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Editorial

In the feature article of the current issue, the author described the rationale and current management paradigm for early-stage breast cancer. Following such multidisciplinary management, the vast majority of early-stage breast cancer patients are cured of their disease. These encouraging results are based on painstaking collaborative work involving countless laboratory researchers, academic clinicians and community oncologists over many years. Through carefully designed clinical trials involving thousands of patients, incremental improvement in cancer patient survival has been achieved.

The principles of cancer management has evolved from empiricism to evidence-based medicine, whereby rational personal choices of treatment are made by patients together with their physicians. While early stage-breast cancer can now be successfully managed, advanced metastatic breast cancer is largely incurable and associated with shortened lifespan. Recent advances in molecular genetics have clearly demonstrated that cancer is the end result of cumulative and multiple genetic or epigenetic mishaps, resulting in dysregulated growth and proliferation of an abnormal clone of cells. New pharmaceuticals that target such abnormal gene products and related aberrant cell proliferation and signalling pathways have revolutionized the systemic treatment of multiple haematologic and solid malignancies. We now stand at the dawn of an era where cancer is no longer considered an inevitable death sentence, but one of many degenerative disorders which can be controlled with relatively nontoxic medications for years on end.

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Life is so good! Thank you

Dear Doctor,

Life is so good since I got the all clear. Thank you so much for giving me the opportunity to beat my breast cancer.
it was easier to cope with than I imagined. Thank you.

Dear Doctor,

After hearing I had cancer, the idea of chemotherapy was really scary. However, it was easier to cope with than I imagined.
Management of Early-stage Breast Cancer

Breast cancer is the major cause of cancer deaths among Hong Kong women, and its incidence continues to rise. In the US, despite increasing incidence, the rate of breast cancer death has decreased by 2% every year during 1990–2000. This success has been equally attributed to early diagnosis through screening mammography in the community, and to more effective treatment of early breast cancer. Indeed, effective implementation of multidisciplinary treatment remains the best option to reduce breast cancer mortality.

Management of Ductal Carcinoma in Situ – Stage 0

Early breast cancer ranges from stages 0 to 2, in which cancer is still clinically localized and the systemic burden of micrometastases is still low enough to be eradicated by effective systemic treatment.

Breast cancer develops along a continuum of histological changes, from hyperplasia to dysplasia, eventually resulting in ductal carcinoma in situ (DCIS) and then frank carcinoma. (Figure 1) Accumulating along the way are multiple genetic changes, which cause aberrant cell growth, proliferation, and apoptosis. If left untreated, 30%–40% of DCIS will eventually develop into invasive cancer.

DCIS accounts for up to 20% of cancer detected in community screening programmes, usually occurring as suspicious microcalcifications. The objective of treatment of DCIS is therefore to achieve local control by either total mastectomy (which almost always results in a cure) or lumpectomy to clear margins followed by radiotherapy. Axillary lymph nodes can be sampled in cases of large tumours or high grade histological features, as 15% of such cases may harbour microinvasive elements.

Management of Stage I and II Cancer

Local Management
The goal of local management (ie, surgery and radiotherapy) is eradication of local disease and prevention of recurrence in the remaining breast and chest wall. Since breast tumours diagnosed through screening nowadays are smaller in general, surgical procedures are becoming less radical and mutilating. In most cases, lumpectomy followed by breast radiotherapy has supplanted total mastectomy, resulting in better cosmesis. Mature 20-year survival data from randomized clinical trials comparing the two surgical approaches showed absolutely no difference in either overall survival or metastatic rates. With careful attention to achieving clear surgical margins and radiation dosage, in-breast recurrence can be kept below 10%.

At present, conservative breast-preserving surgery can be considered for all patients in whom the tumour’s location and size relative to the breast allow favourable postoperative cosmesis. In addition, well-designed clinical studies have shown that the first echelon sentinel lymph nodes in the axilla accurately represent the status of residual axillary lymphatics, so that patients with negative sentinel lymph nodes (70%–80% of patients) can be spared the consequences of a full axillary lymph node dissection which can result in lymphoedema and arm weakness.

Systemic Management
The use of different types of pharmacotherapies not only decreases local recurrence, but more importantly may eradicate distant micrometastases, and thereby increase cure rates. Such therapies now include hormonal, chemical and biologic agents.

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Systemic Management
The use of different types of pharmacotherapies not only decreases local recurrence, but more importantly may eradicate distant micrometastases, and thereby increase cure rates. Such therapies now include hormonal, chemical and biologic agents.
**Adjuvant Hormonal Therapy**
Adjuvant hormonal therapy should be considered for all breast cancer patients with positive oestrogen or progesterone receptor status. Tamoxifen (a selective oestrogen receptor modulator) given for 5 years after surgery reduces the risks of recurrence by 47% and death by 26%, irrespective of menstrual or nodal status.6

Recent clinical trials have shown that aromatase inhibitors (AIs), another class of hormonal agents which block the conversion of androgen to oestrogen in the body, are more effective than tamoxifen in postmenopausal women with breast cancer. This added benefit can be achieved either by substituting tamoxifen with an AI from the start, or by switching to an AI after 2 to 3 years of tamoxifen.6,7 Since there is a continuing risk of relapse even after 5 years of tamoxifen, adding an AI for an additional 5 years after tamoxifen can further reduce relapse and the risk of cancer deaths.8 Prolonged adjuvant hormonal therapy should therefore be considered for higher-risk patients with positive lymph nodes.

**Adjuvant Chemotherapy**
Adjuvant chemotherapy has been used in node-positive breast cancer patients since the 1970’s. Long-term results indicate a 23.5% reduction in recurrence and 15.3% reduction in cancer death.9 Initial trials utilized regimens such as CMF (cyclophosphamide, methotrexate and 5-FU) for up to 12 months. The addition of anthracyclines (doxorubicin, epirubicin) in newer regimens such as AC (cyclophosphamide and doxorubicin) or FEC (5-FU, epirubicin and cyclophosphamide) has improved efficacy by 10% and shortened treatment to 4–6 months. The taxanes (paclitaxel, docetaxel) were introduced into adjuvant trials in the 1990’s and showed additional benefits, so that current chemotherapy regimens usually combine taxanes and anthracyclines either concurrently or sequentially for 6–8 cycles over 4–6 months.10

**Adjuvant Biologics**
Twenty to thirty percent of breast cancer carries a cell surface receptor called epidermal growth factor receptor 2 (HER2). Such cancers are inherently more aggressive and carry a worse prognosis.

Trastuzumab is a monoclonal antibody that antagonizes HER2 and neutralizes this malignant potential. In clinical trials, the use of trastuzumab in combination with chemotherapy was more effective than chemotherapy alone. In the adjuvant setting, 1 year of trastuzumab either concurrently with or sequentially after chemotherapy has resulted in a 50% risk reduction in the composite event of relapse, second primary cancer and death.11-13 However, trastuzumab does carry a slight temporary risk of cardiac dysfunction, and should not be used

| Table 1. Definition of risk categories for patients with operated breast cancer |
|---------------------------------|----------------------------------|
| **Low risk**                    | **Node negative and all of the following features:** |
|                                 | • pT ≤2 cm; and                        |
|                                 | • Grade 1; and                        |
|                                 | • Absence of peritumoural vascular invasion; and |
|                                 | • HER2/neu gene neither overexpressed nor amplified; and |
|                                 | • Age ≥35 years                       |
| **Intermediate risk**           | **Node negative and at least one of the following features:** |
|                                 | • pT >2 cm; or                        |
|                                 | • Grade 2–3; or                       |
|                                 | • Presence of peritumoural vascular invasion; or |
|                                 | • HER2/neu gene overexpressed or amplified; or |
|                                 | • Age <35 years                       |
| **Node positive (1–3 involved nodes) and:** | **HER2/neu gene neither overexpressed nor amplified** |
| **Node positive (4 or more involved nodes) and:** | **HER2/neu gene overexpressed or amplified** |

HER2 = epidermal growth factor receptor 2; pT = pathological tumour size

<table>
<thead>
<tr>
<th>Figure 2. Recurrence score vs distant recurrence in node-negative, negative, and oestrogen receptor-positive breast cancer</th>
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<tbody>
<tr>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td>Group average: 7%</td>
</tr>
<tr>
<td>(95% CI: 4%–12%)</td>
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<tr>
<td><strong>Intermediate risk</strong></td>
</tr>
<tr>
<td>Group average: 14%</td>
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<tr>
<td>(95% CI: 8%–20%)</td>
</tr>
<tr>
<td><strong>High risk</strong></td>
</tr>
<tr>
<td>Group average: 31%</td>
</tr>
<tr>
<td>(95% CI: 24%–37%)</td>
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*For reference scores >50, group average rate of distant recurrence and 95% CI shown.*
concurrently with other cardiac-toxic agents such as anthracyclines.

**Choice of Systemic Adjuvant Therapy in Early Breast Cancer**

The choice of systemic adjuvant therapy is based on a rational and careful consideration of individual recurrence risk and biological characteristics of breast cancer. The risk of recurrence and death is primarily based on the stage of disease (usually defined by size and number of positive lymph nodes). The efficacy of systemic treatment is defined by the presence or absence of breast cancer targets, namely hormonal and HER2 receptors.

International experts have reached consensus and formulated adjuvant treatment paradigm based on risk classification into low, intermediate and high categories. (Table 1) While low-risk patients may require no adjuvant therapy or hormonal agents only, most intermediate- and high-risk patients may require chemotherapy to improve the likelihood of survival.

As hormonal agents have been shown to improve survival in almost all breast cancer patients with positive hormone receptors irrespective of nodal and menopausal status, its use is advocated in almost all stages of such cancer. One year of trastuzumab therapy should be considered in all HER2-positive patients at intermediate or high risk of relapse.

Among patients with hormone receptor-positive tumour and negative axillary lymph nodes, there is a wide spread of recurrence risk from 5% to 30%. Recently, a 21-gene assay (Oncotype) has become available to provide a better molecular profile and risk assessment, so that such patients can be more accurately segregated into low or higher recurrence scores whereby chemotherapy will be administered only to the higher-risk individuals.14 (Figure 2)

Extension of these clinical trial results to bedside patient care has led to markedly improved survival in early-stage breast cancer. Nowadays, even with node-positive disease, 75% to 85% of breast cancer patients can enjoy recurrence-free survival at 5 years.

**References:**


A complete list of references can be downloaded from www.SOPHYSICIANSHK.org
Herceptin is the foundation of care in women with HER2-positive breast cancer.

**Minimum Product Information**

**Herceptin (trastuzumab):** Powder for Concentrate for Infusion - 150 mg single dose vial & 440 mg multidose vial (with solvent)

**Indications:** HER2-positive patients with: (i) metastatic breast cancer (MBC), either as monotherapy following at least 2 CT regimens; or in combination with paclitaxel for patients who have not received chemotherapy (CT); or in combination with docetaxel for patients who have not received CT; or in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone receptor-positive MBC, or (ii) early breast cancer (EBC) following surgery, CT (neoadjuvant) and radiotherapy (if applicable); or (iii) metastatic gastric cancer (MGC) in combination with capecitabine or S-1 and lapatinib.

**Dosage & Administration:** Please refer to Herceptin PI for full guidance. HER2 testing mandatory. EBC/MBC/MGC - 3 weekly loading dose: 8mg/kg; subsequent doses: 6mg/kg repeated at 3-weekly intervals; EBC weekly: loading dose - 4mg/kg; subsequent doses: 2mg/kg weekly. Administer as IV infusions over approx. 90 min. Infusion time reduced to 30 min for subsequent doses if initial loading dose was well tolerated. Do not administer as an IV push or bolus. Observe for infusion-related symptoms. In MBC or MGC, treat until disease progression. Patients with EBC should be treated for 1 year or until disease recurrence.

**Contraindications:** Known hypersensitivity to trastuzumab or any excipients.

**Warnings & Precautions:** Discontinue Herceptin infusion in case of serious adverse reactions. Patients experiencing dyspnoea at rest may be a risk of fatal infusion reactions or severe pulmonary reactions. Infertile lung disease may occur as part of an infusion-related reaction or with a delayed onset. Heart failure has been observed. Caution in patients with symptoms of heart failure, history of hypertension or documented coronary artery disease and in EBC, in those patients with an LVEF ≤<55%. Conduct patients should undergo baseline cardiac assessment and risk-benefit assessment. Monitor cardiac function during treatment. Consider discontinuing treatment in patients whose LVEF has not improved or declined further, or in patients who develop clinically significant heart failure unless benefits outweigh risks. Safety of continuation or resumption in patients experiencing cardiotoxicity has not been studied. Benzoic alcohol contained in the solvent for 440mg vial. Caution for use in pregnancy as oligohydramnios has been reported. Avoid breast feeding during therapy. Not recommended for children <18 years old.

**Undesirable Effects:** For full listings please refer to the Herceptin PI. MBC: Common adverse reactions: abdominal pain; anemia; chest pain; chills; fever; headache; pain, diarrhoea; nausea, vomiting; arthralgia; myalgia; rash. MGC: Common adverse reactions: Nausea, vomiting, diarrhoea; constipation; stomatitis; abdominal pain; neutropenia, anemia; thrombocytopenia; fatigue; anemia; pyrexia; mucosal inflammation; anemia; palmar-plantar erythrodysesthesia syndrome; dizziness, weight decrease, renal impairment. NCCN, otitis & nasopharyngitis. Post Marketing - refer to package insert.

**Date of preparation:** November 2010

**Full prescribing information should be viewed prior to prescribing.**
Atypical Femoral Fractures and Bisphosphonates: New Aspects

Introduction

Osteoporotic fractures are a major public health concern worldwide. Oral bisphosphonates have been used as a first-line agent for prevention and treatment of osteoporotic fractures. Recent interest has centred on clinically observed, unusually sited subtrochanteric and femoral diaphyseal fractures associated with the use of bisphosphonates. Occurrence of these unusual fractures has raised concern over long-term use of bisphosphonates. This paper tries to summarize current understanding of these atypical fractures with bisphosphonates and the recommendation on prevention of these fractures.

Clinical Features of Atypical Femoral Fractures

Oral bisphosphonates have become a mainstay of treatment, but concerns have emerged that their long-term use may suppress bone remodelling to the degree that bone turnover becomes insufficient to maintain skeletal strength, leading to unusual fractures. Since the first case series from Singapore in 2007, a number of bisphosphonate-associated atraumatic fractures at the subtrochanteric and femoral diaphyseal region have been published. Characteristics of those fractures include prodromal thigh pain a few weeks to 2 years prior to the fracture, complete absence of trauma precipitating the fracture, and bilateral fractures in some patients. The diaphyseal fractures exhibited a characteristic fracture pattern of thickened lateral cortices at the proximal fracture fragment, and all had either transverse or short oblique fractures. (Figure 1)

Among all femoral fractures, the overall incidence of subtrochanteric and shaft fractures combined is below 30 per 100,000 person-years. Thus, this type of fracture is much less common than proximal femur (hip) fracture. Furthermore, the unique “atypical” fracture type is a subset of all subtrochanteric and femoral shaft fractures. The number of atypical fractures in association with bisphosphonates is estimated to be one per 1,000 per year. A local retrospective study at a regional hospital demonstrated an increased incidence of atypical fractures in the past 5 years, from 0% in 2003–2004 to 25% in 2007/2008. This increasing trend coincides with the increasing use of bisphosphonates over the time of the study, but could not really demonstrate a causal relationship with bisphosphonate use.

Risk Factors for Atypical Fractures

The putative mechanism of atypical fractures is unknown, and the duration of bisphosphonate use in the published reports and case series varies from 1 to 10 years. Retrospective analyses of phase III trials of bisphosphonates, however, do not show an increased risk of subtrochanteric fractures with bisphosphonate use. Park-Wyllie et al recently conducted a population-based, nested case-control study to explore the association between bisphosphonate use and fractures in a cohort of elderly women treated with an oral bisphosphonate. Compared with transient bisphosphonate use, treatment for 5 years or longer was associated with a 2.74-fold increased risk of subtrochanteric or femoral shaft fracture. A reduced risk of typical osteoporotic fractures was found among women with more than 5 years of bisphosphonate use.

Key words: Atypical fractures (非典型骨折), bisphosphonates (雙磷酸鹽)
therapy (adjusted odds ratio, 0.76; 95% confidence interval, 0.63–0.93). Among 52,595 women with at least 5 years of bisphosphonate therapy, a subtrochanteric or femoral shaft fracture occurred in 71 (0.13%) during the subsequent year, and in 117 (0.22%) within 2 years. These results suggested that among older women, treatment with a bisphosphonate for more than 5 years was associated with an increased risk of subtrochanteric or femoral shaft fractures; however, the absolute risk of these fractures is low compared to the much reduced risk of typical osteoporotic fractures.

Vestergaard et al conducted a nationwide cohort study in Denmark in all users of bisphosphonates and other drugs against osteoporosis during 1996–2006 (n=103,562) as the exposed group, and three age- and gender-matched controls from the general population (n=310,683). They observed a 2.41-fold increased risk of subtrochanteric fractures with alendronate. Increased risk was also observed with etidronate and clodronate, but not with raloxifene. However, an increased risk of subtrochanteric fractures of two- to 10-fold was also present before the start of alendronate, etidronate, clodronate, raloxifene, and strontium ranelate. Similar trends were seen for femoral shaft fractures and overall fracture risk. Although an increased risk of femoral shaft fractures and subtrochanteric fractures were seen with the use of several types of bisphosphonates, the increased risk before the start of the drugs may point at an effect of the underlying disease being treated. The increased risk may therefore be due to confounding by indication rather than the use of bisphosphonates.

Giusti et al reviewed all published case reports and case series, and identified the use of glucocorticoids and proton pump inhibitors as important risk factors of atypical subtrochanteric fractures, but they were unable to give insights into the pathogenesis of these fractures. It is of interest that many of these patients had no bone mineral density scans prior to their fractures, and were started on bisphosphonates without any clear clinical indication. Although it was postulated that the cause of these fractures might be related to over suppression of bone turnover, many of those with available data showed normal biochemical markers of bone turnover.

The Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis and the International Osteoporosis Foundation have recently reviewed the evidence for a causal association between subtrochanteric fractures and long-term treatment with bisphosphonates. The association remains unproven, and more research is needed. Were the case to be proven, the risk-benefit ratio still remains favourable for the use of bisphosphonates to prevent fractures. Although the pathology of these fractures remains unclear, it has to be appreciated that effects may differ with each bisphosphonate’s route of administration and residual activity after discontinuation.

Conclusion

In conclusion, there is no rationale to withhold bisphosphonate therapy from patients with osteoporosis, although continued use of bisphosphonate therapy beyond a treatment period of 3 to 5 years should be re-evaluated annually. To prevent these atypical fractures, current strategies include annual review of fracture risk in patients on bisphosphonates, targeting bisphosphonates appropriately to individuals at increased risk of fracture. Whether a drug holiday in clinically stable patients whose BMD T score is above -2.0 is effective in preventing atypical fractures without compromising the prevention of typical osteoporosis fractures remains to be proven.

References


Journal Report – Lithium Delays Cognitive Decline

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Following previous reports from clinical and animal studies that lithium may delay the progression of Alzheimer’s disease (AD) symptoms and pathology, a new study by Orestes V. Forlenza, MD, PhD from the University of San Paulo, Brazil provided further support for the hypothesis.

Forty-one patients aged >60 suffering from amnestic mild cognitive impairment (aMCI) without psychiatric illness were randomized to receive lithium (n=21) or placebo (n=20) for 12 months. Progression of cognitive deterioration was tracked with the Clinical Dementia Rating Scale including the sum of boxes score, and the Alzheimer’s Disease Assessment Scale – cognitive subscale. Memory, attention, and executive function were evaluated using the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) delayed recall test, Sequence of Letters and Numbers (SLN) and Trail Making tests. Laboratory tests included total and phosphorylated tau (p-tau) in cerebrospinal fluid. Secondary outcomes included conversion from aMCI to AD.

At the end of the study, all participants experienced a decline in memory and cognitive function. The decline was significantly less in the lithium group. Patients in the treatment group had a decrease in p-tau, while those in the placebo group had an increase.

There was also a non-significant higher conversion to AD in the control group.

Lithium is postulated to work via inhibition of the GSK-3B enzyme.

New Data

VIBE Study

Monthly BONVIVA® vs weekly bisphosphonates
In elderly patients (aged ≥65 years old)*

Vertebral
- Significantly lower in BONVIVA group by 72% (p=0.030)

Hip
- Comparable

Nonvertebral
- Comparable

Any clinical
- Significantly lower in BONVIVA group by 35% (p=0.033)

Unadjusted incidence of fracture (%)

*Analysis includes monthly ibandronate n=1,811 and weekly bisphosphonate n=14,648

Reference 1:

Further information available
Management of Pattern Hair Loss in Asians

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Key words:
Male pattern baldness (雄性脫髮/雄禿); hereditary alopecia (遺傳性脫髮)

Background

The term androgenetic alopecia (AGA) was coined by Orentreich in 1960. Different names have been used in the past for the same condition, including male pattern alopecia, common baldness, male pattern baldness, hereditary alopecia and male pattern hair loss (MPHL).

Although AGA has been used to describe pattern hair loss in women, it causes confusion and underestimation of the complex aetiology involved. Female pattern hair loss (FPHL) is sometimes used to describe a mixed pattern of hair loss in women. Although AGA is normally made clinically. In most men, AGA involves the frontotemporal area and the vertex, following a pattern corresponding to the Hamilton–Norwood scale. (Figure 1) In some instances, however, men develop diffuse thinning of the crown with retention of the frontal hairline, with a pattern that resembles the Ludwig type observed in women.

FPHL may have three different patterns:
1. Diffuse thinning of the crown with preservation of the frontal hairline, as in the three-point Ludwig scale (Figure 2);
2. Thinning and widening of the central part of the scalp with breach of frontal hairline (Christmas tree pattern in the Olsen scale);
3. Thinning associated with bitemporal recession (Hamilton–Norwood type).

As treatment strategies differ, other conditions must also be considered:

Epidemiology

The prevalence of PHL in Caucasians is well documented. A study of Caucasian men in the USA revealed a predominantly frontal baldness (type A variant) in 12% and a type III or worse pattern in 16% of subjects 18–29 years old; the prevalence increased progressively to 53% in those 40–49 years old.

According to epidemiologic studies in different Asian countries, 41% to 73% of Asians develop PHL at some point in their lives, and the prevalence increases with advancing age. Hair loss is associated with significant psychosocial impact and individual healthcare expenditure.

Classification

The first systematic classification of PHL was established by Hamilton. This was refined by Norwood in 1975, classifying baldness based on frontoparietal and frontal recession and vertex thinning. An additional pattern was introduced in the Hamilton–Norwood classification in a clinical trial of finasteride in MPHL. Subsequently, Olsen proposed assigning separate designations (temporal, frontal, mid, and vertex) to areas of the scalp that turn bald at different rates in different individuals with MPHL, as well as a density scale.

For FPHL, Ludwig emphasized preservation of the frontal fringe and progressive centrifugal loss over the top of the scalp, and arbitrarily designated three gradations of hair loss. Olsen proposed that frontal accentuation (or the “Christmas tree” pattern) be considered as another pattern of hair loss in women. Lee et al from Korea used basic and specific (BASP) classification, which may prove particularly useful in communicating the exact amount and distribution of hair loss in those with PHL.

Among various classifications, the Hamilton–Norwood classification for MPHL and Ludwig classification for FPHL are the most commonly used.

Clinical Features and Differential Diagnoses

The diagnosis of AGA is normally made clinically. In most men, AGA involves the frontotemporal area and the vertex, following a pattern corresponding to the Hamilton–Norwood scale. (Figure 1) In some instances, however, men develop diffuse thinning of the crown with retention of the frontal hairline, with a pattern that resembles the Ludwig type observed in women.

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As treatment strategies differ, other conditions must also be considered:
1. Telogen effluvium — a common type of hair loss occurring as a large percentage of scalp hairs shift into the shedding phase. The causes may be hormonal, nutritional, drug-associated, or stress-associated.

2. Alopecia areata — a disorder that causes patchy hair loss ranging from diffuse thinning to extensive areas of baldness with “islands” of retained hair.

3. Trichotillomania — hair loss due to trichotillomania is typically patchy, as compulsive hair pullers tend to concentrate the pulling in selected areas.

4. Congenital triangular alopecia — loss of hair in the temporal areas that sometimes begins in childhood: Hair loss may be complete, or a few strands of fine, thin-diameter hair may remain.

5. Scarring alopecia — hair loss due to scarring of the scalp area: Examples are Lichen planopilaris, scleroderma and discoid lupus erythematosus.

**Pathogenesis**

As the name AGA implies, both androgens and genetic factors work together to produce PHL. The inheritance can be maternal and/or paternal, with an autosomal dominant and/or a polygenic pattern of variable penetrance.

The role of androgens was first identified through observation of eunuchs, who did not have MPHL unless androgen was given. The androgen implicated in PHL is dihydrotestosterone (DHT). Androgens exert the influence on hair by diffusing passively into skin cells, and are converted into DHT, a more potent metabolite, by the enzyme 5-alpha-reductase (5AR). Type II 5AR is found in great preponderance in the outer root sheath of scalp hair follicles and dermal papillae (as well as in the prostate), while type I 5AR is found in the pilosebaceous units and sebaceous gland. DHT binds to the specific receptor and induces conformational change, and then binds to the DNA. A messenger RNA is then released, leading to the synthesis of specific proteins to inactivate the hair follicles. Alternate pathways exist which will bypass the 5AR pathways and render treatment targeting type II 5AR ineffective.

As a result of MPHL, affected hair demonstrates the hallmark feature of progressive miniaturization of terminal hair follicles. With each anagen cycle, the hair grows thinner and lighter, and the anagen phase shortens, so that the hair becomes vellous. Finally, the vellous hair will fall, leaving behind a shiny bald scalp. The miniaturization process may take years or decades with individual variations.

Other than DHT, factors associated with FPHL remains elusive. While a proportion of patients with hyperandrogenic conditions may suffer from FPHL, the majority involved other mechanisms that are poorly understood.

**Management**

**Education and Counselling**

PHL is often associated with heavy psychosocial embarrassment. Empathy and support are essential in managing patients with hair loss. The media is super-
saturated with promotional content and practice myths, based on which patients often initiate self-treatment. Therefore, acknowledgement of individual patient’s attitudes, concerns, previous self-treating efforts, and expectations is crucial for effective management of men seeking medical treatment for MPHL. Research has shown that most men (and women) with unwanted hair loss have distressing experience that diminishes their body image.

Managing patient’s expectation is important and essential right from the beginning of treatment. In the author’s experience (Hau KL, Hairborn Transplant Centre, unpublished data, 2008–2010), the most common cause of treatment failure is lack of patience to continue with the treatment. Moreover, 45% of patients will discontinue the treatment programme when they find no or little effect in the first month of treatment, and 60% will do so in the first 3 months. In contrast, if the patients can stay for 6 months or beyond, the drop-out rate can be lowered to 25%, although it is still unacceptably high.

Misconceptions such as the belief that MPHL is due to excessive male hormones should be respectfully identified. Unnecessary restrictions on hair and grooming, such as hairstyling, teasing, use of hair spray, frequency of hair washing, hair colouring or perming, should be corrected. Some self-treatment options adopted by patients can be bizarre and harmful for health.

Medical Treatment

Generally, with medical treatment, reduction in hair loss is usually seen in the first 6 months and hair regrowth in 6–12 months. Continuous treatment is needed to sustain benefit. However, medical treatments currently available are not curative, and it is of paramount importance that patients understand the limitations.

For Male

Topical minoxidil and oral finasteride are approved by the US Food and Drug Administration (FDA) for treatment of PHL. The main benefit of topical 5% minoxidil solution appears to be prolongation of the anagen phase and increase of hair shaft diameter, irrespective of the underlying cause. Its efficacy varied in different studies. Patients should be warned that temporary hair shedding may occur in the first 2–8 weeks in some cases; this is self-limiting and will subside when subsequent anagen regrowth begins, and should not be a cause for treatment cessation. Recently, a 5% topical minoxidil foam has been developed as a hair loss treatment. Finasteride (translated into Chinese as 保法止 in Hong Kong and Macau, 保法止 in mainland China, and 柔沛 in Taiwan) is a potent type II 5AR inhibitor. In clinical trials over a 2-year period in men aged 18–41 years, 48% had hair regrown (slightly in 30%, moderately in 16%, greatly in 2%), 51% had hair loss stabilized, and 1% had progressive hair loss after 1 year of oral finasteride treatment. At 2 years, 66% had hair regrowth, 33% had hair loss stabilized, and 1% lost hair. The number of responding hairs was established after 1 year, and continued treatment increased the length, diameter and pigmentation of those hairs so that coverage of the scalp increased. On stopping finasteride, the regrown hair remained, but the balding process resumed. An extension of the study to 5 years showed that finasteride 1 mg/day was well tolerated, and led to durable improvements in scalp hair growth.

Finasteride is generally well tolerated by men, with rare side effects that may include some loss of libido and erectile function. Currently, there is no proven benefit in women.

For Female

Topical minoxidil 2% and 3% solutions are indicated for treatment of PHL in female. The 5% solution was compared with the 2% solution in two studies involving 493 women. On the basis of hair count, the 5% solution was not significantly more effective than the 2% solution. Like male patients, temporary hair shedding may occur in some female patients in the initial 2–8 weeks of treatment; again, this is self-limiting and will subside when subsequent anagen regrowth begins, and should not be a cause for treatment cessation.

Side effects of topical minoxidil include hypertrichosis (3%–5% of women using 2% minoxidil, higher with the 5% solution). It occurs on the face and resolves within 1–6 months after stopping treatment.

Other treatments such as topical 0.025% alfatradiol and antiandrogens (eg, cyproterone acetate, spironolactone, flutamide) can be used as alternatives. Alfatradiol increases conversion of testosterone to 17-beta-oestradiol and androstenedione to oestrone, thus improving hair growth, although reports of its efficacy have shown variable results. Most of the antiandrogen therapies have not been rigorously studied in FPHL. The role of 5AR inhibitors such as finasteride is not well defined, as mentioned before.

Surgical Treatment

Despite advances in medical therapy, hair transplantation remains the only means of permanent hair restoration in severe PHL.

The donor hair is taken from an area not genetically susceptible to future loss. It is commonly collected at the mid-occipital area measuring about 5 cm in
width, and transplanted on the designed hairline. Various methods have been used. The traditional one involves strip excision of the whole thickness of skin containing the donor hair, and the follicular units are collected by microscopic dissection. It requires skilled assistants and good stepwise quality control.

Follicular unit extraction (FUE) involves harvesting the whole naturally occurring individual follicular units and transplanting the donor hair units directly. It causes less trauma to the donor site but is more tedious. Automated follicular implantation with machine-assisted donor harvesting and graft implant can greatly facilitate the surgical process, but there is a higher risk of graft transection and implant failure if not performed properly.

“**The most common cause of treatment failure is lack of patience**”

Various medical conditions such as hypertension, cardiac disease and diabetes have to be controlled before hair transplantation. Local diseases such as cutaneous lupus erythematosus, morphea, alopecia areata and scalp folliculitis have to be stabilized and quiescent for at least 6 months before hair transplantation.

Complications of hair transplantation include ingrown hairs and foreign body reactions, infection, cobblestoning, graft depression, epidermal cysts, bleeding, headaches, scarring, keloid and hypertrophic scar, poor hair growth, arteriovenous fistula, osteomyelitis, wound dehiscence, telogen effluvium, accelerated hair loss, delayed temporary marked thinning, curly and lusterless hair, chronic mild folliculitis, and patient dissatisfaction.  

Artificial hair implantation involves the use of artificial fibres with excellent biocompatibility to human tissues. This technique is suitable for patients with little available hair for transplant, and the supply is infinite. Previously, poorly controlled and designed manufacturing as well as improper clinical methods had led to a number of complications, and some prosthetic hair fibres were listed as banned devices by the US FDA.

**Medical Devices and Aesthetic Aids**

Medical devices and aesthetic aids can be used as alternative tools for treatment of PHL.

Medical devices refer to the use of laser and light sources. Light interacts with human tissue and cells, and produces therapeutic effects such as those seen in phototherapy. Various light sources were used to facilitate hair growth, such as medical light emitting diode (LED) photomodulation and lasers. Low-level laser therapy (LLLT) is FDA-approved for the treatment of hair loss. In a study, seven patients were exposed to LLLT twice weekly for 20 minutes each time over a period of 3–6 months. On average, patients had a decrease in the number of vellous hairs, an increase in the number of terminal hairs, and an increase in shaft diameter after treatment. However, none of these changes was statistically significant.

The mechanism behind light-stimulated hair growth is complex, involving photon-photorcepter activation, cellular respiratory chain energy production, and singlet oxygen interaction resulting in cell proliferation and stimulation. Although laser/light sources appear to be safe and effective in the treatment of MPHL and FPFL, most of the commercially available light sources are not up to therapeutic standard. Well-designed studies are needed so physicians can more accurately counsel patients on the efficacy, long-term benefit and downside of laser/light sources in the treatment of hair loss.

Nonmedical approaches such as aesthetic aids can provide cosmetic relief to men and women with thinning hair if medical treatments are not indicated, not effective, or not desired by the patient. They can also be used as adjuvant therapy with medical or surgical treatment.

Examples are wigs, hair pieces, hair extensions, topical powder make-up, and hair dyeing agents.

**References:**

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10:00 am – 10:30 am  **Fatty liver – is it too benign to ignore?**  
Dr. Pang Hing Yan (彭慶茵醫生) Specialist in Gastroenterology and Hepatology

10:30 am – 11:00 am  **Recent advances in the management of gouty arthritis.**  
Dr. Lee Ka Wing (李家榮醫生) FRCP, Specialist in Rheumatology

11:00 am – 11:30 am  **Stroke prevention and management – what can we do in 2011?**  
Dr. Leung Ho Wan (梁浩雲醫生) Specialist in Neurology

11:30 am – 11:45 am  ----------- Tea break  -----------

11:45 am – 12:15 pm  **Recent advances in the management of coronary heart disease.**  
Dr. Lam Chiu Wah (林劍華醫生) FRCP, Specialist in Cardiology

12:15 pm – 12:45 pm  **How early shall we treat diabetes mellitus?**  
Dr. Cheung Fu Keung (張富強醫生) Specialist in Diabetes and Endocrinology

12:45 pm – 1:00 pm  **Q&A**

1:00 pm – 2:00 pm  ※※※※※ Lunch ※※※※※

**Welcome note: Dr. Lam Tat Chung Paul 林達聰醫生**  
FRCP, FHKAM (Medicine), FHKAM(Psychiatry)  
President, The Society of Physicians of Hong Kong

2:00 pm – 2:30 pm  **Transcatheter repair of aortic and mitral valve-where are we now?**  
Dr. Li Siu Lung, Steven (李少隆醫生) FRCP, Specialist in Cardiology

2:30 pm – 3:00 pm  **Management of eczema and psoriasis for general practitioners.**  
Dr. Chiu Lai Shan, Mona (趙麗珊醫生) Specialist in Dermatology

3:00 pm – 3:30 pm  **Office management of asthma and chronic obstructive pulmonary disease.**  
Dr. Li Sing Tao, Thomas (李聲濤醫生) Specialist in Respiratory Medicine

3:30 pm – 4:00 pm  **Common haematological disorders for general practice.**  
Dr. Chan Man Hon, Helen (陳敏航醫生) Specialist in Haematology

4:00 pm – 4:30 pm  **Q&A**

**Place:**  The Langham Hotel, 8 Peking Road, TST, Kowloon

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References:

1. Data on file, Galderma.
4. Regueiro P et al. A new shampoo formulation of clobetasol propionate 0.05% is at least as efficacious and safe as clobetasol propionate gel 0.05% in the treatment of scalp psoriasis. Poster presented at AAD 2003.
5. Regueiro P et al. Clobetasol propionate shampoo 0.05% and clobetasol propionate gel 0.05%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. J Dermatol Treat 2005;16(1):31-6.

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Dr Loh Kai Tsu, Kevin (陸凱祖醫生)
FACP, FRCPC
Specialist in Medical Oncology

References: