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Introduction

Lung cancer is a leading cause of cancer in Hong Kong. In 2014, it was the second most common cancer, with 4,674 new cases, and the most common cause of cancer mortality, with 3,866 deaths.¹

Early studies suggested that patients with advanced non-small cell lung cancer (NSCLC) harbouring sensitizing epidermal growth factor receptor (EGFR) gene mutations should receive EGFR tyrosine kinase inhibitors (EGFR TKIs) as first-line therapy.² Commonly used first-line therapies include gefitinib, erlotinib and afatinib.

Mok TS, et al showed that patients with EGFR-mutation positive advanced adenocarcinoma treated with gefitinib can

Figure 1. Chemical structure of osimertinib

Figure 2. Key development milestones of osimertinib for NSCLC

Key words:
Osimertinib (奧斯替尼), T790M Mutation (T790M突變)
achieve an objective response rate superior to those treated with carboplatin-paclitaxel treatment (71.2% vs 47.3%). Rosell R, et al revealed that when erlotinib was given to advanced NSCLC patients with a sensitizing EGFR mutation, the objective response rate was 64% compared with 18% with standard chemotherapy.

Despite the superior initial outcome of first-line EGFR TKIs, the majority of patients will have disease progression within 1–2 years after treatment initiation (acquired resistance). In around 60% of patients, the mechanism of acquired resistance is the development of an additional EGFR mutation, T790M. Other forms of acquired resistance included MET amplification, HER2 amplification, small-cell histological transformation and epithelial-to-mesenchymal transition.

A T790M mutation leads to an enhanced affinity of tumour cells for adenosine triphosphate (ATP), thereby reducing the ability of ATP-competitive reversible EGFR TKIs to bind to the tyrosine kinase domain of EGFR. One strategy to overcome this mechanism of resistance is through the use of irreversible EGFR TKIs.

Osimertinib

Osimertinib is an oral, potent, irreversible EGFR TKI that targets sensitizing EGFR mutations and T790M resistance mutations (Figure 1).

In November 2015, the US Food and Drug Administration (FDA) granted accelerated approval for osimertinib for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy (Figure 2).

**Evidence of osimertinib in EGFR T790M mutation-positive patients**

The AURA phase 1 study (Janne PA, et al) demonstrated that patients who...
had advanced EGFR mutation-positive tumours who progressed after EGFR TKI therapy, treatment with osimertinib was associated with a 61% (95% confidence interval [CI], 52–70%) response rate when EGFR T790M was found in tumours whereas the response rate was 21% (95% CI, 12–34%) when EGFR T790M was not confirmed in tumours (Figure 3). The median progression-free survival was 9.6 months (95% CI, 8.3 months to not reached) in EGFR T790M-positive patients and 2.8 months (95% CI, 2.1–4.3 months) in EGFR T790M-negative patients (Figure 4).

The most common adverse events were diarrhoea (47%), rash (40%), nausea (22%) and decreased appetite (21%). However, adverse events leading to dose reduction or drug discontinuation were observed in only 7% and 6% of all patients, respectively.

Authors concluded that osimertinib was highly active in patients with lung cancer harbouring the EGFR T790M mutation who had had disease progression during prior EGFR TKI therapy.

Subsequent to the positive results of the AURA phase 1 study, the AURA phase 2 study was conducted and published in October 2016.

AURA 2 was a phase 2, open-label, single-arm study for patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who progressed on previous EGFR TKI therapy. Patients were given osimertinib 80 mg orally once daily.

Of 199 patients, 140 (70%; 95% CI, 64–77) achieved an objective response, measured by a blinded, independent cen-

![Figure 5. Waterfall plot for best percentage change in target lesion size in patients treated with osimertinib](image-url)

Adapted from Lancet Oncology 2016;17:1643-52

![Figure 4. Progression-free survival according to EGFR mutation status in patients treated with osimertinib](image-url)


EGFR, epidermal growth factor receptor
tral review; confirmed complete responses were achieved in 6 (3%) patients and partial responses were achieved in 134 (67%) patients (Figure 5). Median progression-free survival was 9.9 months (95% CI 8.5–12.3 months; Figure 6).

The most common all cause grade 3 and 4 adverse events were pulmonary embolism (7 [3%]), prolonged electrocardiogram QT (5 [2%]), decreased neutrophil count (4 [2%]), anaemia, dyspnoea, hyponatraemia, increased alanine aminotransferase and thrombocytopenia (3 [1%] each).

Serious adverse events were reported in 52 (25%) patients, of which...

Figure 6. Kaplan-Meier curve for progression-free survival in all patients treated with osimertinib

Figure 7. Progression-free survival in patients with EGFR T790M mutation-positive advanced NSCLC treated with osimertinib versus platinum-pemetrexed

A Patients in intention-to-treat population

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<th>0</th>
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<th>6</th>
<th>9</th>
<th>12</th>
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<td>162</td>
<td>88</td>
<td>50</td>
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<td>44</td>
<td>17</td>
<td>7</td>
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Median progression-free survival

- Osimertinib: 10.1 (8.3–12.3) months
- Platinum–pemetrexed: 4.4 (4.2–5.6) months

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41) p<0.001

B Patients with CNS metastases

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<th>9</th>
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<tr>
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<td>51</td>
<td>32</td>
<td>9</td>
<td>4</td>
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</table>

Median progression-free survival

- Osimertinib: 8.5 (6.8–12.3) months
- Platinum–pemetrexed: 4.2 (4.1–5.4) months

Hazard ratio for disease progression or death, 0.32 (95% CI, 0.21–0.49)
11 (5%) were investigator assessed as possibly treatment related. Seven deaths were due to adverse events. The only fatal event assessed as possibly treatment related by the investigator was due to interstitial lung disease.

Authors concluded that osimertinib showed clinical activity with manageable side effects in patients with EGFR T790M mutation-positive NSCLC. It could be a suitable treatment for patients with EGFR T790M mutation-positive disease who have progressed on prior EGFR TKI therapy.

With promising results from AURA 1 and 2, the AURA 3 trial was designed to compare the efficacy of osimertinib versus standard platinum-pemetrexed therapy in patients who progressed on prior EGFR TKI therapy and harbour the EGFR T790M mutation.10 AURA 3 was an international, randomized, open-label, phase 3 trial. Patients with EGFR T790M mutation-positive advanced NSCLC who had disease progression after EGFR TKI therapy were randomized to receive either oral osimertinib 80 mg daily or intravenous pemetrexed 500 mg per square meter body surface area plus either carboplatin area under the curve (AUC) 5 mg/mL/min body surface area plus either carboplatin pemetrexed 500 mg per square meter every 3 weeks for up to 6 cycles.10 The primary end point was investigator-assessed progression-free survival.

Results showed that the median duration of progression-free survival was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 months vs. 4.4 months; hazard ratio, 0.30; 95% CI, 0.23–0.41; p<0.001; Figure 7A). The objective response rate was significantly better with osimertinib (71%; 95% CI, 65–76%) than with platinum therapy plus pemetrexed (31%; 95% CI, 24–40%; odds ratio for objective response, 5.39; 95% CI, 3.47–8.48; p<0.001).

Among 144 patients with metastases to the central nervous system (CNS), the median duration of progression-free survival was longer in patients receiving osimertinib than in those receiving platinum therapy plus pemetrexed (8.5 months vs 4.2 months; hazard ratio, 0.32; 95% CI, 0.21–0.49; Figure 7B).

The proportion of patients with grade 3 or higher adverse events was lower with osimertinib (23%) than with platinum therapy plus pemetrexed (47%).

The authors concluded that osimertinib had significantly greater efficacy than platinum therapy plus pemetrexed in patients with EGFR T790M-positive advanced NSCLC (including those with CNS metastases) in whom disease had progressed during first-line EGFR-TKI therapy.

Conclusion
Osimertinib was proven to be an effective targeted therapy with manageable side effects for patients with advanced NSCLC harbouring the EGFR T790M mutation who progressed on prior EGFR TKI therapy. Its efficacy was maintained in patients with CNS metastasis.

It has been incorporated by the National Comprehensive Cancer Network as a standard recommendation in this category of patients.

References
Lung cancer remains the number one leading cause of cancer death in Hong Kong. For the majority of patients (~75%) at diagnosis, the disease is at an advanced stage which is not amenable to surgery. Falling short of this, systemic treatment with or without radiotherapy would be the standard of care. Previously, chemotherapy was the mainstay of treatment. Since its advent a decade ago, oral targeted therapy has been considered the preferred first-line treatment in patients with tumours harbouring favourable epidermal growth factor receptor (\(\text{EGFR}\)) mutations. Instead of targeting gene mutations, immunotherapy works by disabling the tumour’s ability to evade the immune response of the host. This can be achieved by manipulating the immune checkpoint programmed death receptor 1 (PD-1) on immune cells or its ligand programmed death ligand 1 (PD-L1) on cancer cells to restore recognition and destruction of cancer cells by the immune system. Drugs targeting PD-1 (pembrolizumab and nivolumab) or PD-L1 (atezolizumab, durvalumab, and avelumab) have been approved or are in the late stages of development. Criteria required to use immunotherapy as first-line treatment includes the percentage of expression of PD-L1 in the cancer cells. Immune checkpoint inhibitors can be used either as monotherapy or in combination with platinum-based chemotherapy. While the results of larger randomized controlled trials are awaited, the importance of obtaining adequate tissue biopsies from tumours is being revisited. Liquid biopsy is inadequate for quantifying expression of PD-1/PD-L1, \(\text{EGFR}\) mutations, and many other driver oncogenes.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a bronchoscopic sampling method conducted under ultrasound guidance that enables real-time aspiration of lesions adjacent to the trachea or large bronchi. The use of EBUS-TBNA has rapidly increased, because of its high diagnostic accuracy and safety profile. The use of EBUS-TBNA as a primary diagnostic and staging tool for lung cancer has expanded rapidly in recent years. A local, real-world study of 259 patients with known or suspected lung cancer found the sensitivity of this procedure to be 87%, with a diagnostic accuracy of 91%. EGFR mutation testing was possible in 95% of cases in which it was requested. There were no serious complications. Given its favourable safety and efficacy profile, EBUS-TBNA is now regarded as the most useful approach for repeated lung cancer tissue sampling. Patient satisfaction with EBUS-TBNA under conscious sedation was reported to be high. According to one study, 98% of patients reported that they would “definitely return” for EBUS-TBNA in the future if required. The suitability of specimens from EBUS-TBNA for assessment of PD-L1 status is currently being investigated with respect to viable tumour cell numbers for interpretation and validation of PD-L1 assays on EBUS-TBNA specimens. Initial clinical trials suggested that EBUS-TBNA is a promising method for evaluating PD-L1 expression in lung cancer.

In patients with locally advanced or metastatic NSCLC without driver oncogenes (ie, \(\text{EGFR}\) mutation or \(\text{ALK}\) translocation), platinum-based chemotherapy is the current standard first-line
treatment. In a recent phase II randomized controlled trial published in *Lancet Oncology*, addition of pembrolizumab to standard platinum-based chemotherapy nearly doubled the objective response rate (55% vs 29%; *p*=0.0016; Figure 1) and nearly halved the risk of progression or death (HR=0.53; 95% confidence interval, 0.31–0.91; *p*=0.0102; Figure 2) compared with those treated with chemotherapy alone in patients with non-squamous NSCLC. However, rates of grade 3/4 adverse effects were higher in the combined treatment group than in the chemotherapy group (39% vs 26%) whilst the median treatment exposure time was longer in the combination group (8 months vs 4.9 months). The possible adverse outcomes of immune aetiology were thyroid dysfunction and pneumonitis.6

The preliminary results support the use of combined immunotherapy and chemotherapy in select patients with nonsquamous NSCLC not suitable for oral targeted therapy. The next question would be whether we can use immuno-

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**Figure 1. Confirmed objective response rate in patients treated with pembrolizumab plus chemotherapy versus chemotherapy alone**

<table>
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<th>Pembrolizumab + chemotherapy</th>
<th>Chemotherapy alone</th>
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<tr>
<td><strong>ORR (%)</strong></td>
<td>55%</td>
<td>29%</td>
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<td><strong>p</strong></td>
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**Date cut off:** August 8, 2016.

**Figure 2. Progression-free survival in patients treated with pembrolizumab plus chemotherapy versus chemotherapy alone**

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<td><strong>Events, n</strong></td>
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<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.53 (0.31–0.91)</td>
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</tr>
<tr>
<td><strong>p</strong></td>
<td>0.0102</td>
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**Date cut off:** August 8, 2016.
randomized to receive either pembrolizumab or platinum-based chemotherapy. Pembrolizumab as first-line treatment demonstrated superior progression-free survival (HR=0.5; Figure 3). Unlike combined immunotherapy with chemotherapy, the safety profile of pembrolizumab monotherapy was favourable over chemotherapy with half the incidence of grade 3/4 toxicities (26% vs 51%). As one-third of patients with advanced NSCLC have high PD-L1 expression, immunotherapy should become a new standard for first-line therapy in this select group of patients.

In summary, while the role of liquid biopsy for detecting EGFR mutations in blood is yet to be defined, there have been advancements in the identification of targets. Specific cell type, molecular profiling and PD-L1 expression rekindle the importance of tissue biopsy. EBUS-TBNA has a high diagnostic accuracy and a good safety profile; patient satisfaction promotes its rapidly increasing use in lung cancer. Chemotherapy is no longer the only treatment option for advanced lung cancer. Oral targeted therapy or immunotherapy is now the preferred treatment option in select populations, based on information obtained by tissue biopsy. The advancement of diagnostic and treatment modalities over the past decade has improved patients’ quality of life and survival.

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5. Yuichi Tambo, Rie Sakakibara, Noriko Motoi et al; CCancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan. Feasibility of EBUS-TBNA specimens for PD-L1 expression test in lung cancer. J Clin Oncol 34, 2016 (suppl; abstr e23112)

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Subject to availability and for local doctors only.
Now Approved for patients previously treated advanced NSCLC whose tumors express PD-L1.²

In patients previously treated with platinum-containing chemotherapy and, if appropriate, with approved therapy for ALK or EGFR mutations

SUPERIOR OVERALL SURVIVAL
VS DOCETAXEL IN PD-L1+ NSCLC¹,²

START INFORMED. TREAT WITH KEYTRUDA.

14.9-MONTH MEDIAN OS
with KEYTRUDA 2 mg/kg Q3W (95% CI, 10.4–NA) vs 8.2 months with docetaxel (95% CI, 6.4–10.7)
(PD-L1 ≥50%)

Test for PD-L1 (clone 22C3), along with other biomarkers, at diagnosis

Case Report

Mr Chan was a 35 year old lifetime nonsmoker with good past health. He complained of subacute onset of chronic cough for 4 months. The symptoms gradually progressed to exertional dyspnoea and mild weight loss. A chest radiograph showed an anterior mediastinal opacity, and he was referred to a respiratory specialist for further care. At presentation, he was noted to be tachycardic, tachypnoeic, and with stridor detected on the right chest. Features of superior vena cava obstruction were not detected. There was a palpable enlarged right supraclavicular lymph node. The peak expiratory flow rate was markedly reduced to 180 L/minute. He was admitted to hospital for suspected thymoma with upper airway obstruction. Positron emission tomography–computed tomography (PET-CT) scan showed an irregular enhancing mass of 9.5 cm infiltrating the superior and anterior mediastinum down to the subcarinal and right hilar region, with extension to the right side. There was superior vena cava encasement and narrowing, as well as encasement of the lower trachea, carina, right main bronchus, and right upper lobe bronchus causing severe luminal narrowing. The maximum standardized uptake value (SUVmax) of the mediastinal mass was 17.3. There were multiple mediastinal, hilar, subcarinal, right jugular and supraclavicular lymphadenopathies with markedly elevated SUVmax (Figure). The clinical picture was suggestive of malignant thymoma. Core biopsy of the right supraclavicular lymph node was performed. Histological analysis revealed poorly differentiated large cell carcinoma, with the primary site being the lung or thymus. Contrary to the initial suspicion of thymoma, immunohistochemical analysis revealed lung instead of thymic origin. The patient was diagnosed with lung cancer of nonsmoking young age. Further analysis revealed negative EGFR, ALK, ROS1 and PD-L1 mutations. Oncological and supportive treatment was initiated accordingly.

Lung cancer in the young and nonsmokers

Most studies define young lung cancer as an age of onset of younger than 40–45 years. Although the proportion of young lung cancer cases remains low (2.6% in Hong Kong, 2.2% in the USA, 2.9% in Canada), a significant number of young people’s lives are lost due to the high incidence of the disease. To put this into perspective, in the USA, the annual mortality rate for breast cancer patients younger than 54 years was around 8,300, while over 21,000 young adults younger than 50 years died from lung cancer.1-4

The rising trend of non-small cell lung cancer (NSCLC) among nonsmokers is remarkable. The proportion of NSCLC among never-smokers climbed from 8.9% in 1990–1995 to 19.5% in 2011–2013 in the USA, and from 13% to 28% from 2008 to 2014 in the UK. The characteristic demographic features of young, nonsmoking NSCLC cases includes a higher proportion of females (51–54%), Asians and Pacific Islanders (14%), adenocarcinoma histology (33–59%) and a higher likelihood of presenting with distant metastases (68%). Male sex, non-adenocarcinoma histology, and main bronchial primary tumour site were independent negative prognostic factors among the young. The diagnostic challenge for physicians is highlighted by the fact that 52% of young, nonsmoking NSCLC patients had no clear symptoms at presentation. Specific symptoms, such as haemoptysis, occurred in only 11% of patients, and nonspecific symptoms, such as chest infection, were experienced by 18%. Cough was a presenting symptom in 34% of patients, and incidental imaging detected lung cancer in 36%.5-8

Why, what and what’s next

In essence, many cases of young nonsmoking lung cancer patients are clinically evasive and have their window of early detection missed. Annual screening by low-dose CT thorax for patients at risk of lung cancer has been advocated by the International Early Lung Cancer Action Program for over 10 years. However, young nonsmokers are not yet recognized as a high-risk group.9 Clearly, it is not going to be cost-effective to screen the entire population of nonsmokers for lung cancer. Family history is an important risk identifier for young lung cancer, as the risk of developing the disease was almost 5-fold higher with a first-degree relative diagnosed with lung cancer before age of 60. However, over 80% of NSCLC patients had a
negative family history. The challenge for physicians to identify at-risk young, nonsmoking lung cancer patients for appropriate surveillance remains unresolved.

Although the exact reasons of the changing epidemiology of NSCLC among young nonsmokers remains unclear, data are revealing the potential roles of the combined effects of underlying cancer-predisposing genes and exposure to second-hand smoke, pollution, radon and small particles in the air. Thanks to the recent major advances in clinical genetic technologies that powered the understanding of carcinogenesis of young NSCLC through whole exome sequencing, over a dozen genes with mutations that raise a person’s hereditary risk of developing lung cancer have been identified (Table). Up to 8% of NSCLC cases are considered inherited. This opens a new horizon of clinical options for clinicians to identify at-risk, young nonsmoking NSCLC patients, especially with the markedly reduced cost of clinical genomic testing. Testing for genetic cancer risks of healthy individuals has been adopted in the past 10 years to help identify previously covert, at-risk patients to be followed by a personalized surveillance and prevention program. The Policy Statements of the American Society of Clinical Oncology and the American College of Medical Genetics and Genomics recommended the following strategies in adopting genetic testing for cancer susceptibility:

- Recognition and management of individuals with an inherited susceptibility to cancer are core elements of oncology care.
- Absence of family history does not preclude genetic cancer susceptibility of an individual.
- Clinical utility of genetic testing should take into account effects on diagnostic or therapeutic management; implications for prognosis; health and psychological benefits for patients and their relatives; and economic impact on the healthcare systems.
- Given the complexity of genetic testing technologies, laboratory accreditations, results interpretation and implications, it is recommended that genetic testing only be conducted in the setting of pre- and post-test genetic counseling.

These recent advances in medical practices and genetic technologies constituted the Precision Medicine Initiatives that have revolutionized the healthcare system in the USA since 2015.

The Addario Lung Cancer Medical Institute (ALCMI), a partner organization of the Bonnie J. Addario Lung Cancer Foundation (ALCF), is taking the lead on answering the ultimate genetic question of why young nonsmokers are developing NSCLC. ALCMI launched the Genomics of Young Lung Cancer Study in 2015 to determine whether lung cancer in young patients harbours a unique spectrum of genetic mutations that could be a potential target for treatment. It is the first multicenter, international study to prospectively analyze the genomes of young lung cancer patients. Geoff Oxnard, an assistant professor of medicine at the Dana-Farber Cancer Institute and Harvard Medical School said, “The young are a population who need this kind of extra testing, turning over every rock to find that hidden genetic signature, which may be something you’ve heard of or something that you haven’t.”

Figure. PET-CT scan of a patient with lung cancer of nonsmoking young age

PET-CT, positron emission tomography-computed tomography

Table. Genes associated with a raised inherited risk of lung cancer

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Source: US National Library of Medicine, National Institute of Health

A complete list of references can be downloaded from www.SOPHYSICIANSHK.org
Introduction

Approximately 240 million people worldwide are chronically infected with hepatitis B virus (HBV), with the highest prevalence in Asia. Tenofovir disoproxil fumarate (DF) is a nucleotide reverse transcriptase inhibitor that has potent activity against HBV. New data on tenofovir DF will be discussed.

Updates in the treatment of chronic HBV infection with tenofovir DF

Efficacy

Tenofovir DF is effective for the treatment of chronic HBV in patients who are HBV envelope antigen (HBeAg) positive or negative, and can lead to regression of liver cirrhosis. In a clinical study of 5 years of treatment with tenofovir DF, 97% of patients reached an HBV deoxyribonucleic acid (DNA) level of <169 copies/mL. At year 7, viral suppression was maintained in 99% of patients. In patients with cirrhosis at baseline, 74% had regression of cirrhosis after 5 years of treatment. The safety profile of tenofovir DF was favourable.

Partial virologic response to entecavir

Entecavir has been widely used for treatment-naïve patients with chronic HBV. However, about 20% of patients show partial virologic response (PVR) after 2 years of entecavir therapy. If HBV DNA continues to be detected, underlying liver disease may progress and lead to an increased risk of hepatocellular carcinoma (HCC).

This concept is illustrated in a recent cohort study of 1,680 patients with chronic HBV with PVR to entecavir treatment for at least 3 years. During 7 years of follow-up, 150 (8.9%) patients developed HCC. The 7-year cumulative incidence of HCC was 12.3% (95% confidence interval [CI], 8.9–15.7%) versus 8.2% (95% CI, 6.4–10.0%) in patients with detectable and undetectable HBV DNA at year 2 respectively (log rank p=0.004). Therefore, detectable HBV DNA after 2 years of entecavir treatment is an independent risk factor of HCC.

Resistance to tenofovir

HBV resistance to tenofovir DF does not occur. Although tenofovir-resistant HIV mutations have been reported, there is no corresponding site in the HBV genome.

Among 641 treatment-naïve patients with chronic HBV treated with tenofovir DF over an 8-year period, there was no evidence of resistance to tenofovir DF. Of the 41 episodes of virologic breakthrough, the majority were associated with nonadherence.

Reduced risk of HCC

Nucleos(t)ide analogues can reduce the risk of developing HCC. A prospective study evaluated the incidence of HCC in 634 patients with chronic HBV (482 without cirrhosis and 152 with cirrhosis) who were treated with tenofovir DF for 7 years. Over the course of the study, 14 cases of HCC developed (four within the first year). Among those without cirrhosis, the observed incidence of HCC was significantly lower than the incidence that was predicted using the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B model (standardized incidence ratio 0.40; 95% CI, 0.199–0.795). In addition, no cases of HCC occurred in patients with cirrhosis after 3.7 years.

Prevention of mother-to-child transmission

Women who are HBV surface antigen (HBsAg)-positive should have further
testing to measure baseline HBeAg, antibodies to the HBV envelope (anti-HBe), HBV DNA, and aminotransferase levels. Women who have high HBV DNA (ie, >2×10⁵ IU/mL or >10⁶ copies/mL) or elevated aminotransferase levels, and/or a positive HBeAg should be closely monitored. Women with low HBV DNA levels in the first trimester should have repeat HBV viral load testing at around weeks 26–28 of gestation. If the levels have increased, antiviral therapy should be considered.

Antiviral therapy for HBsAg-positive mothers with high HBV DNA levels, in addition to standard passive-active immunization of the infant, can further reduce the risk of mother-to-child transmission.11

In a randomized controlled trial, 200 mothers who were positive for HBeAg and who had an HBV DNA level higher than 200,000 IU/mL were randomly assigned to receive usual care without antiviral therapy or to receive tenofovir DF from 30 to 32 weeks of gestation until postpartum week 4. All of the infants received immunoprophylaxis. At postpartum week 28, the rate of mother-to-child transmission was significantly lower in the tenofovir DF group than in the control group (5% vs. 18%; p=0.007). In addition, no significant differences in the rate of birth defects between babies born to treated and untreated mothers (2.1 vs. 1.1%; p=1.00) were noted. After treatment was discontinued, more of the mothers who received tenofovir DF had elevations in their alanine aminotransferase levels, but none of the mothers had severe flares or hepatic decompensation.12

In 2017, the European Association for the Study of the Liver recommended that all pregnant women with high HBV DNA levels (>200,000 IU/mL) or HBsAg levels >4 log IU/mL receive tenofovir DF prophylaxis at weeks 24–28 of gestation, continued for up to 12 weeks after delivery.13

**HBV reactivation associated with corticosteroid therapy**

The natural course of HBV infection is determined through the interplay between viral replication and the host's immune response. HBV persists in the body of all patients with infection, even those with evidence of serological recovery. Thus, individuals with a history of HBV infection who receive immunosuppressive therapy are at risk for HBV reactivation.14 The number of drugs that are associated with HBV reactivation is constantly expanding. Such agents include traditional chemotherapeutic agents and glucocorticoids, as well as biologic agents (eg, anti-CD 20 agents, anti-tumour necrosis factor [TNF] agents), and new classes of drugs, such as tyrosine kinase inhibitors and mechanistic target of rapamycin (mTOR) inhibitors.15 Since corticosteroids are commonly prescribed, this will be further discussed.

Among HBsAg-positive patients receiving glucocorticoids, HBV reactivation has occurred with both high-dose, rapidly tapered regimens and moderate-dose, prolonged regimens.16

Patients are considered at high risk for reactivation (11–20% risk of reactivation) if they have HBsAg-positive and are going to receive high-dose glucocorticoids (eg, prednisolone ≥20 mg/day for at least 4 weeks). Antiviral therapy should be administered prior to initiating immunosuppressive therapy (Grade 1B).13 Tenofovir or entecavir is the drug of choice (Table). Treatment should be maintained for at least 6 months after withdrawal of immunosuppression (with the exception of anti-CD20 therapy). However, reactivation has not been well described with low-dose regimens (ie, <20 mg prednisone per day), even over prolonged periods.

HBV replication increases in the presence of glucocorticoids. Despite the increase in viral replication, serum aminotransferase levels tend to decline. However, when glucocorticoids are withdrawn; viral replication declines while aminotransferase levels increase.17 The peak rise in aminotransferase levels typically occurs 4–6 weeks after withdrawal.18

**Safety**

Tenofovir DF is associated with worsening kidney function in some patients. If possible, tenofovir DF should be avoided in patients with reduced kidney function. Patterns of kidney injury due to tenofovir DF include proximal tubular dysfunction, acute kidney injury, and chronic kidney disease. This can lead to renal impairment characterized by increases in serum creatinine, proteinuria, glycosuria, hypophosphatemia, and acute tubular necrosis. Large-scale treatment trials and observational studies have reported low rates of renal toxicity (<2%) in such patients.19,20 In a meta-analysis that compared entecavir to tenofovir DF in 1300 patients, no significant differences were found in renal safety or hypophosphatemia over approximately 18 months.21

Tenofovir DF may reduce bone density in patients with chronic HBV monoinfection.22 Decreases in bone density appear to be related to an increased loss of phosphate through the kidneys. Although the effect appears to be mild, the effect is more prominent in children, and therefore tenofovir should generally be avoided in children.

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**Table. Recommendations for patients undergoing immunosuppressive therapy or chemotherapy**

| All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression (Evidence level 1, grade of recommendation 1). |
| All HBsAg-positive patients should receive ETV or TDF as treatment or prophylaxis (Evidence level II-1, grade of recommendation 1). |
| HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation (Evidence level II-1, grade of recommendation 1). |

ETV, entecavir; HBc, hepatitis B core; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

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