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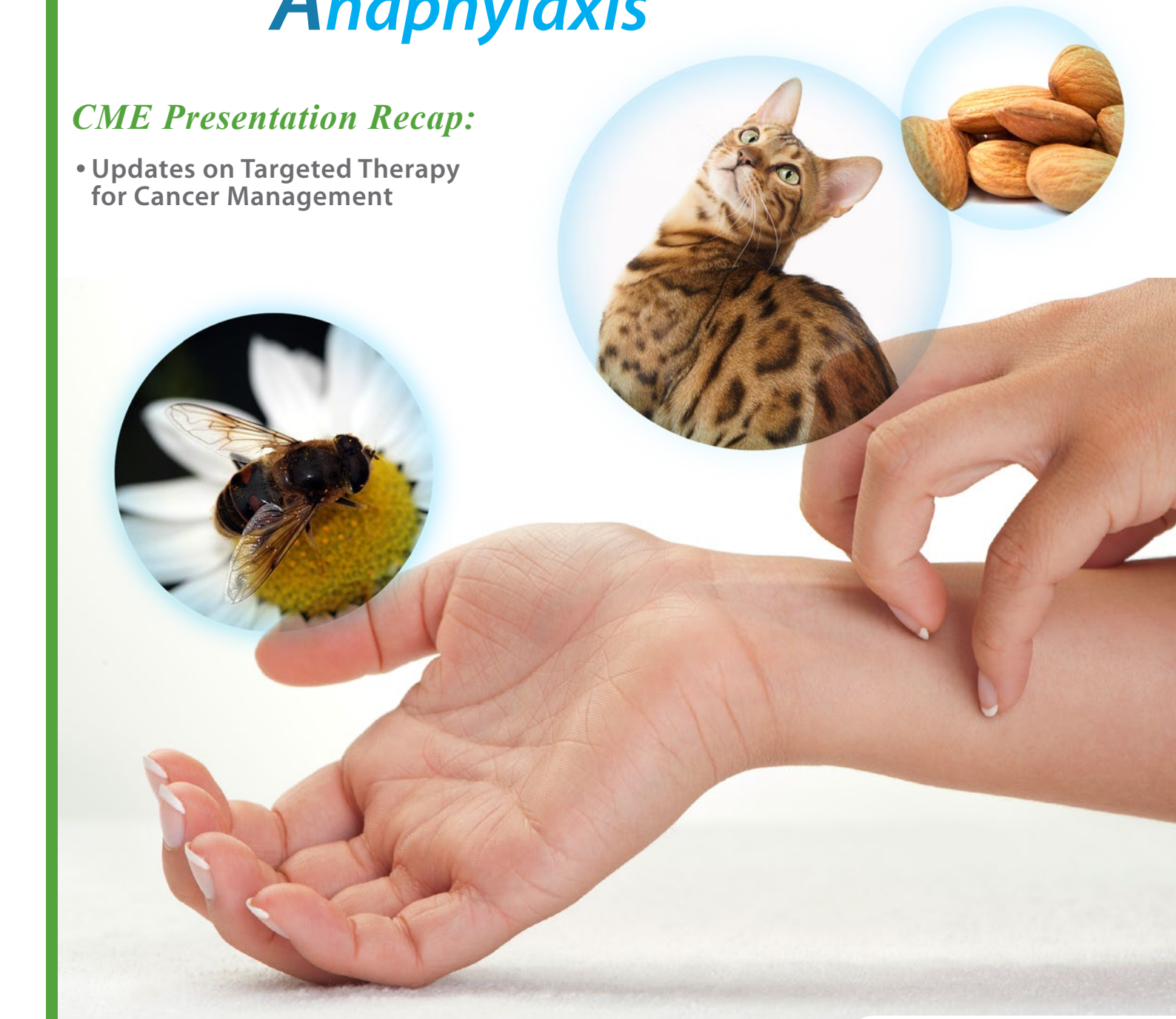
NewsLetter 院訊

An Overview of *Anaphylaxis*

CME Presentation Recap:

- Updates on Targeted Therapy for Cancer Management



MEDICAL ARTICLE

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An Overview of *Anaphylaxis*

Definition

Anaphylaxis is an acute-onset, potentially fatal systemic allergic reaction. It is usually triggered by an agent such as an insect sting, food, or medication, through a mechanism involving IgE and the high-affinity IgE receptor on mast cells or basophils. Anaphylaxis episodes range in severity from those that are mild and resolve spontaneously to those that are fatal within minutes.

Pathogenesis

In many individuals with anaphylaxis, IgE plays a pivotal role. Synthesized in response to allergen exposure, it becomes fixed to FceRI on the surface membranes of mast cells and basophils. Aggregation of receptor-bound IgE molecules on re-exposure to the allergen results in cell activation, mediator release, and the immediate hypersensitivity response.

Other immunologic mechanisms that do not involve IgE are less commonly implicated and less definitively proven. These include IgG-antigen complexes, activation of the complementand coagulation systems, and possibly other mechanisms such as cytotoxicity, T-cell activation, neuropeptide (substance P) release, or autoimmunity.(1)

Nonimmunologic factors, which activate mast cells by mechanisms not yet fully understood, include exercise, cold air or water exposure, radiation, ethanol, insect venom constituents, radiocontrast media, and medications such as opioids and vancomycin.(2)

In the same patient more than 1 mechanism might contribute to an anaphylaxis episode. Regardless of the initiating trigger and mechanism, cellular events involving activation of tyrosine kinases and calcium influx in mast cells and basophils result in rapid release preformed mediators such as histamine, tryptase, carboxypeptidase A3, chymase, and proteoglycans, including prostaglandins and leukotrienes and synthesis of platelet-activating factor.

Triggers

The number of potential anaphylaxis triggers is infinite. The most common food triggers are peanut, tree nuts, shellfish, fish, milk, and egg.(3,4,5). Hidden food triggers include food contaminants (eg, storage mites), food additives.

Medication triggers include beta-lactam and other antibiotics; aspirin, ibuprofen, and other analgesics (6)
Venom from a stinging insector,less commonly, saliva from a biting insect can induce anaphylaxis. Other triggers include natural rubber latex, inhalant allergens such as horse, hamster, or other animal dander and grass pollen.

Diagnosis

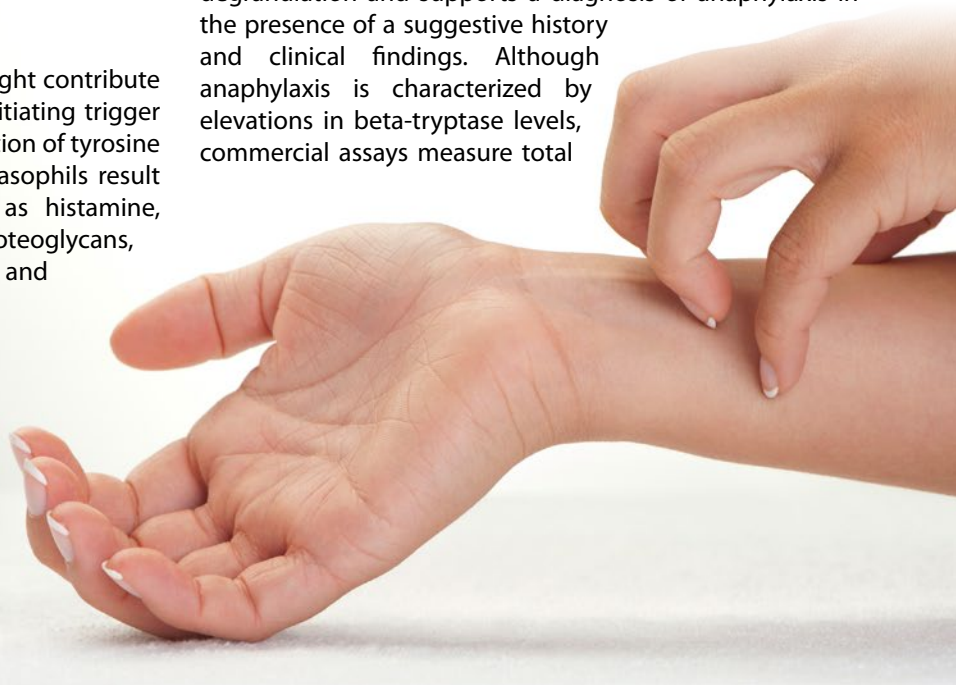
Clinical diagnosis is based on a meticulous history of an exposure or event precedingcharacteristic symptoms and signs. (see *TABLE 1*)

Among individuals recognized as having anaphylaxis, target organs include skin (90% of episodes), respiratory tract (70%), gastrointestinal tract (30% to 45%), cardiovascular system (10% to 45%), and central nervous system (CNS; 10% to 15%). (see *TABLE 2*)

Laboratory tests

Currently, histamine and total tryptase are the only biomarkers measured in clinical laboratories. These tests have limitations, including suboptimal specificity and sensitivity, when used to confirm the diagnosis of an acute anaphylaxis episode.(1)

An elevated serum tryptase level 1 to 6 hours after a suspected anaphylactic reaction indicates mast cell degranulation and supports a diagnosis of anaphylaxis in the presence of a suggestive history and clinical findings. Although anaphylaxis is characterized by elevations in beta-tryptase levels, commercial assays measure total



tryptase. Serum tryptase concentration may, however, be normal even in fatal anaphylaxis. (7)

Plasma histamine levels peak at 15 to 30 minutes and return to baseline values within 1 hour of the onset of anaphylaxis. Although of limited use, measurement of plasma histamine concentration within minutes of a possible anaphylactic reaction may be helpful diagnostically in some patients.

Management

Rapid assessment of airway, breathing, circulation, and mental status is mandatory. Initial stabilization includes administration of supplemental oxygen, establishment of an airway, insertion of 1 or more large-bore intravenous lines for fluid replacement. Prompt intramuscular injection of epinephrine is lifesaving.

Epinephrine's life-saving alpha 1-adrenergic vasoconstrictor effects prevent and relieve upper airway obstruction caused by mucosal edema and prevent and relieve shock. The recommended epinephrine dose in acute anaphylaxis is 0.01 mg/kg, to a maximum adult dose of 0.5 mg.

H1-antihistamines, H2-antihistamines, glucocorticoids and inhaled beta 2-adrenergic agonists can be given but cannot be dependent on to prevent fatality.

To date, no randomized controlled trials have been conducted for any of the pharmacologic interventions used to treat anaphylaxis.

All published national anaphylaxis guidelines agree that epinephrine is fundamental to acute management, although they do not agree on the initial dose or route of injection of epinephrine.(8)

Summary

Anaphylaxis is potentially fatal condition. Prompt recognition and treatment is mandatory.

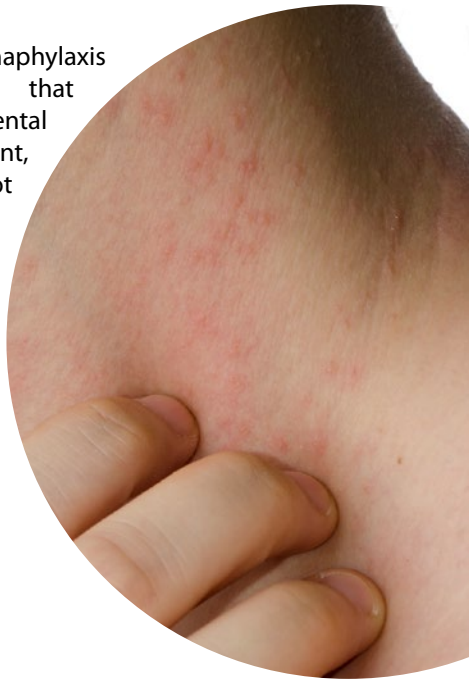


TABLE 1: Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, and swollen lips-tongue-uvula) AND at least 1 of the following: A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow rate, hypoxemia) B. Reduced BP or associated symptoms of end-organ dysfunction (eg, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen (minutes to several hours): A. Involvement of the skin–mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow rate, hypoxemia) C. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) D. Persistent gastrointestinal symptoms (eg, cramping abdominal pain, vomiting)
3. Reduced BP after exposure to a known allergen (minutes to several hours): A. Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP* B. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Adapted from (Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy ClinImmunol 2006;117:391-7.)
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg 1 [2 3 age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80 to 140 beats/min at age 1 to 2 years, from 80 to 120 beats/min at age 3 years, and from 70 to 115 beats/min after age 3 years. Infants and young children are more likely to have respiratory compromise than hypotension or shock.

TABLE 2: Symptoms and signs of anaphylaxis

Cutaneous / Subcutaneous / Mucosal tissue Flushing, pruritus, urticaria, swelling, morbilliform rash Periorbital pruritus, erythema and swelling of lips, tongue, uvula/palate, conjunctival erythema, tearing
Respiratory Nose: pruritus, congestion, rhinorrhea, sneezing Larynx: pruritus and tightness in the throat, dysphonia and hoarseness, dry cough, stridor, dysphagia Lung: shortness of breath, chest tightness, cough, wheezing/ bronchospasm (decreased peak expiratory flow)
Cyanosis Gastrointestinal Nausea, cramping abdominal pain, vomiting , diarrhea
Cardiovascular Chest pain, palpitations, tachycardia, bradycardia, or other dysrhythmia Hypotension, shock, cardiac arrest
CNS dizziness, confusion

Reference

1. 12009 American Academy of Allergy, Asthma and Immunology.doi:10.1016/j.jaci.2009.08.025
2. Simons FER, Frew AJ, Ansotegui IJ, Bochner BS, Finkelman F, Golden DBK,et al. Risk assessment in anaphylaxis: current and future approaches. J Allergy ClinImmunol 2007;120:S2-24
3. Simons FER. Anaphylaxis, killer allergy: long-term management in the community.J Allergy ClinImmunol 2006;117:367-77.
4. Lieberman PL. Anaphylaxis. In: Adkinson NF Jr., Bochner BS, Busse WW, HolgateST, Lemanske RF Jr., Simons FER, editors. Middleton's Allergy: Principlesand Practice. 7th ed. St Louis: Mosby, Inc; 2009. p. 1027-49.
5. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactionsto food in children and adolescents. N Engl J Med 1992;327:380-4.
6. Celik W, Pichler WJ, Adkinson NF Jr. Drug allergy. In: Adkinson NF Jr., BochnerBS, Busse WW, Holgate ST, Lemanske RF Jr., Simons FER, editors. Middleton'sAllergy: Principles and Practice. 7th ed St Louis: Mosby.
7. Ann Allergy Asthma Immunol. 2004;92:619– 628
8. Alrasbi M, Sheikh A. Comparison of international guidelines for the emergencymedical management of anaphylaxis. Allergy 2007;62:838-41.

PRESENTATION
RECAP AT CME

Updates on Targeted Therapy for Cancer Management

16th April 2013

Dr. Choi Ho Keung, Peter
Specialist in Clinical Oncology

Targeted Therapy of Breast Cancer

The first molecular target for breast cancer therapy was the estrogen receptor. Tamoxifen, Aromatase inhibitors (AI) and ER-degrading agents improve survival both in women with early and advanced disease. In the meta-analysis performed by EBCTCG , 5 years of tamoxifen reduce the recurrence and mortality by 12% and 9 % respectively. Several randomized phase III trial comparing AI's (anatrozole, latrozole and exemestane) with tamoxifen in adjuvant setting demonstrated significant improvement in DFS. Unfortunately, the long term efficacy of hormonal therapy in advanced disease is limited by the eventual development of resistance of the tumour cells. In preclinical studies mTOR inhibitors such as everolimus may be able to overcome resistance to hormonal treatment in ER+ patients. In a phase III trial, patients with ER+ve breast cancer resistant to non-steroidal AI, everolimuswas found to have a PFS of 6.9 month as compared to 2.8 months with placebo only.

Approximately 25% of the breast cancer patients have tumours that overexpressed HER2. This group of patient has significant poorer prognosis and overall survival.

Currently there are several agents including monoclonal antibodies and small molecule, tyrosine kinase inhibitors approved by FDA in the treatment of HER2 over expressed breast cancer.

Trastuzumab is a humanized, monoclonal antibody, that binds to the HER2 receptor. Monotherapy with Trastuzumab in patient with HER2 overexpression yielded a response rate of 21%. Randomized trials comparing combination of Trastuzumab with chemotherapy versus chemotherapy alone demonstrated a significant overall survival improvement (25.1 months vs. 20.3 months, p = .05).

Addition of the Trastuzumab to combination chemotherapy in adjuvant therapy showed significantly improvement in DFS and overall survival in early breast cancer patient with HER2 overexpression. The combined result of the US studies showed an absolute gain of 13.9% in DFS and 8.8% in overall survival with a median follow up of 8 years. In HERA study when trastuzumab was given sequentially after adjuvant chemotherapy for one year, the absolute gain in DFS was 6.9%.

Lapatinib is a small molecule tyrosine kinase inhibitor that is administered orally. In a randomizedtrial comparing Laptinib combined with capecitabine against capecitabine alone in patients with locally advanced or metastatic disease progress after treatment that included anthrocyclines, taxanes, and trastuzumab showed a significant improvement in DFS (8.4 months vs. 4.4 months, $p < 0.001$), but there was no difference in overall survival (HR 0.92; $p = 0.72$).

Pertuzumab is a humanized, monoclonal antibody that binds to a different epitope at the HER 2 extracellular domain than trastuzumab. In the Phase III CLEOPATRA trial, the efficacy and safety of pertuzumab plus trastuzumab plus doectaxel versus placebo plus trastuzumab and doectaxel in first line HER2 positive metastatic setting was assessed. The median PFS of the study group was 18.5 months against 12.4 months in the placebo group. There was no increase in cardiac toxicity in the pertuzumab combination arm.

Ado-Trastuzumab Emtansine(TDM-1) is an antibody-drug conjugate incorporate trastuzumab and cytotoxic drug DM 1. This drug has shown to have activity in Her2 overexpressed breast cancer with favorable safety profile and already approved by FDA for the treatment of metastatic HER2 overexpressed breast cancer.

Targeted Therapy for Colorectal Cancer

Dr. Yau Tsz Kok
Specialist in Clinical Oncology

In contrast to the rather limited choice of chemotherapeutic agents, there are at least five targeted drugs (bevacizumab, cetuximab, panitumumab, regorafenib and aflibercept) that have been approved for colorectal cancers (CRC) in the last decade and still more agents are in the pipeline. These drugs interfere with specific pathways involved in cancer cell growth or survival and have a very different toxicity profiles from that of chemotherapy. Despite their promising potential, they still have no proven role in the adjuvant treatment of CRC. They are solely used in metastatic or recurrent CRC and largely supplementing rather than replacing the standard fluoropyrimidine-based chemotherapy.

The molecular targets of these drugs can be broadly divided into three categories:

1. Vascular endothelial growth factor (VEGF): Bevacizumab, Aflibercept
2. Epidermal growth factor receptor (EGFR): Cetuximab, Panitumumab
3. Multiple pathways: Regorafenib

Bevacizumab, a recombinant humanised monoclonal anti-VEGF antibody, inhibits angiogenesis by binding directly to VEGF and prevents its interaction with VEGF receptors and activation of downstream signalling pathways. Phase III studies (AVF2107g) have shown that the addition of bevacizumab to first-line irinotecan-based chemotherapy will improve both the overall survival (OS)(HR: 0.66; P < .001) and progress-free survival (PFS)(HR: 0.54; P < .001). Similar benefits have been shown in its combination with oxaliplatin-based chemotherapy in either first-line or second-line setting. So far no biomarkers have been identified to predict the clinical benefit of bevacizumab. Hence, unless there are medical contraindications, it can be considered in all metastatic CRC patients.

Aflibercept is a new class of anti-angiogenetic agent. Its approval in 2012 is based on a randomized double-blind placebo-controlled trial that enrolled metastatic CRC patients whose disease progressed after oxaliplatin-based combination chemotherapy. However, its OS and PFS benefits of 1.5 months are rather modest.

Cetuximab is a chimeric IgG1 monoclonal antibody that binds to the extracellular domain of epidermal growth factor receptor (EGFR), blocks the downstream ligand-induced receptor signaling and modulates tumour proliferation. Although overexpression of EGFR is very common in CRC, cetuximab is not useful in around 40% patients who have *K-ras* mutation since this signal growth pathway will be active regardless of the EGFR activation. Hence determination of tumour *ras* mutation status is essential before considering this targeted agent. For *K-ras* wild-type patients, randomized study (CRYSTAL) showed the addition of Cetuximab to first-line irinotecan-based chemotherapy would increase the response rate from 43% to 59% (p=0.0025) and extend the PFS (HR 0.68, p=0.017). Its clinical benefit has also been demonstrated in the second and third line setting. Acneform rash will develop in 80% patients receiving Cetuximab and, interestingly, a rash of grade 2 or higher is strongly associated with improved survival. Panitumumab works similarly as Cetuximab but has much less infusion reaction due to its fully humanized nature. Recent studies showed tumours with *RAS* mutations beyond *K-ras* also do not benefit from Panitumumab and hence additional testing of mutant *RAS* (including NRAS) is now recommended.

Regorafenib is an oral multikinase inhibitor targeting multiple tumor pathways. It is currently only approved for patients with metastatic colorectal cancer that fail all standard therapy.

For patients with *RAS* wildtype, the optimal sequence in employing EGFR-antibodies and VGEF-antibodies remain controversial. In general, for patients with potentially resectable liver-limited disease, EGFR-antibodies are more preferable as they may give better tumour shrinkage before surgery. Otherwise, bevacizumab is often used in combination with first-line chemotherapy due to its better toxicity profile and slightly lower cost; EGFR-antibodies can then be reserved in the second or third line setting.

Targeted Therapy for Lung Cancer

Prof. Sham Shun Tong, Jonathan
Specialist in Clinical Oncology

There were major advances in all treatment modalities for lung cancer, these include minimally invasive surgery, 3rd generation chemotherapy, high precision radiotherapy, and targeted therapy (which was the latest development in the past decade).

The role of targeted therapy for lung cancer is mainly limited to advanced cases of adenocarcinoma, targeted therapy has no role in the management of early cases of lung cancer, treatment of such cases is radical surgery with or without adjuvant chemotherapy, and for the more advanced cases when surgery is not feasible (stage IIIA and some stage IIIB cases), treatment is radical chemoradiotherapy. Targeted therapy has minimal role in treatment of small cell lung cancer and squamous carcinoma. There is some early evidence that Avastin may improve response of small cell lung cancer to chemotherapy. Squamous carcinoma of lung are usually not associated with EGFR nor ALK gene mutation, and use of Avastin in squamous carcinoma is associated with increased risk of hemorrhage.

There are 4 groups of targeted drugs for lung cancer: epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) which are given orally (namely Iressa and Tarceva); antibody against EGFR (namely Erbitux);anti-angiogenesis agent (namely Avastin); and protein kinase inhibitor for anaplastic lymphoma kinase (ALK) fusion gene (namely Crizotinib).

For Iressa, Tarceva and Crizotinib, they are particularly effective in patients with the corresponding driver mutation in the cancer cells (EGFR gene mutation for Iressa and Tarceva, ALK fusion gene for Crizotinib, and biomarker to predict good response to these agents are the corresponding gene mutation or gene fusion).

Iressa and Tarceva has been shown to produced better progression-free survival, overall survival, and quality of life than chemotherapy when used as first line treatment for metastatic or recurrent lung cancer patients with EGFR gene mutation. Iressa and Tarceva when used as maintenance after completion of 4 to 6 courses of chemotherapy produce better progression-free survival than placebo.

Both Iressa and Tarceva are able to penetrate blood-brain-barrier to control brain metastases from lung cancer. Because of the poor penetration (less than a few percent), for patient with prolonged control using EGFR TKI, the brain is a common site of progression.

For patients who progressed after initial response to EGFR TKI, after control using chemotherapy for some time, some of these patients can respond to EGFR TKI re-challenge.

Both Avastin and Erbitux (Cetuximab) are used in combination with chemotherapy, and will improve the progress-free survival and overall survival of advanced lung cancer patient. There is no biomarker to predict better response to these agents.

Crizotinib when used in advanced or recurrent lung cancer patients with ALK gene re-arrangement, will produce better progression-free survival and quality of life when compared with use of chemotherapy.

CME Announcement

Topic	Chairman	Speakers
17/09/2013 **Metabolic Disease in Hong Kong** 1. Cardiac Arrest in a Newborn 2. Expanded Newborn Screening in Hong Kong	*Dr. Sylvia Doo* Specialist in Paediatrics, St. Paul's Hospital	1. *Dr. Yuen Kar Ngai, Robert* Specialist in Paediatrics 2. *Prof. Lam Ching Wan* Specialist in Pathology, The University of Hong Kong

Time: 7:30pm - 9:00pm (Light Refreshment Provided at 7:00pm)
Venue: Conference Room, 2/F, St. Paul's Convent
Registration: Ms. Sally Pun, Tel: 2830 3905, Fax: 2837 5271, Email: sph.sdd@mail.stpaul.org.hk
CME/ CPD Accreditation for all colleges (Pending approval). CNE Point: 1 Point

與鼻鼾聲講Bye Bye

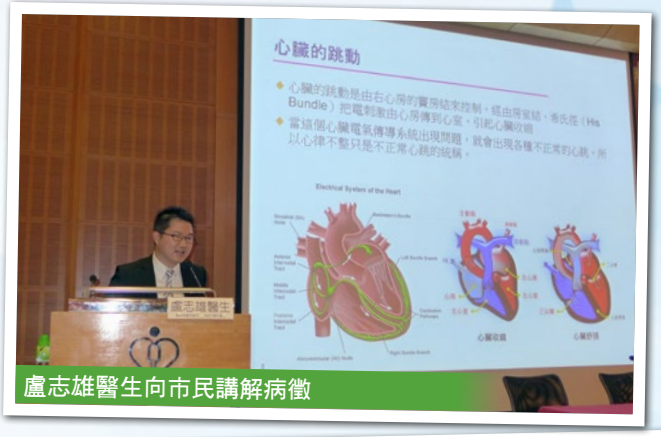
(08/06/2013)

本院耳鼻喉專科陳鍵明醫生獲香港各界婦女聯合協進會之邀請，於二零一三年六月八日在香港婦協郭得勝服務中心舉行之健康講座擔任嘉賓講者，講座之主題為「與鼻鼾聲講Bye Bye」。陳醫生耐心地向參加者講解有關睡眠窒息症對身體的影響，市民獲益良多。

陳鍵明醫生與香港婦協會員拍照留念

聖保祿醫院執行董事張柱見修女接受香港婦協創會主席林貝聿嘉所送贈之感謝狀


市民耐心聆聽講座



盧志雄醫生向市民講解病徵

心房纖顫與缺血性中風

(27/07/2013)

「關心你的心」心臟病友互助組織於二零一三年七月十七日邀請了本院腦神經專科盧志雄醫生為病友及公眾人士舉行心臟病及中風之健康講座，主題為「心房纖顫與缺血性中風」。當天出席人數多達二百人。於問答環節部份，參加者十分踴躍，盧醫生耐心地一一作答，令市民對此疾病有更多的認知，以提高警覺。


健康講座多達二百名市民參加

問答環節市民反應熱烈，盧醫生耐心作答

OUTREACH
ACTIVITIES

澳門外展健康檢查日
(28/7/2013)

除熱心服務本港居民外，本中心的外展活動更遍及澳門。於七月二十八日，本中心與澳門社會服務中心合辦健康檢查服務，多達三十五名本院熱心醫護人員、修女、醫生及義工參與。沙爾德聖保祿女修會何美蘭省會長、聖保祿醫院醫務總監何兆煒醫生及聖保祿醫院總經理梁兆鏘先生亦前往澳門出席，全力支持此活動。

義工們除替超過二百名澳門街坊及長者量度血壓及骨質密度測試外，亦替百多名市民提供眼科檢驗及血液檢驗，包括膽固醇及血糖。當日更有數十名市民進行超聲波檢查，包括肝膽腎超聲波掃描、頸動脈及盤腔超聲波檢查。


修女及義工們為市民量度血壓及血液檢驗

本院管理層接受澳門社會服務中心頒發感謝狀

舉辦單位大合照


修女及醫生為市民量度骨質密度

本院放射科醫生、醫護人員、眼科醫生及義工代表接受感謝狀