocytic differentiating cells were observed **(Figure 5b, c),** which mean both UA and OA are potential differentiation inducing compounds.

Combined Effect of p-Coumaric Acid and Other Compounds on HL-60 Cells

Median effect plot analysis, isobolgrams at IC_{50} and zero interaction response surfaces of combined activities of PCA and other compounds are presented in Figure 6-8. In combination with other drugs, PCA showed different effects with SC and two related compound, UA and OA. Synergistic interactions between p-coumaric and SC were observed over all the killed fraction at the SC:PCA drug ratios of 1:1, 8:1 and 1:8 **(Figure 6a)**. Similar results were determined in the IC_{50} isobolgram that nearly all data points fell on the left side of envelope of additive **(Figure 9a)**. In the graph of zero interaction response surfaces, it clearly demonstrates that synergistic interactions were found between PCA and SC among a wide range of drug ratios **(Figure 12a)**. In contrast, UA and OA showed antagonisms in combination with p-coumaric acid. In the evaluation by combination index, antagonisms were found with a wild range of killed fractions and drug ratios **(Figure 6b,c)**. Synergisms could also be found in particular killed fraction. For example, killed fraction 0-0.6 of dose ratio of UA:PCA at 1:8, killed fraction 0.5-1.0 at dose ratio of OA:PCA at 1:1 and 8:1 were found to produce synergistic effects. The interactions between p-coumaric acid and two related compounds, UA and OA acid, were drug ratio and fraction killed dependent. In

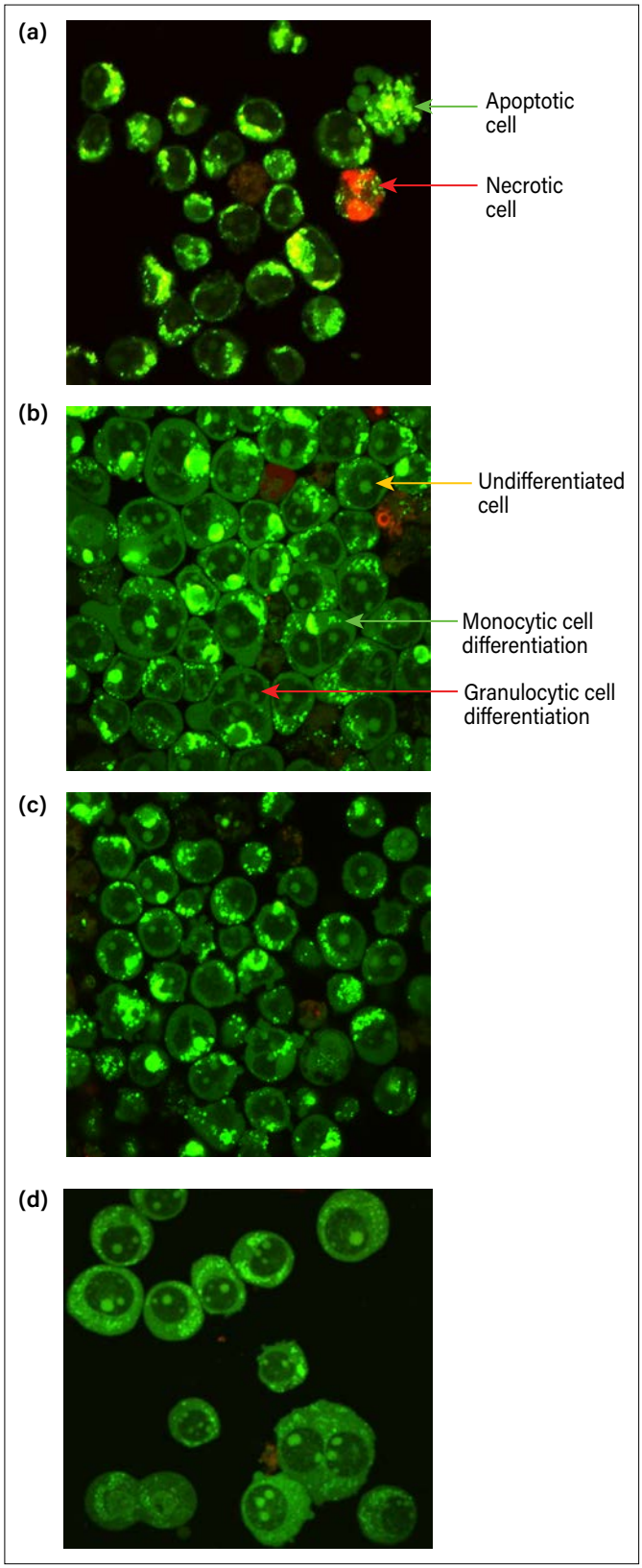

Figure 5. Fluorescence images of HL-60 cells after drug treatments. *HL-60 cells were treated with 10μg/ml scutellarein (a) or incubated with 7.5μg/ml ursolic acid (b) and 7.5μg/ml oleanolic acid (c) for 3 days and normal differentiating cells as control (d).*

IC_{50} isobolgrams of PCA in combination with UA and OA, all the data points fell on the right side of envelope of additive **(Figure 9b,c)**. Also, same interpretations were drawn from the zero interaction response surface of p-coumaric acid in combination with UA and OA which

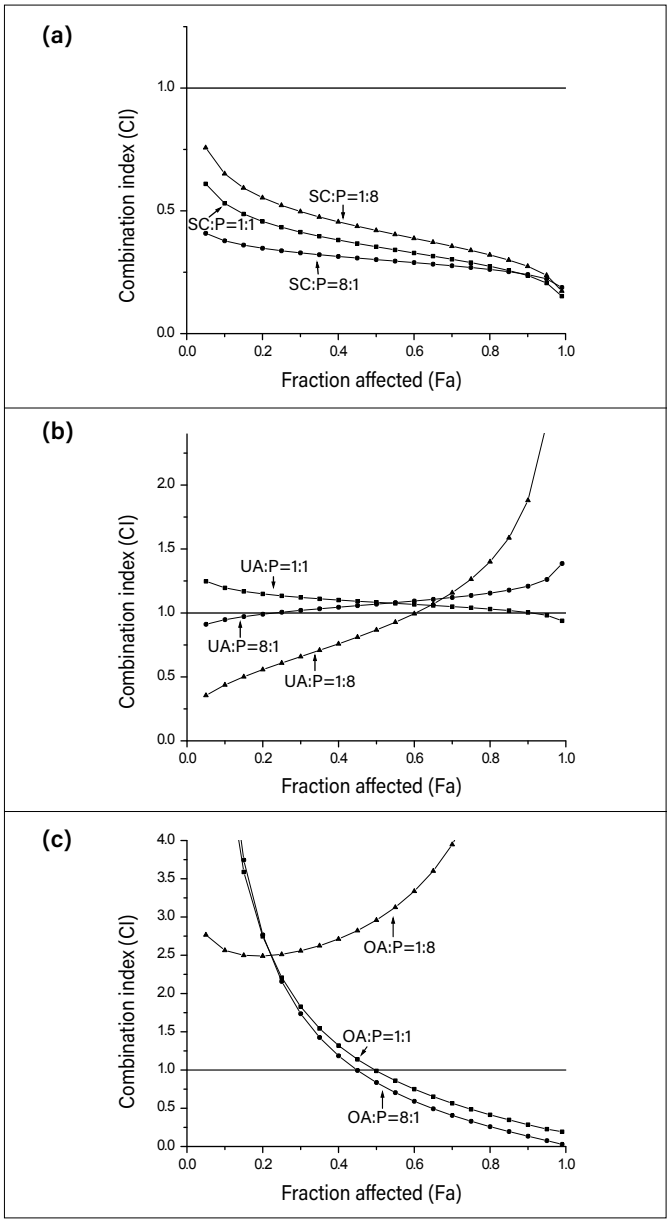

Figure 6. Combination effects of p-coumaric acid (P) in combined with (a) scutellarein, (b) ursolic acid and (c) oleanolic acid. *At the dose ratios of 1:1(■), 8:1(●) and 1:8(▲). Data points give CI >1 indicate antagonism; data points give CI = 1 indictae additive; data points give CI < 1 indicate synergism.*

most of the data points fell below the zero interaction response surfaces **(Figure 12b,c)**.

Combined Effect of Stearic Acid and Other Compounds on HL-60 Cells

The interactions between stearic acid and other compounds on HL-60 cells were drug ratio dependent. From the median effect plot analysis, it is concluded that synergism was found in SC:ST at dose ratios 1:1 and 8:1 while antagonism was found at dose ratio 1:8 **(Figure 7a)**. Similar results were found in method of isobolgram **(Figure 10a)** and zero interaction response surfaces **(Figure 13a)**. In combination with UA and OA, ST showed different interactions which depended on the dose ratio of drugs. For the dose ratios of UA:ST

or OA:ST = 1:1, antagonistic interactions were found **(Figure 7b,c)**. For the dose ratio of UA:ST or OA:ST = 8:1, marginal synergistic interactions were found **(Figure 7b,c, 10b,c and 13b,c)**. For the dose ratio of SA:UA or OA = 1:8, synergistic interactions were found **(Figure 7b,c, 10b,c and 13b,c)**.

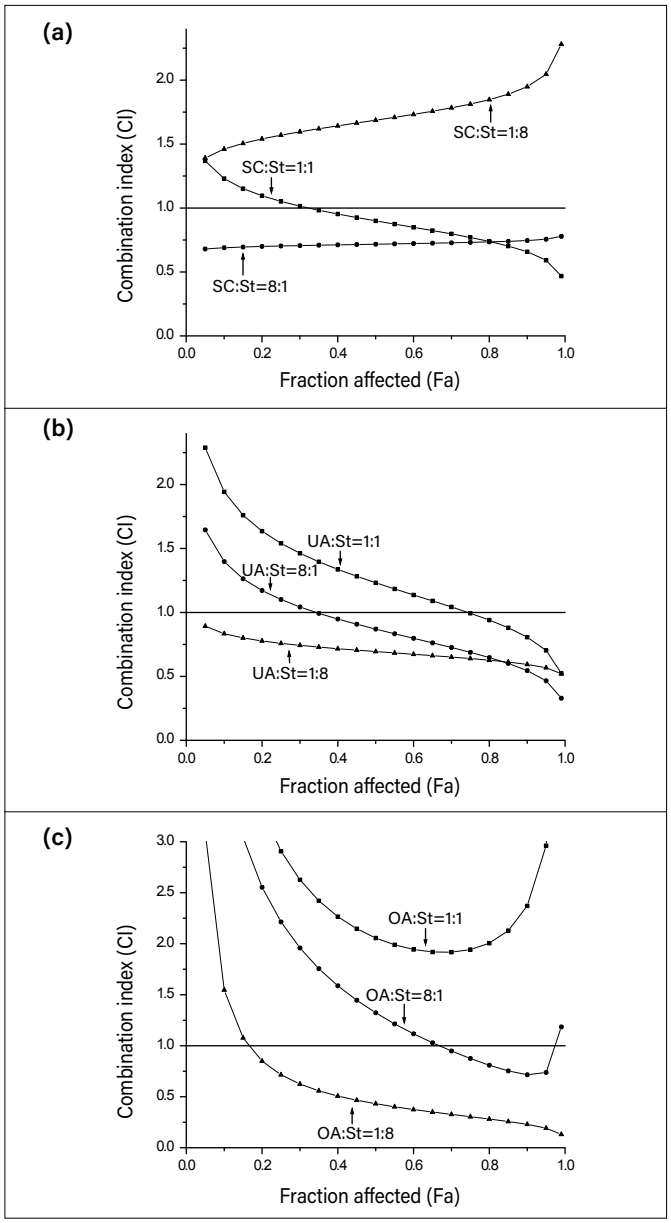

Figure 7. *Combination effects of stearic acid (St) in combined with (a) scutellarein, (b) ursolic acid and (c) oleanolic acid at the dose ratios of 1:1(■), 8:1(●) and 1:8(▲). Data points give CI >1 indicate antagonism; data points give CI = 1 indictae additive; data points give CI < 1 indicate synergism.*

Effect of Drug Combinations of Scutellarein, Ursolic Acid and Oleanolic Acid in HL-60 cellsC

Interestingly, scutellarein showed synergism in combined with oleanolic acid but antagonism in combined with ursolic acid. For median effect plot analysis, antagonistic interactions were found for SC in combination with UA in a wide range of inhibition levels **(Figure 8a)**. On the other hand, synergistic interactions were determined at the level indicating more than 50% of growth inhibition when SC was combined with OA **(Figure 8b)**.

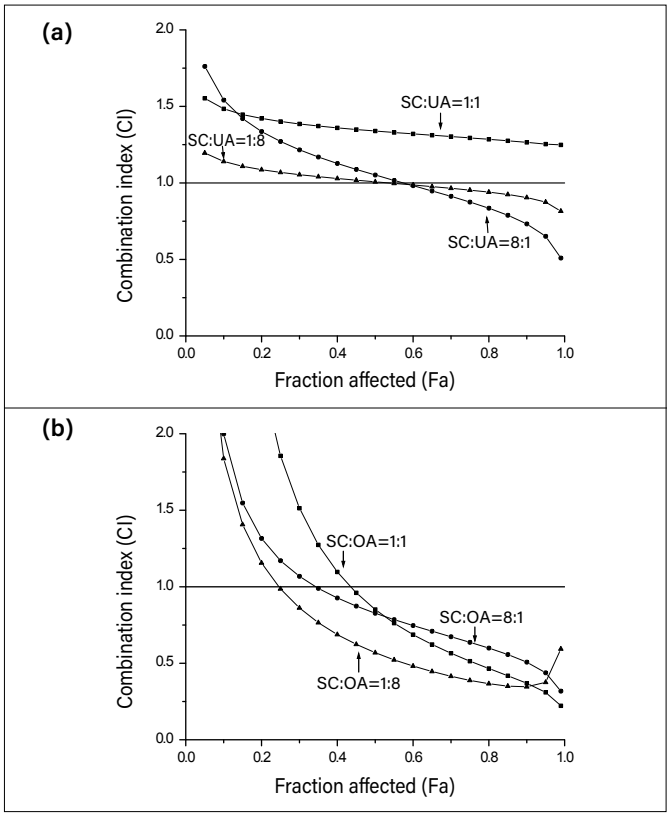

Figure 8. Combination effects of scutellarein combined with (a) ursolic acid and (b) oleanolic acid. *At the dose ratios of 1:1(■), 8:1(●) and 1:8(▲). Data points give CI >1 indicate antagonism; data points give CI = 1 indictae additive; data points give CI < 1 indicate synergism.*

Effect of stigmasterol and sitosterol on the cytotoxicity induced by various compounds

The effects of a fixed amount of two sterol compounds on the cytotoxicity of various compounds were analyzed. The tests were done at least two times. Generally, stigmasterol and sitosterol increased the cytotoxicity on HL-60 cells in low inhibitory levels while antagonism was fond at high inhibitory levels (data not shown). However, the increase in the cytotoxicity could be due to the cytotoxic effect of two sterols itself or some interactions between sterols and other drugs.

DISCUSSION

In recent years, many reports suggested that myeloid leukemias in human can be inhibited by various chemical compounds such as butyrate,[37] homoharringtonine,[38] retinoic acid,[39-40] vitamin D analogues[40-43] and ascorbate.[44] However, high dose of these compounds always induces adverse effects in human. For example, high dose of retinoic acid induces harmful effects to a wild range of human organ.[45] Alternative treatments such as continuous infusion of low dose of drugs or usage of similar structure compounds usually rise the drug resistance effects and toxicity problems.[46-47] One effective approach is the use of those drugs in combination with other drugs to solve the problems.

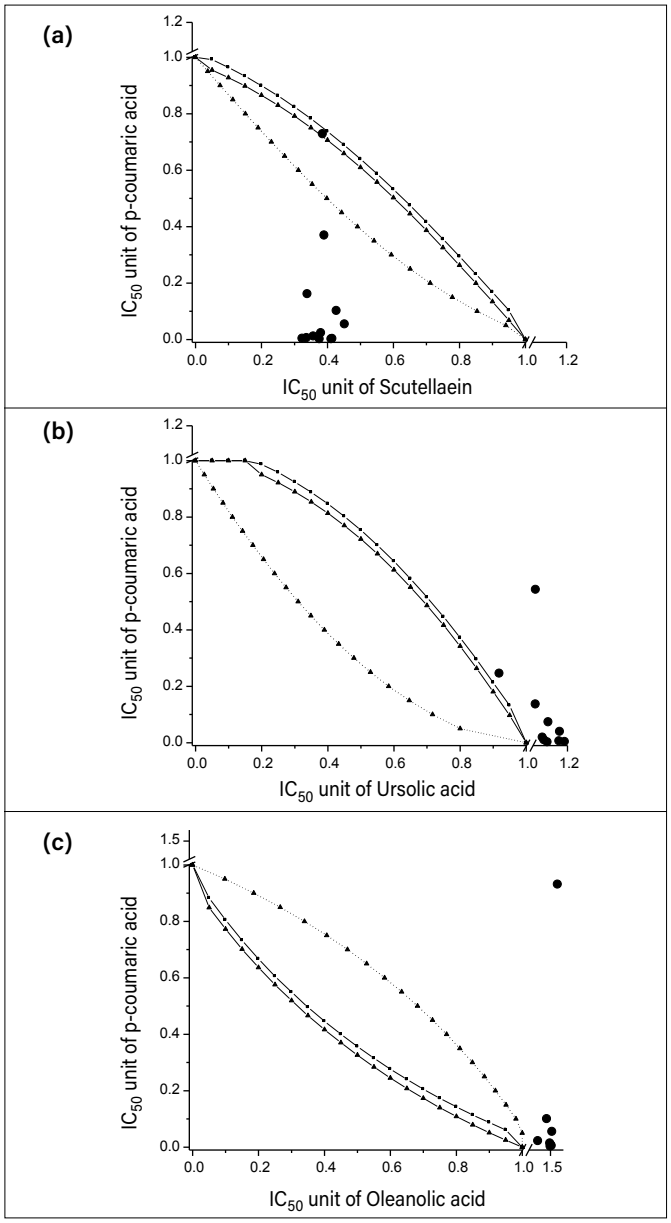

Figure 9. IC_{50} isobolgrams of p-coumaric acid. *In combination with (a) scutellarein, (b) ursolic acid and (c) oleanolic acid.*

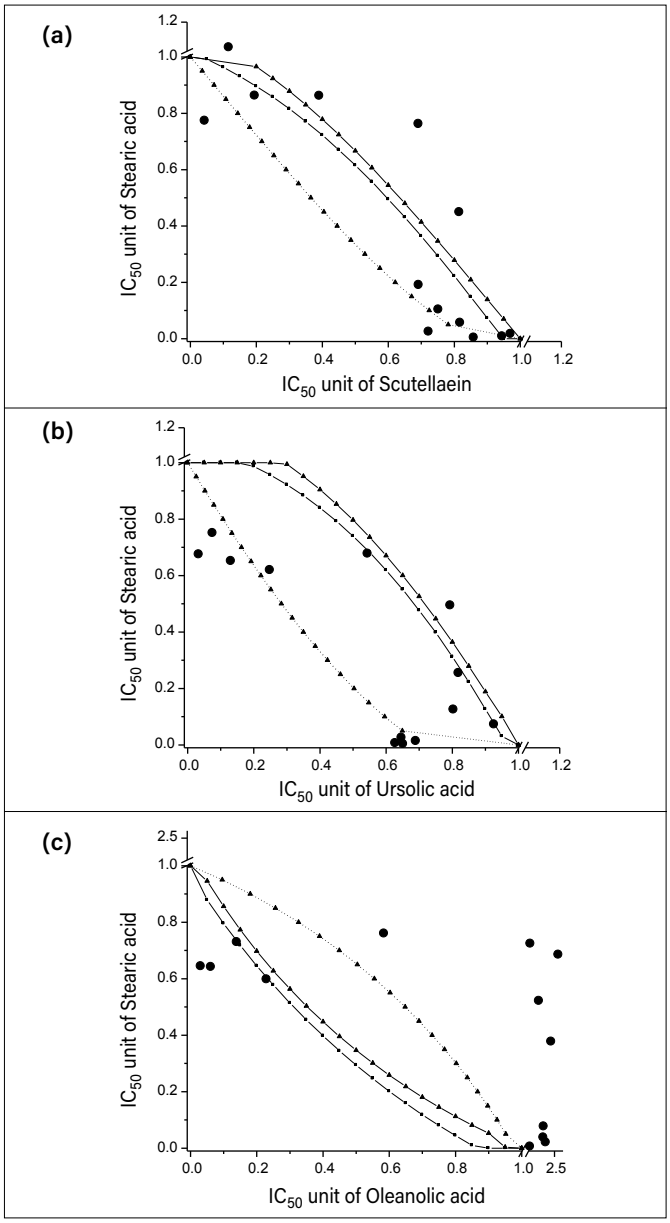

Figure 10. IC_{50} isobolgrams of stearic acid in combination with (a) scutellarein, (b) ursolic acid and (c) oleanolic acid.

The present study was carried out as a pre-clinical screening of potential application of combination of bioactive components in Chinese herbs for cancer prevention and therapy. It is the first study to bring out the concept of combined effects of Chinese herbal medicines on cancer chemotherapy. We used several methods described in literatures to investigate the effects of drug combinations.

In the past, the method of multiple dose-responses curves was used to examine the interaction between two drugs. As shown in **Figure 1**, effect of drug combination was evaluated by the shift in the dose-responses of one drug. However, this method cannot clearly define and verify the synergism statistically.[28] In drug combinations, three variables are involved; namely concentrations of drugs and their biological effects on cells and the combination ratio. For the method of median effect plot analysis and isobolgram, only two variables are found in the 2-D graph. In median effect plot analysis, the biological effects and ratio of two drugs are shown in the 2-D model. Greco *et al*[30] have pointed out the major disadvantages of this method including inadequate derivation of the mutually nonexclusive model, lack of modern statistical analysis and some practical problems; e.g. absence of drug ratios in the graph.This leads to an incomplete picture of combined effect of two drugs. For example, antagonism was found in drug ratio of scutellarein:p-coumaric acid at 1:64 but it was not shown in the graph of median effect plot analysis. Therefore, this 2-D model is insufficient to show the complex interactions between these two drugs at particular ratios.

The combined effects of various bioactive compounds on HL-60 cells were analyzed by the isobolgram method. The traditional isobolgram method was developed by Steel and Peckham.[25] The concept of the “envelope of additivity” constructed by three iso-effect curves is a variation of the isobolgram method. As stated in method section, two methods have been used

to construct the iso-effect curves. Aoe et al [36] described that the envelope of additivity can be constructed by only the m values of two drugs. According to the method described by Aoe *et al*,[36] the IC_{50} unit and all the IC_{50} values used in the isobolgram analysis were determined by the Hill model. As described in the review of Greco *et al*,[30] if one drug does not follow the Hill mode, the approach to determine IC_{50} value is invalid. Thus, we used the method described by Kano *et al* [34-35] to create the envelope of additivity and also the same approach to find out the IC_{50} values. Indeed, there are some significant differences for the determination of synergism, antagonism or additive interactions between two methods. There are many disadvantages of using isobolgram method to analyze the effect of drug combination including the need of large number of data points and the deviation by the dissimilar site assumption. In this study, the shortcoming of isobolgram is their concentration dependent analysis. The isobolgrams were constructed at endpoint of 50% inhibition of growth. However, potential synergism or antagonism might occur at higher endpoints. This could be seen in the comparison of the median effect plot analysis and isobolgram for a particular drug combination. Recently, some researcers constructed their isobolgram at endpoint IC_{80} to show more valuable results in related to the clinical trial.[48-50]

We have also used 3-D model to analyze the effects of drug combinations. The 3-D graph can overcome the inadequacy of the 2-D model. First, 3-D model showed all the three variables in the drug combination. It can broadly show the synergistic or antagonistic drug interactions by comparing the drug combination data points to the dose-response surface. Second, a relatively smaller number of data points can produce the same results as the 2-D model. Third, Combitool, the program used for analysis of combination of agents in this experiment, can analyze the data to both Loewe additivity and Bliss independence thus both criteria can be accomplished.[26] In this study, the zero interaction response surface is constructed under the Loewe additivity in order to compare the results with isobolgram method.

Chinese herbal medicines are always used in combining two to twenty or even more herbs together. General, two strategies are involved in the fight against cancer. The first strategy depends on the diversity of attack of biological active components on cancer cells. In the present experiment, the biological active components inside *Scutellaria barbata* and *Hedyotis diffusa* have multiple targets to attack the cancer cells. The structure related flavonoids of scutellarein have different target on killing the cancer cells. Genistein induced differentiation of SK-MEL-131 by down-regulation the protein tyrosine kinases.[51] Apigenin and related flavonoids induced HL-60 cells apoptosis through cytochrome c release and activation of caspase cascades.[52] Flavone acetic acid analogue was found to induce the production of tumour nerosis factor α.[53] In our own study, scutellarein was shown to induce HL-60 cells apoptosis by down-regulating the *bcl-2* and *c-myc* levels (data not published). Ursolic acid was shown to arrest MCF-7 cell cycle at G1 phase,[54] increase intracellular Ca^{2+} level[55] and down regulate the MMP-9 gene in transcription level.[56] Stearic acid and its analogues inducd apoptosis of HL-60 cells by modulating the membrane fluidity.[57] The second strategy relies on the ever changing of the content and interactions of components inside the herbs. This strategy is somehow being showed in the present study. The cytotoxicity was totally depended on the drug ratios and the different types of drug combinations. In fact, drug combination is a common approach to due with the practical problems in the use of drug. By synergistic interaction between two drugs, fewer amounts of drugs can achieve the same efficiency in order to eliminate the side effect caused by individual drug. This may be the reason why Chinese herbal medicines can deal with cancer in a safety way. In fact, the drugs or structural related drugs used in this study are shown to have negligible side effect on human.[58-61]

Generally, p-coumaric acid caused synergistic effects with scutellarein but antagonistic effects to the cytotoxicity of ursolic acid and oleanolic acid. The mechanism is not clear. Controversy, p-coumaric acid protects the apoptotic effects caused by low-density lipoproteins (LDL) by blocking the intracellular Ca^{2+} level.[62] On the other hand, curcumin, a structure related phenolic compound, induces the differentiation of HL-60 cells in combined with low level of vitamin D_3 by affecting the formation of reactive oxygen species (ROS).[63] Indirectly evidences showed that p-coumaric acid may also alternate the formation of ROS because the antioxidant properties are found in its structural related compounds.[60,64] We suggest that p-coumaric acid might increase the differentiation level of HL-60 cells induced by scutellarein and also the cytotoxicity on the cells. Jing and Waxman[65] pointed out that the differentiation induction and growth inhibition by isoflavones were depended on their structures. In our laboratory, scutellarein was found to have mildly differentiation effect on HL-60 cells by nitroblue tetrazolium dye reduction (data not published). Thus, p-coumaric acid may increase the differentiation level induced by scutellarein in order to increase its cytotoxicity. The mechanism of antagonistic interactions between p-coumaric acid and ursolic acid and oleanolic acid remains unknown. The intracellular Ca^{2+} level may be the key of antagonism. Intracellular Ca^{2+} level is an important signal in the trigger of apoptosis. As mention above, Baek *et al* [55] reported that apoptosis on HL-60 cells caused by ursolic acid was related to the increase of intracellular Ca^{2+} level. Vieira *et al* [62] showed that p-coumaric acid blocked the intracellular Ca^{2+} level induced by LDL and this may contribute to the antagonistic effects between p-coumaric acid and ursolic acid and oleanolic acid.

The interactions between stearic acid and various drugs were drug ratio and endpoint dependent. When the ratios of scutellarein:stearic acid were 1:1 and 8:1,

synergistic effects were found **(Figure 13a)**. For their drug ratio at 1:8, antagonistic interactions have been shown **(Figure 13a).** The mechanism is unclear. Stearic acid has been proved to increase the membrane fluidity of HL-60 cells that leads to the induction of apoptosis.[57] Since there are no findings for any receptors of scutellarein, we suggest that stearic acid altered the membrane fluidity, which in turn help scutellarein to influx to cell or enhanced the rate of influx of scutellarein into the area of target. The antagonistic interactions between these two drugs for drug ratio of scutellarein:stearic acid at 1:8 may be due to the antioxidant properties of scutellarein. Scutellarein was illustrated to have ability to inhibit the microsomal peroxidation and scavenge oxygen free radicals *in vitro* [66] and this might contribute to the blocking of the way of stearic acid induced apoptosis. When combined with stearic acid, ursolic acid and oleanolic acid shared the similar drug ratio dependent characteristic on the drug interactions properties. When stearic acid and ursolic acid or oleanolic acid were mixed in equal amount (1:1) **(Figure 13b,c)**, antagonisms were shown. As mentioned, the induction of apoptosis of HL-60 cells by ursolic acid is related to the increase of intracellular calcium level.[55] Indirect evidence shows that the antagonism between stearic acid and ursolic acid was due to the blocking of intracellular Ca^{2+} level. Okajima *et al* determined that 1-stearoyl lysophosphatidylcholine was inhibitory for the phospholipase C/Ca^{2+} system in HL-60 cells.[67] Another evidence for explanting the antagonistic interaction is related to the membrane fluidity of cells. Ip and Cooper[68] determined that dimethyl sulfoxide-induced differentiation of HL-60 cells was accompanied with the changes in membrane fluidity. On the other hand, the induction of differentiation of HL-60 cells by 12-O-tetradecanoylphorbol-13-acetate (TPA) had no observed effect to the membrane fluidity of HL-60 cells.[68] In fact, ursolic acid and oleanolic acid had been proved to have differentiating effect on HL-60 cells[61,69-70] In our investigation, ursolic acid has been shown to have dose dependent differentiation characteristic on HL-60 cells (data not shown). Therefore, the author recommended that differentiation, as a way for inhibitory of growth of HL-60 cells, was inhibited by the modulated of membrane fluidity by stearic acid. The reason for the synergistic interactions between at other drug ratios is not clear.

Interestingly, scutellarein was shown to have marginal synergism with oleanolic acid but antagonism with ursolic acid **(Figure 8a,b, 11a,b** and **14a,b)**. Since ursolic acid and oleanolic acid are regioisomers, it is hard to explain

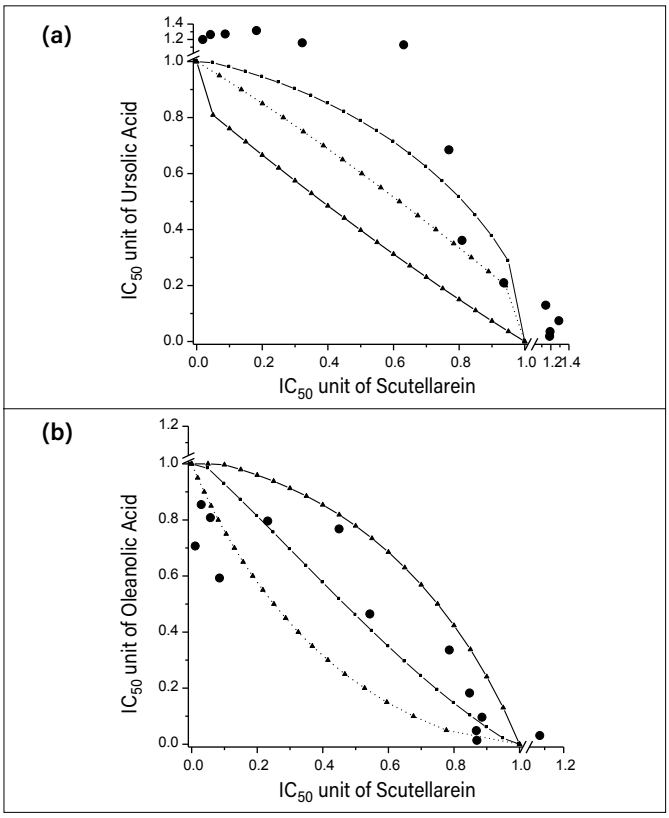

Figure 11. IC_{50} isobolgrams of scutellarein in combination with (a) ursolic acid and (b) oleanolic acid.

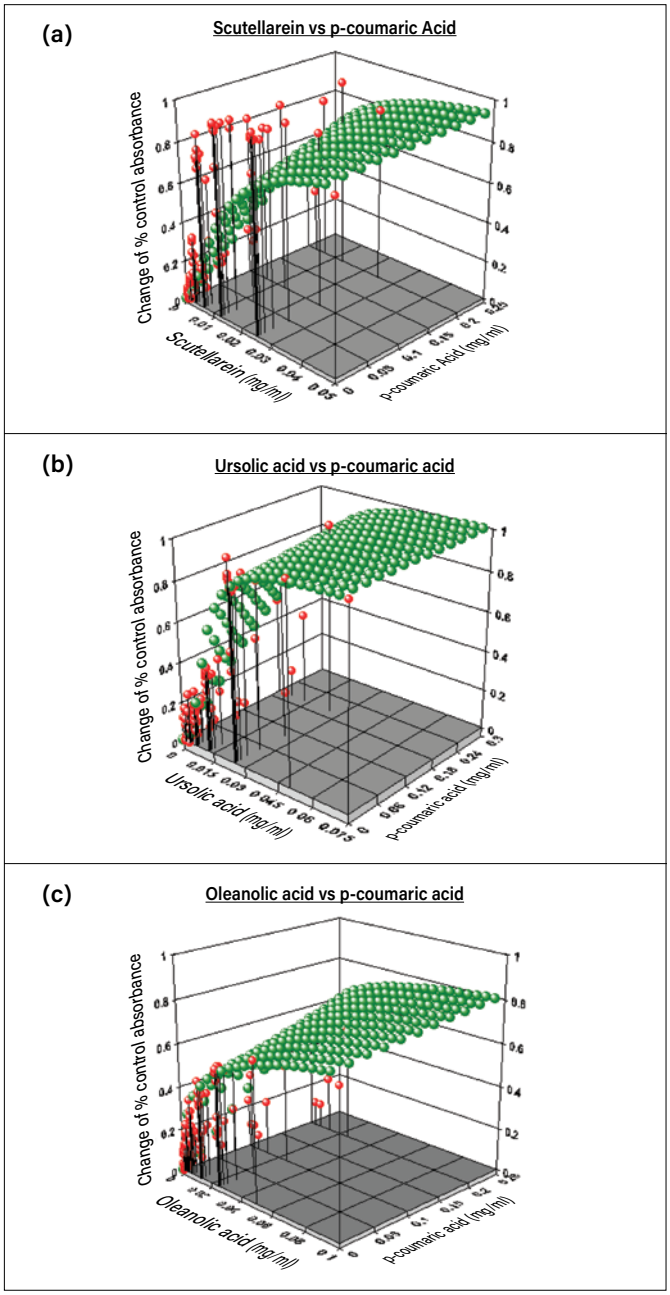

Figure 12. Zero interaction response surface for a 4 days drug exposure of p-coumaric acid in combined with (a) scutellarein, (b) ursolic acid and (c) oleanolic acid.

the observed data. From the literatures, we know that ursolic acid and oleanolic acid have different potency in various circumstances, for example, anti-inflammation effect, induction of apoptosis and other pharmacological effects.[61] Hsu *et al*[71] have suggested several reasons for their different potency. In our opinion, we suggested that the antagonism between scutellarein and ursolic acid might be due to the influence at the cell physiology level. From the details of the dose response curves **(Figure 3)**, the cytotoxicity at low inhibitory level (< 30%) of oleanolic acid was higher than that of ursolic acid. This might be due to the dose response differentiation of ursolic acid as mentioned before. Thus, scutellarein, as an apoptosis inducer (data not shown), influenced the differentiation of HL-60 cells by ursolic acid as a result of the antagonistic effect. However, the mechanism of synergism between scutellarein and oleanolic acid is not clear.

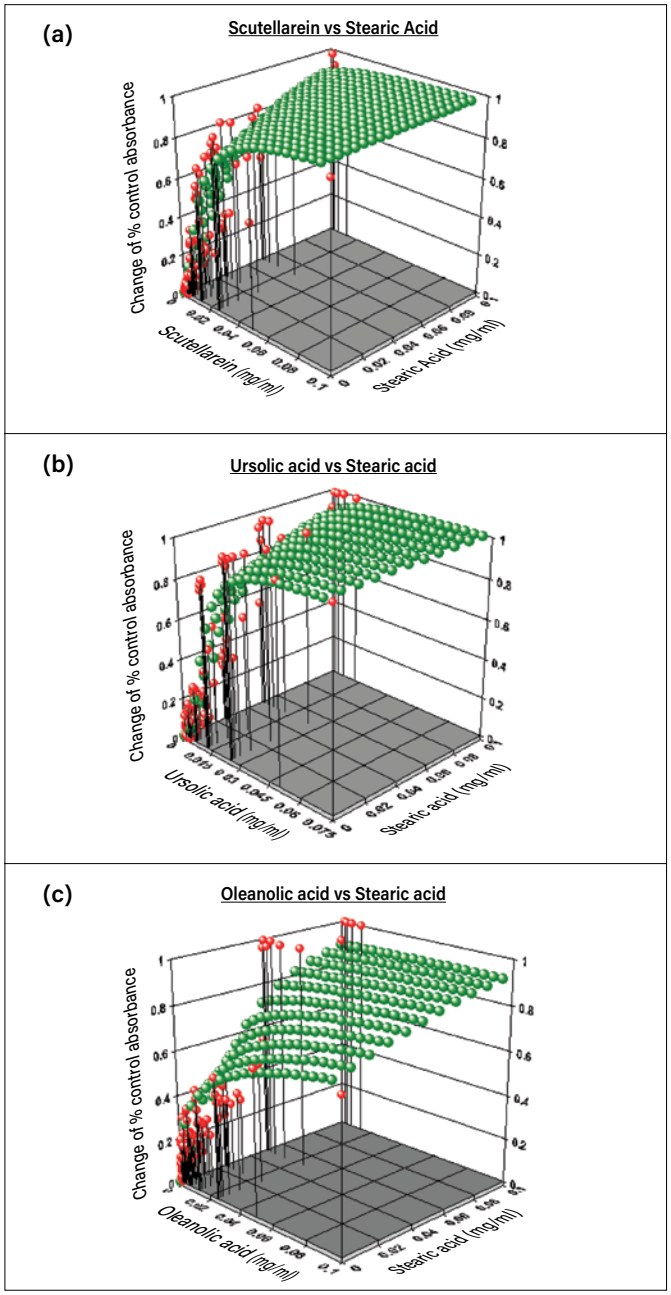

Figure 13. Zero interaction response surface for a 4 days drug exposure of stearic acid in combined with (a) scutellarein, (b) ursolic acid and (c) oleanolic acid.

In Hong Kong, China and many foreign countries, government usually uses the term "Chinese practitioners" instead of "Chinese medical doctor". The pharmacology of Chinese herbal medicines is somehow based on the repeated practices and the experiences from predecessors. Thus, we must keep in mind that clinical active drug combinations need not produce synergism *in vitro*. Conversely, the synergism of drugs found *in vitro* do not necessarily produce synergistic clinical effects. Moreover, there are several limitations for the studying of drug combinations. First, the constant level of drug exposure of the cells *in vitro* may be complicated with drugs of differing half-life and resulting changes in drug ratios over time *in vivo*. Second, synergism acts on cancer cells may also lead to the synergistic destruction on normal tissue. Third, the different absorption rate of drugs in our intestine may contribute to the change of drug ratio *in vivo*. For example, quercetin, structural related bioflavonoid of scutellarein, was found to be anticipated in human and animal studies.[58] In fact, in Quan guo Zhong cao yao hui bian, a handbook of usage of Chinese herbal medicines, suggested that the treated crude extracts of *Scutellaria barbata, Hedyotis diffusa* and several herbs should be taken as an injection to the blood.[72]

In conclusion, we have made a comparison between the characteristics of different methods in the evaluation of drug combinations. Zero interaction response surface,

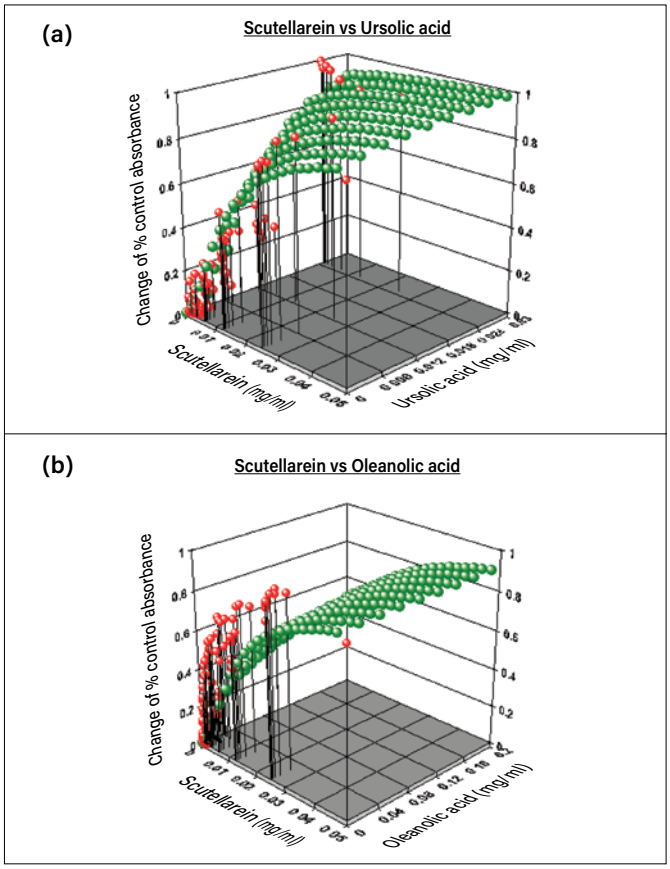

Figure 14. Zero interaction response surface for a 4 days drug exposure of scutellarein in combined with (a) ursolic acid and (b) oleanolic acid.

a 3-D model in presenting the drug combination results, is encouraged to be use in the future. Moreover, we have found that the complicated cytotoxic effects of biological active compounds in Chinese medical herbs may be valuable in cancer prevention and therapy. Clinical trails are encouraged to test the synergistic interactions *in vivo*. However, more investigations should be done in the future. For the drug combinations which produced synergistic interactions, tests should be done for investigating whether the same effect would be found in their structural related compounds. We can save the time and manpower if an analogue of compounds produces synergistic interactions with another analogue of compounds since isolation of an analogue of compounds is much cheaper than the isolation of a single chemical. Since Chinese herbal medicines are taken in schedule, schedule dependent effects should be taken into account for evaluating the effect of drug interactions. Recently, a number of researches have shown the value of the schedule dependent drug treatment.[49,73-74] Moreover, different cell lines should be tested in order to find out the application value of particular drug combination on different types of cancer.

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Author's background

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SHPHK – Keep the Momentum Going!

*Reported by **Vienna Leung**, Pharmacist of The Society of Hospital Pharmacists of Hong Kong*

2019 has been an amazing year!

This year, there has been a significant breakthrough for the Society of Hospital Pharmacists of Hong Kong (SHPHK) - In collaboration with The University of Hong Kong and KeySteps@JC, members of the Society have participated in the delivery of flu vaccination services in the community for the first time during the flu season. Although the scale of the outreach service was modest, we believe it could create a demonstration effect for the Hong Kong Pharmacists, the policy makers as well as the general public. The role of Hong Kong Pharmacists is far beyond dispensing and accuracy check. Their role in primary care should never be neglected!

In 2020, SHPHK will continue to collaborate with different local and overseas organisations and institutions to promote, improve and assist the advancement of pharmacy practice in Hong Kong!

Various activities have been organized by the Society in Q4 2019.

Activities in Q4 2019

In the fourth quarter of 2019, the Society has successfully organized a number of seminars on different clinical topics, including biosimilars, hepatitis C, and total parenteral nutrition.

1. Paediatrics Total Parenteral Nutrition Seminar

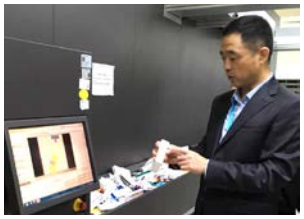
The seminar on Paediatrics Total Parenteral Nutrition held on 7th December 2019 is the last SHPHK event of the year. Over 60 healthcare professionals including pharmacists, physicians, nurses and dietitians attended the symposium. There were lots of fruitful discussions between the speakers and the audience.

2. The Shanghai-Hong Kong Hospital Pharmaceutical Management Summit Forum

On 16th and 17th November 2019, 17 delegates from the Society went to Shenzhen to join the 1st Shanghai-Hong Kong Hospital Pharmaceutical Management Summit Forum (滬港醫院藥學管理高峰論壇). The Forum was co-organised by SHPHK and the Shanghai Pharmaceutical Association (上海市藥學會).

Day One

The team made a pre-forum visit to The University of Hong Kong – Shenzhen Hospital. Mr. Wang Nan-song Nathan, Senior Pharmacist (Operation) of the Hospital showed the team how the pharmacy automation systems installed in the hospital could help improve the effectiveness of pharmacy operation. Mr. Wang also explained to the team the history and future development of the hospital.



Mr. Wang Nan-song Nathan, Senior Pharmacist, The University of Hong Kong – Shenzhen Hospital was illustrating how the machine could automatically put the medicines back on the shelves.

Day two

The forum started at 8:30 a.m. In the forum, pharmacists of Shanghai, Hong Kong, Macau and Taiwan exchanged their knowledge and ideas with each other and shared their experience in clinical pharmacy with the participants.

There were also many renowned and outstanding speakers of different regions reporting the latest research findings on ***Alzheimer's disease, cancers,*** etc. to the participants. Other topics including ***'Innovative Ways of Delivering Patient-centred Care Services'*** and ***'Opportunities for Developing Healthcare Services in the Greater Bay Area'*** were also discussed in the forum.

The Society would like to thank Ms. S C Chiang, honorary advisor of SHPHK; Mr. Lam Kam-mo Kemo, Committee member of SHPHK; and Ms. Chan Ho-yan Tammy, member of SHPHK for representing the Society to give presentation on ***'The Development of Pharmacy Service in Primary Care in Hong Kong', 'Update on Clinical Oncology Pharmacy Services in Hong Kong'*** and ***'The Role of Clinical Research Pharmacists in Hong Kong'*** in the forum, respectively.

The forum attracted over 100 pharmacists from Shanghai, Hong Kong, Macau and Taiwan.

The 2nd Hospital Pharmaceutical Management Summit Forum will be held in March 2020 in Shanghai. Members of SHPHK are welcome to join the forum to meet pharmacists of different regions. Details of the forum will be announced in due course.

Seventeen delegates from SHPHK attended the 1st Shanghai-Hong Kong Hospital Pharmaceutical Management Summit Forum (滬港醫院藥學管理高峰論壇) in Shenzhen on 17th November 2019.

SHPHK Activities: 2019 In Review

January	1. Movie Night: Dying to Survive (我不是藥神)
	2. Evening Symposium on Multiple Myeloma
March	3. SHPHK Annual General Meeting
	4. Hong Kong Symposium in Travel Health 2019 (co-organised with Hong Kong Society for Travel Medicine Founding Group)
	5. Seminar on Novel Synergy of Insulin and GLP-1 Receptor Agonist for Management of Type-2 Diabetes Mellitus
April	6. Official Meeting with Pharmaceutical Society of Shanghai
May	7. Oral Exam Skills Workshop
June	8. Interview Skills Workshop
	9. Antiviral ABC Lecture – HIV/AIDS
August	10. Antiviral ABC Lecture – Hepatitis B
September	11. Seminar on 'Grab Your AIR – New Approach to Asthma Management'
	12. Dinner Conference on The Massachusetts General Hospital Pharmacy Automation Journey
October	13. Seminar on Biosimilars
	14. Antiviral ABC Lecture – Hepatitis C
November	15. 滬港醫院藥學管理高峰論壇
December	16. Symposium on Paediatrics Total Parenteral Nutrition and Nutrition

The Society is always committed to organizing different educational seminars and workshops for its Members, hoping to help pharmacists of different sectors to identify and achieve their learning goals. More educational events will be organized by the Society in 2020! Please stay tuned!

RTHK Broadcasting: 精靈一點 on Radio One

Starting from 3rd December 2019, SHPHK will be broadcasting on RTHK Radio One 精靈一點 programme every Tuesday for five consecutive weeks. Our pharmacists will be sharing useful self-care tips for better health and practical advice on personal medication management with the audience. Archive will be available at www.rthk.hk after the programme.

2020 – An exciting year ahead!

Hong Kong Pharmacy Conference 2020 – We Believe, Pharmacists Can!

Hong Kong Pharmacy Conference (HKPC) is one of the biggest and most important events of the pharmacy profession in Hong Kong. There are many new and exciting arrangements for HKPC 2020. Firstly, Pharmacists who wish to submit their abstracts to the Committee are required to film a 5-minute video regarding the overview of their posters. Secondly, conference participants can view and rate the video and poster by scanning the QR code on the poster using the Conference App on-site. Finally, gamification will be introduced into HKPC 2020! There will be an introductory section on Day 1 to show the audience how to maximize the use of the conference App to make the conference more fun and enjoyable!

It is still not too late to register at https://www.pharmacyconference.org. We will see you all at HKPC 2020!

SHPHK Membership Update

Good news! If you are a pharmacy intern in Hong Kong or an undergraduate pharmacy student of CUHK/HKU, you may have your membership fee waived until 31st December 2020! Why not take this great opportunity to join the Society and explore the ideas of advancing the pharmacy profession with other Members together? We look forward to meeting you at the SHPHK event in 2020!

As 2019 comes to an end, the Committee of SHPHK would like to thank its Members for their continuous support to the Society.

Wish you all a Merry Christmas and a Happy New Year!

You are most welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

「管好我健康」藥劑師推動隱閉性非傳染病檢測計劃及*研究*

是次計劃主要由沙田區議會衞生及環境委員會健康城市及國際復康日工作小組主辦，香港藥學會慈善基金有限公司合辦，協辦機構為健康連線有限公司，香港中文大學醫學院賽馬會公共衞生及基層醫療學院則負責研究工作。

香港藥學會藥劑師及藥劑學生團隊在2018年9月至12月期間到訪了8個屋苑，為771位18歲以上沙田區居民進行免費的體檢測試。

體檢測試目的

盡早發現隱閉性非傳染病患者及受訪者不健康的生活模式；提升市民對於預防疾病及自我健康管理的能力；並盡早為發現隱閉性非傳染病的潛在患者提供專業醫療及健康生活的意見（包括飲食及運動等），有需要時會作出跟進及轉介，以便及早改善生活模式及得到適當的治療。計劃中所收集的數據可用於籌劃更具針對性及切合地區特色的地區康健中心。

體檢測試方法

主要針對常見的隱閉性非傳染病及其風險因素，例如：心血管疾病、糖尿病、高膽固醇及高血壓等；測試項目包括血壓、血脂(高密度膽固醇及整體膽固醇)、血糖、脈搏及未來十年心血管疾病風險預測。並會對已測試者進行問卷調查。

體檢測試結果

為數不少的隱閉性非傳染病的潛在患者而不自知，顯示不少市民對慢性病的意識不足。在報稱沒有高血壓的受訪者中，49%被驗出一期／二期血壓；在報稱沒有膽固醇問題的受訪者中，32%被驗出膽固醇偏高/過高；在報稱沒有糖尿病的受訪者

中，當中有10%於血糖檢測中亦發現血糖偏高／過高。隱閉性高血壓和糖尿病於男性比例較高，隱閉性高膽固醇則在女性比例較高。而隱閉性高血壓和高膽固醇亦會發生在18-34歲較年輕的年齡層。

另外根據測試結果已知患有慢性病的市民對自身的病情控制不足。有高血壓問題的受訪者中，87%的血壓測試結果仍屬於一期／二期高血壓；膽固醇過高患者中，有45%膽固醇測試結果仍屬偏高／過高；糖尿病患者中，有42%的血糖檢試結果仍為偏高／過高，反映患有慢性病的市民需要加強控制病情的意識，包括藥物治療及改變生活模式。在健康狀況及生活習慣調查中（見**表1**），57%的受訪者沒有定期身體檢查，52%沒有定期做運動，睡眠質素僅得6.8／10分，37%的受訪者有輕度至非常嚴重焦慮，以及54%受疼痛之苦。

表1 受訪者健康狀況及生活習慣

特徵	總計 N (%)* / 平均數±標準差	女性 N (%)* / 平均數±標準差	男性 N (%)* / 平均數±標準差
慢性疾病			
確診患有慢性疾病@	398 (60.5%)	265 (59.7%)	133 (62.1%)
心血管疾病	195 (49%)	127 (47.9%)	68 (51.1%)
肌肉及骨骼病	97 (24.4%)	60 (22.6%)	37 (27.8%)
眼病	72 (18.1%)	47 (17.7%)	25 (18.8%)
內分泌及新陳代謝疾病	70 (17.6%)	49 (18.5%)	21 (15.8%)
精神科疾病	20 (5%)	15 (5.7%)	5 (3.8%)
生活習慣			
吸煙	25 (3.8%)	6 (1.3%)	19 (8.8%)
定期做身體檢查	285 (43.3%)	197 (44.3%)	88 (41.3%)
每星期做最少3次運動#			
從未如此	64 (9.7%)	43 (9.7%)	21 (9.9%)
甚少/間中如此	278 (42.2%)	195 (43.8%)	83 (39%)
時常/總是如此	316 (48%)	207 (46.5%)	109 (51.2%)
生活質素			
入睡時間 (小時)	6.4 ± 1.4	6.3 ± 1.5	6.6 ± 1.3
睡眠質素評分 (滿分：10)	6.8 ± 1.7	6.6 ± 1.8	7.2 ± 1.6
生活質素評分 (滿分：10)	7.7 ± 1.4	7.6 ± 1.4	7.9 ± 1.4

* 缺失數據不計入百分比中；@ 各慢性疾病分類的百分比是以患有慢性疾病的人數為基數；# 每次20-30分鐘運動

是次計劃更應用了歐洲五維健康量表（EQ5D）[1]來量度受訪市民的健康狀況。歐洲五維健康量表（EQ5D）是一套經驗證用作量度參加者健康生活質素的測量工具。受訪者會就五個維度以五個不同的水平挑選最能形容自己受訪當日的身體狀況。團隊會邀請受訪者以一個由0（想像中最壞的身體狀況）到100（想像中最好的健康狀況）的尺度，形容自己受訪當日的身體狀況有多好或多壞。受訪者對自己當日的健康評分平均為80.2分（100分為滿分，標準差為13.8分）。男性的健康評分平均為79.4分（標準差為13.8分），女性則為81.9分（標準差為13.8分）。而於行動、自我照顧、平常活動、疼痛／不舒服及焦慮／沮喪五方面的健康狀況中，分別有86%，96%，89%，46%及71%的受訪者認為自己沒有任何問題。

參加者評價

從**表2**可見受訪者對計劃的整體經驗，97%非常滿意／滿意活動，對整個活動的平均評分為9.3／10分，95%對活動時間及地點非常滿意／滿意，98%受訪者非常滿意／滿意藥劑師表現。是次活動令97%的受訪者更了解自己身體的狀況，亦有97%的受訪表示有興趣知道更多的健康資訊。

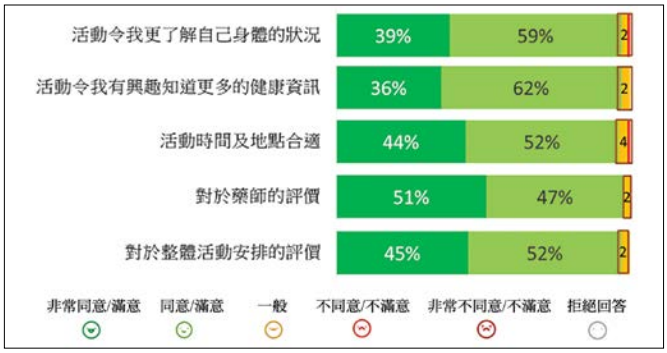


表2 計劃的整體經驗

整體建議

此項計劃令參加者更了解自身的健康狀況，從而提升其預防疾病及自我健康管理的關注度、能力及意識。透過是次體檢及藥劑師諮詢服務，發現為數不少的參加者有潛在慢性病而不自知，市民需要恆常檢查，透過藥劑師介入的快速檢測找出隱閉個案從而作出健康建議。同時，亦建議政府把醫療券擴展到65歲以下人士均可使用作身體檢查。

另外，通過計劃發現部份慢性病患者對病情的控制並不理想。建議增強社區藥劑師的角色並透過藥劑師了解其用藥情況。這次計劃得到參加者高度評價，因此建議定期舉辦非傳染病檢測計劃及諮詢服務，以加強公共衛生教育及健康生活宣傳，及提升市民對自我健康照顧的知識，關注度及管理。

除此之外，政策的配合也同樣重要。政府跨部門協作以改善社區公共空間及運動設施。政府亦應全禁電子煙及加熱煙，並加強酒精禍害的教育和宣傳。在未來的沙田康健中心應要著重疾病預防及控制、痛症及精神健康方面的工作。

香港藥學會慈善基金會會長
龐愛蘭BBS, JP

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1. Wong, E. L., Ramos-Goñi, J. M., Cheung, A. W., Wong, A. Y., & Rivero-Arias, O. (2018). Assessing the Use of a Feedback Module to Model EQ-5D-5L Health States Values in Hong Kong. *The Patient-Patient-Centered Outcomes Research*, 11(2), 235-247.

香港藥學會疫苗注射訓練課程及外展服務

等都已完滿完成。我們很高興已有十多位香港藥學會的藥劑師完全掌握疫苗注射的技巧、熟悉流程及處理危機的方香港藥學會成員完成學會舉辦的「疫苗注射訓練課程及實踐」計劃後，正式參與了衛生署疫苗資助計劃。由課程、實習、外展疫苗注射法。該批香港藥學會藥劑師已經完成超過600個疫苗注射工作。

本會的藥劑師亦曾參與美國、英國及本會的疫苗注射訓練課程。鑑於本會的課程更實用和配合本地環境及需要，香港藥學會會繼續安排訓練及外展疫苗注射的實踐工作，期望在不久的將來有更多的藥劑師能掌握相關技巧及知識，以爭取未來擴大藥劑師的專業工作領域。

藥劑師在香港藥學會安排的外展疫苗注射中為市民注射流感疫苗。

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