detect only > 10^5 copies/ml of virus. Evidence now indicates that carriers with < 10^5 copies/ml of HBV are not exempt from liver diseases [23,24]. A further assumption was that HBV would progress only if HBeAg was positive and serum HBV-DNA was > 10^5 copies/ml; recent studies have shown that this is not always true [25]. Accordingly, various professional organizations have recommended several modifications to treatment guidelines (15,20,21).

Another rationale for not recommending treatment for apparently inactive chronic HBV carriers is that current antiviral drugs seem to be effective only in patients with evidence of ongoing host immunity. This is another point of controversy in contemporary hepatology and pharmacology. Patients with liver damage are recommended for therapy based on the assumption that they exhibit features of HBV-related host immunity. Detailed studies have shown that the extent of liver damage does not reflect the magnitude of HBV-related host immunity in such patients [26]. Due to ongoing controversy over the treatment of chronic HBV-infected patients, treatment guidelines are frequently updated, although they will not become a gold standard until the pathogenesis of chronic HBV infection is understood in detail.

In addition to various scientific limitations to developing appropriate treatment guidelines for chronically HBV-infected individuals, the condition is complicated still further by global heterogeneous socio-economic conditions. Terms such as 'treatment recommended' are frequently used in treatment guidelines. This can confuse general physicians and patients, especially those in developing countries where information is rarely updated. Most patients and even many physicians in developing countries assume that if treatment is not recommended, then therapy is not required and the patients are not at risk. Although chronic HBV carriers are followed up in developed countries, the duration of follow-up varies, whereas those in developing countries are rarely followed up due to primitive healthcare delivery systems.

All major liver associations recommend antiviral therapy for chronically HBV-infected individuals during the immune clearance phase and for patients with complications [15,20,21]. The levels of HBV replication, extent of liver damage and HBeAg positivity are usually used as markers for the initiation of therapy. Patients with liver damage irrespective of HBV replication are also recommended for therapy. On the other hand, some studies indicate that patients with high HBV DNA levels irrespective of extent of liver damage should be treated [3,5,6,18,27-29]. Patients in the reactivation phase of chronic HBV infection with evidence of liver inflammation are also recommended for therapy. In general, these patients have evidence of liver inflammation associated with lower HBV DNA levels compared with HBeAg-positive patients [30]. In addition, several prognostic factors for disease progression can be considered to guide treatment; these include male gender, genotype C, and family history of HCC, as well as ongoing alcohol abuse and coinfection with HIV, HCV, or hepatitis D virus [31,32].

3.5 Treatment options for HBV

The various antiviral agents that have been approved or that are under clinical development are categorized depending on their mechanism of actions, as non HBV-specific antiviral drug such as IFNα 2a and 2b, as well as their pegylated forms, and viral polymerase inhibitors that belong to the NA family. Interferons are immune modulators that also possess antiviral properties. Although NA are primarily antiviral agents, they can influence host immunity either directly or indirectly [5-7,11,14,19]. Antiviral drugs for treating CHB patients have been available for about three decades. Many patients could not have benefited from previous treatment, and thus emphasis is placed on designing treatment guidelines for naive and previously treated patients. Data from randomized clinical trials and other types of studies are accumulating regarding the scope and limitations of antiviral drugs in patients with CHB. We will provide a comprehensive outline of therapy for chronically HBV-infected subjects, and readers may consult related review articles for a deeper insight [3,5-7,9,11,14,15,19,21].

3.5.1 Treatment of chronic HBV infection using IFNs

Most guidelines suggest that HBeAg-positive patients with active diseases should be treated for 16 – 24 weeks with standard IFN. However, many experts in the field now prefer to use pegylated IFN for treating such patients. About 30% of patients undergo HBeAg seroconversion induced by IFN, and the probability of HBe seroconversion is higher among patients with comparatively high ALT levels, moderate liver damage and low serum HBV DNA levels [33-35]. In addition, some studies have shown a better prognosis for females and patients aged < 35 – 40 years. The durability of the IFN response is variable. Some responders also undergo HBe seroconversion during follow-up, but the time varies among studies. Pegylated IFN for 24 or 52 weeks can also induce similar levels of seroconversion [36,37]. The durability of the pegylated IFN-induced response is under investigation. Clearance of HBsAg and seroconversion to anti-HBs due to treatment with standard IFN varies considerably among studies, and this might depend on ethnic features of the patients and route of HBV transmission. Standard or pegylated IFN elicit little virological response in anti-HBe-positive CHB patients, whereas about 40% of patients develop a biochemical response. However, the ratios of sustained responses are not so promising [38,39].

3.5.2 Treatment of chronic HBV infection using viral polymerase inhibitors

Several NA that block HBV replication by inhibiting the activities of viral polymerase are now available worldwide [40-51]. Although their mechanisms of action differ, all of these drugs potently inhibit HBV replication.

3.5.3 Antiviral effect of NA in HBeAg-positive chronic HBV-infected individuals

The administration of lamivudine for 1 year reduces the mean HBV DNA concentration by about 4.5 logs [43]. Although

adefovir has less potent antiviral activity, it also causes a mean viral reduction of 3.5 logs after 1 year of administration [44,45]. On the other hand, entecavir has powerful antiviral activity, causing a mean decline in HBV DNA of about 7 logs [46]. Phase III studies have shown that telbivudine is more effective than lamivudine in suppressing viral load (by 6.5 $\log_{10}$ versus 5.5 $\log_{10}$) and in improving liver histology in CHB patients [47,48]. Tenofovir is now applied in various countries to treat patients with CHB. Among patients with both HBeAg-positive CHB and HBeAg-negative CHB, tenofovir at a daily dose of 300 mg had potent antiviral efficacy [49]. A study has also shown that tenofovir may become an effective alternative for the treatment of patients with lamivudine-resistant HBV infection [50]. Clinical trials have shown that emtricitabine (200 mg/day) produces optimal results in patients with CHB; after 2 years, 53% of patients had serum HBV DNA < 4700 copies/ml, 33% seroconverted to anti-HBe, and 85% had normal ALT levels. After 96 weeks of therapy, 18% of patients had developed resistance mutations [51].

3.5.4 *Effect of NA on HBeAg seroconversion and ALT normalization in HBeAg-positive chronic HBV-infected subjects*

Although most NA have potent antiviral capacity, their immune modulation effects are less promising. Lamivudine for 1 year induces seroconversion to anti-HBe in 16 – 18% patients and adefovir has an HBeAg seroconversion rate of about 12%. The rate of seroconversion by entecavir might be a little higher than that of lamivudine (about 21% after 1 year of therapy). NAs like telbuvidine, tenofovir and emtricitabine are also endowed with HBeAg seroconversion capabilities. Again, this may vary considerably according to the patient's profile. The role of NA on ALT normalization is not uniform and might depend on the nature of patients, duration of treatment and nature of the NA Studies have suggested that NA normalizes ALT in about 40 – 70% of HBeAg-positive patients.

3.5.5 *Role of NAs in anti-HBe-positive chronically HBV-infected patients*

Different NAs are also effective against chronic anti-HBe-positive HBV infection [50,52-54]. However, the actual effects depend upon whether the patients are treatment-naive or previously treated. The rate of HBV reduction by these drugs is also more effective in HBeAg-negative patients than in HBeAg-positive patients. This might be because levels of HBV DNA are lower in HBeAg-negative than in HBeAg-positive patients. The therapeutic efficacy of NA is decreased if anti-HBe-positive patients harbor treatment-induced mutant virus. Normalization of ALT by NA has been documented in 40 – 70% patients with anti-HBe-positive CHB.

4. Treatment-induced viral resistance

Almost all types of NA can reduce titers of HBV DNA. Some patients responding to antiviral agents might also undergo HBeAg seroconversion and ALT normalization. Although NAs are usually more effective if used over the long term, drug resistance can emerge [55-61]. The spontaneous variability of the HBV genome and the slow kinetics of viral clearance might be the biological basis of the selection of drug-resistant mutants. Also, NAs cannot control the virologic effects of cccDNA in chronic HBV carriers. Resistance induced by NA has been studied during lamivudine therapy in detail. Lamivudine leads to resistance in 20% of patients per year and can reach 65 – 70% after 5 years of therapy. When viruses develop resistance due to lamivudine therapy, the patients harbor both wild and resistant mutant types of HBV. Whether replication is slower in mutant than in wild-type HBV has been questionable, and this issue became important in ascertaining whether or not lamivudine treatment should be continued in lamivudine-resistant patients. In fact, disease progresses substantially in patients with lamivudine-resistant infection. Adefovir is also associated with the development of resistant HBV strains, but at a far slower rate than with lamivudine (18% at 4 years and 28% at 5 years). The rate of resistance induced by entecavir is much lower than that of other NAs, especially in treatment-naive patients (1.2% in 5 years).

The management of drug-induced viral resistance CHB patients is challenging, but several approaches have been developed to address these issues. The principle of managing drug-induced viral resistance is to add a drug that has no cross-resistance to that which induced the resistant strain, while continuing with the first drug. Both adefovir and entecavir are used to treat lamivudine-resistant patients [62-64]. Some studies favor adefovir together with lamivudine in lamivudine-resistant patients, whereas others favor either adefovir or entecavir in such circumstances. However, entecavir is also associated with considerable resistance when patients are already lamivudine-resistant. Recent data supports that tenofovir may be a potent drug for treating patients with lamivudine-resistant HBV [50]. As lamivudine has been applied for about 10 years, several lamivudine-resistant patients are now emerging. New data are also accumulating about the effectiveness of other NAs and IFN against lamivudine resistance [65,66]. The long-term outcome of lamivudine resistance on patient survival and hepatocarcinogenesis remains unconfirmed in patients with CHB.

5. Combination therapies against HBV

As the therapeutic effectiveness of IFN or NA is not completely satisfactory in patients with CHB, the concept of combining antiviral agents has surfaced. Patients were treated for 48 weeks and the end points were analyzed 24 weeks later. During therapy, the viral load declined more in the combination than in the single treatment group, and the rate of lamivudine resistance was lower in patients who received lamivudine plus IFN than in those receiving lamivudine alone [67,68]. However, the rate of HBe seroconversion was similar between the two groups at 24 weeks after the

termination of therapy. The additive benefit of combining antiviral agents in treatment-naive patients has not been elucidated in detail, but the outcome should be better if other protocols are used.

6. Approaches to overcome limited therapeutic effects of antiviral drugs in chronic HBV infection

Several clinical trials have shown that NAs are potent inhibitors of HBV replication. These drugs also improve liver damage and hepatic fibrosis in many patients. However, the clinical benefits are not comparable to their antiviral efficacy. The effectiveness of current antiviral drugs might be attributed to their relatively insignificant immune modulator capacity, although this remains a matter of further investigation. Circumstantial evidence favors the notion that HBV can basically be controlled by the host immune response. Patients with acute resolved HBV infection do not require drugs to improve their own immune modulatory capacities. In addition, millions of chronically HBV-infected individuals can also efficiently control HBV replication without any features of liver damage (HBsAg-negative, anti-HBc-positive, anti-HBs-negative chronic HBV carriers). Several HBV carriers spontaneously seroconvert to anti-HBe and even to anti-HBs without any type of antiviral treatment. Although host immunity plays cardinal roles in these clinical scenarios, the exact nature of these events remains elusive. The concept of immune therapy for these patients has surfaced in the face of these realities [69-74]. The immune responses of the HBV-infected persons might be upregulated by immune modulation that is either non-HBV-specific or HBV-specific. Although non-antigen-specific immune modulation by cytokines or growth factors could not stand the test of time, HBV-specific immune therapy using HBV-related antigens (vaccine therapy) might benefit these patients. Clinical trials are currently ongoing to optimize the clinical regimens of vaccine therapy and of cell-based immune therapy (using dendritic cells or activated T cells as vaccine adjuvant) in these patients (summarized in [74]). More importantly, some pilot studies have shown that a combination of antiviral and HBV-specific immune approaches using vaccines have been therapeutically effective in some patients with CHB [72-74]. However, these findings should be confirmed by randomized controlled trials (RCTs) in the near future to design appropriate therapeutic strategies for patients with CHB.

7. Conclusions

Chronic HBV infection is currently treatable, but not curable. Treatment is usually recommended for patients who are likely to benefit from antiviral drugs. Even then, the therapeutic efficacy of antiviral drugs is not completely satisfactory, and they are associated with several side effects [75]. Therapy is not usually recommended for patients with minimal disease, whether in the immunotolerant phase or with inactive infection. This is because of the limited efficacy of antiviral drugs in these patients. Indeed, some recent reports have shown that NAs can alter the natural course of HBV infection in patients with no or minimal liver damage [76]. Antiviral therapy is indicated for patients with CHB proven by ALT elevation and abnormal liver histology, because such therapy decreases the risk of liver disease progression compared with the natural history of the disease. Many physicians favor a finite course of pegylated IFN as the first drug of choice for young patients with predictive factors for favorable responses; however, this is yet to receive international consensus. Nucleotide/nucleoside analogues can be administered to non-responders or patients intolerant to IFN, patients with factors associated with a poor response to IFN, or those with a need for long-term therapy, such as those with HBeAg negative CHB. These features indicate that prolonged or even permanent treatment might be needed for such patients, who may never live drug-free if treatment is started with NA. Whether or not a patient would be able to comply with such a drug regimen to a high degree should be ascertained, and a long-term follow-up system should be accessible to the patient. Arrangements should be in place to handle drug resistance in nearby medical facilities. Regular updating of data from new clinical trials should be useful for developing better therapeutic strategies against chronic HBV infection.

8. Expert opinion

The genesis of chronic infection is related to complex interaction between viruses and the hosts. Upon infection with the basically non-cytopathic HBV virus, patients develop features of liver damage that ultimately progress to serious complications It is apparently true that antiviral drugs have altered the natural course of chronic HBV infection, but controversies remain about the real clinical efficacy of antiviral drugs in chronic HBV-infected subjects [75]. A systemic review about antiviral therapy for adults with CHB for a National Institutes of Health consensus development conference has shown that drug treatment did not improve clinical outcomes of CHB infection in 16 RCTs. In addition, in 60 RCTs that examined intermediate outcomes, no single treatment improved all intermediate outcomes. Only a few RCTs showed improvements of one or two intermediate parameters. Indeed, adverse events occurred during antiviral therapy in 50% of patients [75]; however, most studies excluded patients with complications. In spite of these studies, it is to be accepted that treatment with antiviral drugs improved the quality of life of many CHB patients by decreasing viral load, inducing HBeAg negativity or seroconversion and normalizing ALT levels.

Over 90% of total chronic HBV carriers in the world reside in developing countries. However, most therapeutic recommendations have been issued by AASLD, EASL and the Japan Society of Hepatology (JSH) based on data from clinical trials in developed countries. Recommendations have also

been prepared by APASL, which represents some developing countries, but most of the RCTs were completed in Taiwan, Hong Kong and Singapore, which are developed regions within the APASL area. Our reservations about these recommendations are not simply based upon the fact that they were established from data generated by clinical trials in developed countries. We are concerned that HBV carriers in developing countries cannot be properly treated based on these recommendations. This is not a matter of pure science, but rather of social realities. The healthcare delivery systems of developing countries are poorly organized and not controlled by legal systems. Nucleotide/nucleoside analogues can be purchased from any drug store without a prescription in most developing countries. Drug compliance rates are extremely low. The administration of NAs for prolonged periods or for a lifetime cannot materialize in the context of the socio-economic conditions under which people live in developing countries. Laboratory facilities are also unable to detect viral load or detect drug-resistant strains in most developing countries. However, information about oral NAs has already reached these nations and they are widely used by chronic HBV carriers, mostly without proper supervision by trained physicians. The emergence of mutations due to the use of NAs is usually not monitored in these countries. Even if mutant HBV strains are detected at sophisticated facilities in some developing countries, combative measures are virtually nonexistent. This is a major challenge for treating HBV infection in countries that harbor most of the world's HBV-infected individuals.

Our second concern is about the scientific limitation of complete dependence on only antiviral drugs for treating CHB patients, because data have supported that few people have benefited by using these drugs [75]. Inactive HBV carriers are generally not treated because they do not exhibit HBV-related immune responses. This reflects the notion that antiviral drugs are unlikely to be effective in the absence of host immunity. Some NAs can restore immune competence in some HBV carriers, and this might be associated with the therapeutic effectiveness of these drugs. Hence, appropriate types of host immunity might require induction either before or after NA administration. That non-HBV-specific immune modulators such as cytokines or growth factors have not proven successful in RCTs of CHB patients is unfortunate. However, HBV-specific immune therapy with HBsAg-based vaccines has shown some therapeutic effectiveness in CHB patients [69-74]. More clinical trials with immune therapy using different HBV-related antigens, such as HBcAg or a combination of HBsAg and HBcAg plus NA, might be effective for CHB patients.

In short, we consider that antiviral drugs should be cautiously recommended for treating patients with CHB. Antiviral therapy should not be recommended if proper drug compliance and patient follow-up are impossible. Again, drugs should be used only if measures are developed to tackle drug-induced complications. If oral NAs are used according to current guidelines in developing countries, a new problem with HBV might develop in the near future. Patients with CHB who develop drug resistance due to inadequate use and improper follow-up of NA use might flood communities. Because all means of HBV transmission prevail in developing countries, mutant HBV would also be transmitted to healthy inhabitants of these areas. The rise of more pathogenic mutant HBV over time could cause severe worldwide hazards.

Finally, antiviral drugs should be developed based on the life cycle of HBV. All antiviral drugs that are currently used to treat HBV were originally developed for other viral infections, and only later applied to chronic HBV infection. A drug that can completely eradicate all forms of HBV, including cccHBV DNA in the liver and all other tissues, should be developed. More fundamental studies by basic scientists should examine the nature of HBV.

Taken together, ongoing therapeutic guidelines might suit developed countries with government or corporate insurance systems and improved techniques for diagnosing mutant HBV. Local guidelines should clearly indicate that in the absence of laboratory facilities and patient compliance, no treatment is realistic in developing countries. Various professional organizations should exert political and technical pressure to the law enforcement agencies of developing countries to implement legal drug delivery systems. We can also develop insights about lessons learned through the implementation, in poor resources, of treatment against HIV. It is a true that there are many similarities between anti-HBV and anti-HIV treatment in terms of need for clinical and virological assessment and for compliance, but with a lower incidence of resistance [77].

Although the effectiveness of treatment for chronic HBV infection remains controversial, HBV infection is preventable. Indeed, a potent prophylactic vaccine against HBV has been available for the last three decades. Immunization programs have been accepted in principle by most countries affiliated with the World Health Organization. The development of appropriate guidelines for the treatment and enforcement of prophylactic measures based upon the socio-economic and cultural conditions of different countries would help to control HBV infection from a global perspective.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Meeting Report

日米醫學協力研究會肝炎専門部會（通稱「日米肝炎」）は本年6月30日を以て部會長（三代俊治）と二名部會員（林紀夫/溝上雅史）が退任し，同7月1日，殘留せる二名の部會員（小池和彦/脇田隆字）に新部會員三名（SMF Akbar/茶山一彰/金子周一）を加えた新陣容が發足．

小池新部會長率いるところの此の新陣容部會の初仕事＝米國初見參を，茶山部會員（とアクバル部會員）に御願いして報告して頂いた．

編集委員長　三代俊治

日米肝炎会議（ポートランド）に出席して

今年で31回目となる日米医学肝炎部会（正式には，国際医学協力研究事業日米医学協力委員会肝炎専門部会）ミーティングはHIV部会と合同で9月20日から22日にわたって，オレゴン州ポートランドのHotel Vintage Plazaで開催された．日本からは部会員である小池和彦（東京大学），茶山一彰（広島大学），脇田隆字（国立感染症研究所），Sheikh Mohammad Fazle Akbar（東芝病院）の4名が参加した．もう1名の部会員である金子周一先生（金沢大学）は，残念ながら所用のため出席できなかった．アメリカからはChristopher Walker，Rajen Koshy，Anna Lok，Adrian Di Bicegglie，Michael Gale, Jrが参加した．部会員ではないがMichael Katzeも参加した（小池部会長の推定によると，肝炎部会において日本側部会員の平均年齢が米国側のそれを下回ったのは史上初と思われる）．また，アジア各国から数名ずつの肝炎，あるいはHIV感染の専門家が参加した．HIV部会との合同会議は今回が初めてである．会議ではアジア各国のHIV感染，肝炎ウイルスとの共感染の頻度と治療の状況などが報告された（後述）．Anna Lokのアジアの肝炎ウイルスの感染，治療の状況は薬剤耐性株の時限爆弾爆発寸前の状態であるという衝撃的なテーマに示されたように，未だにラミブジンが第一選択として用いられており，genericで品質がどうかもわからないような薬剤がdrug storeで処方箋もなく入手できるという状況が報告された．

以下にAkbar先生による会議のレポートを示す．

United States-Japan Cooperative Medical Science Program (USJCMSP) U.S.-Japan Joint AIDS-Hepatitis Meeting Portland, OR, USA September 19-21, 2009

In the early 1960s, the founding fathers of the United States-Japan Cooperative Medical Science Program (USJCMSP) suggested that a joint effort be initiated between United States of America (USA) and Japan to develop a health program to aid the people of South-East Asia. Scientists of USA and Japan have done their level best to realize these goals during last four and a half decade. A new move has been initiated in 2009 to come more closer for attainment the objectives of USJCMSP. The US-Japan Joint AIDS and Hepatitis Meeting sponsored by USJCMSP that held at Portland, USA, September 21-22, 2009 has directly taken into consideration the voices of the Asian researchers in these fields, noticed their problems in the context of Human Immune-Deficiency Virus (HIV) and Hepatitis Virus-related pathologies, and discussed about possible interventional strategies. All these induced a sense of optimism among Asian investigators that USA and Japan have not abandoned their causes and concerns.

A team of Japanese Hepatitis Panel led by Professor Kazuhiko Koike, Department of Gastroenterology, University of Tokyo, Japan with three members (Prof. Kazuaki Chayama, Drs. Takaji Wakita and Sheikh Mohammad Fazle Akbar) attended the meeting at Portland. Also, members of Japanese AIDS panel attended the Portland meeting.

Out of the four scientific sessions of Portland meet, three sessions were mainly contributed by scientists from USA, Japan, and other comparatively advanced countries of Asia. The sessions include; (1) Antiviral therapy and resistance in co-infected patients with HIV and hepatitis viruses, (2) Cellular immunity and co-infection, and (3) Development of novel vaccines against HIV and hepatitis C virus (HCV).

(1) Antiviral therapy and resistance in co-infected patients with HIV and hepatitis viruses: The topic was discussed by five speakers with Profs. Kazuaki Chayama, Hiroshima, and Aikichi Iwamoto, Tokyo, as

session chair. These presentations indicated about various difficulties that physicians of respective fields have been encountering to treat patients with mono- and co-infected patients with hepatitis viruses and HIV. Speakers emphasized specially about these limitations in patients from Asian and African countries. The inherent limitations of effective drugs, their high costs and dominant side effects act as barriers for treating these patients.

(2) Cellular immunity and co-infection: After a short introduction by Prof. Chris Walker, Ohio, this session was chaired by Prof. Tetsuro Matano, Tokyo and Dr. Takaji Wakita, Tokyo. From presentations of eight speakers, it became evident that understandings about pathogenesis of AIDS, HCV and hepatitis B virus (HBV) infections are yet to be properly realized before evidence-based therapeutic regimens can be developed against these infections. The nature of innate and adaptive immunity, although play critical roles during acquisition and progression of these diseases, have not been well explored in these patients in spite of having thousands of documented evidences in the literatures.

(3) Development of vaccines against HIV and hepatitis C virus (HCV); Vaccine development against HIV and HCV represents a major challenge to mankind. Prof. Nancy Haigwood, Oregon, described objectives of the session that was conducted by Dr. Rajen Koshy and Prof. Masanori Hayami, Kyoto. Researchers are doing their level best for achieving these goals. When we were returning to Japan, breaking news came about safety and limited efficacy of a new type of HIV vaccine in a large cohort study in Thailand. In addition to HIV and HCV vaccines, it is getting evident that hepatitis B vaccination program should be optimized to address emerging challenges in global context.

In addition to these three scientific session, a distinctive feature of this meeting was arrangement of a session for active participation of researchers and investigators from Asian countries. A session entitled 'Epidemiology of Co-infection' was planned in which data about co-infection of HIV and hepatitis viruses were reported from 12 Asian countries. The session was chaired by Dr. SMF Akbar, Tokyo and Dr. Rod Hoff, Singapore. The presentations were given by investigators of advanced and developed countries like Japan, Hong Kong, and Taiwan, emerging developed countries like China and India, and developing countries like Vietnam, Cambodia, Indonesia, Philippines, Thailand, Bangladesh, and Pakistan.

Extreme heterogeneity was documented regarding prevalence and route of infection of HIV infection and co-infection of HIV with hepatitis viruses among Asian countries. Blood transfusion was the main causative factor for co-infection in Japan with HIV/HCV representing the major bulk. However, HIV/HBV co-infection was dominant type of co-infection in Hong Kong, and sexual transmission being the major route of co-infection. In most other Asian countries, injecting drug users (IDUs) are increasing and this seem to have a dominant role in increased prevalence of co-infection of HIV and hepatitis viruses.

The present trend of management of HIV and hepatitis virus infections also reflected dominant influences of socio-economic and traditional factors in health care delivery system of these countries. Different international donor, non government organization and non political groups provide funds for treatment of HIV. However, there is almost no support for diagnosis, treatment and management of HBV or HCV infection in majority of Asian countries. The prevailing conditions state that persons co-infected with HIV and HBV or HCV receive elegant treatment only for HIV, but almost nothing for HBV or HCV. However, it is paradoxically true that many of these patients suffer from severe liver diseases than HIV-related pathologies. These social and policy discriminations have a negative impact for controlling HBV, HCV and also HIV infection.

Overall, the conference provided important insights to investigators of both developed and developing countries. The researchers of developed countries found that translation of basic research for the benefit of vast majority of people of the world can not be solved by scientific developments only; there is a need to find proper application methodology in the context of socio-economical statuses of various countries. The

investigators of developing nations perceived that they must develop a working research protocol for their own country either on their own effort or by getting assistance from developed countries for formulating their own treatment and management guidelines. To realize these facts, we must put an eye on changing epidemiology of these viruses in various social and economic fields.

In summary, intimate communications among people of different disciplines and of different countries with heterogeneous background allowed sharing knowledge and insights about real pictures of infectious diseases like hepatitis viruses and HIV in developed and developing countries. It is a natural expectation that the inherent attitude of participants of this meeting to view science and reality would be affected by this meeting. The final challenge is to modify our practice for development of a health program to aid the people of Asia. Portland meeting will allow us to reach closer to the basic principle of USJCMSP.

In addition to science, there was a trip to Japanese garden at Portland and we were moved to see how such a garden was planned about a century ago and it is well known for a place of tranquility and Japanese culture.

Toshiba General Hospital　SMF Akbar

以上，肝炎ウイルスとHIVの共感染が増加している状況で開催された会議は，アジアの現状を理解し，今後の対策を講じる上で，各国の参加者に大きなインパクトを与えたものと思われる．日本においてもこの状況は対岸の火事として看過できるものではなく，将来アジアからの耐性ウイルスの流入も視野に入れた対策が重要になるものと考えられることから，引き続きこれらの国との交流を続け，耐性株の発生状況などについても情報を得るとともに，B型肝炎，C型肝炎さらにはHIV共感染例の治療などに関する最新の治療に関する情報提供も行っていく必要があると思われた．

タイトな会議の合間を縫って，エクスカーションもプログラムされており，ポートランドにあるJapanese GardenとNational Primate Centerの見学が行われた．Japanese Gardenは戦後日米の友好を考慮して日本人の有志により設立されたものであり，茶室などを備えた立派なものであった．茶室では毎週茶会も開かれているという．ガイドの日本人男性は大変熱心な方で，日本で日本庭園を訪れたのではとても聞けないような細やかな日本庭園の説明をしていただいた．Primate CenterではB型肝炎ウイルスが感染するRhesus monkeyとともにニホンザルも飼育されていた．海外の日本庭園で日本の知識を得てきた日本人を，彼らはどんな気持ちで眺めたのであろうか．

最終日には，肝炎，HIV会議の主催で食事会が開かれ，みんなでごちそうになった．大味で油濃いアメリカの食事にうんざりしていた筆者の一人である小生はみんなが遠慮してそれほど高いものを頼まなかったのに，大きなロブスターのテイルを注文してごちそうになったが，アメリカで食したものの中ではもっとも美味であった．しかし，日本で食する甲殻類とはほど遠いものではあったが．

以上，本誌編集長の求めに応じて，小池部会長＋3名の日本側参加者を代表して一文を寄稿する次第である．漫筆ご容赦いただきたい．

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COMMENTARY

Swine influenza (H1N1) pandemic: developing countries' perspective

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Swine influenza (H1N1) pandemic: developing countries' perspective
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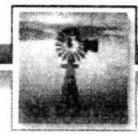
ABSTRACT

Since the first case of the current pandemic (H1N1) 2009 virus reported to WHO on 24 April 2009 on the American continent, the virus has spread in 160 countries and territories. By mid-2009, there were 135 000 cases and 816 deaths recorded. Pandemic preparedness is not advanced in most developing countries. Effective and essential measures include heightened surveillance, early detection and appropriate medical care. The use of local resources and capacity building with the assistance of developed nations will reduce the impact of this pandemic in the developing world.

Keywords: Developing countries, pandemic (H1N1), preparedness plans, surveillance.

The current pandemic (H1N1) 2009

The pandemic (H1N1) 2009 virus has spread from the American continent to other world regions, including Europe, the Middle East, Asia, the Pacific and Africa (Table 1). This complex virus evolved from at least three virus lineages[1-3]. Genetic analysis of the current H1N1 strain shows it to be a reassortment of six gene segments from the known triple reassorted swine virus, and two gene segments (NA and matrix protein) from the Eurasian influenza A (H1N1) swine virus[4]. Human-to-human transmission of this reassorted virus has been reported[5,6]. Based on expert



consultation and assessment of all available information, on 11 June 2009 WHO raised the worldwide pandemic alert level to phase 6, indicating that a global pandemic is underway. Within a short time (from April to July 2009), the virus had spread in 160 countries and territories with 134 503 cases and 816 deaths recorded[7].

Possible impact of current outbreaks in developing countries

To combat and contain the virus, heightened surveillance, the acquisition of up-to-date information, early detection of cases, and the appropriate medical care of cases are crucial. By mid-2009 most pandemic (H1N1) 2009 cases were detected in developed countries but the virus is spreading to developing countries[9]. Developed countries are better prepared to mitigate the effect of the pandemic than developing countries, with Eduardo et al. suggesting that few developing countries are adequately prepared[10]. However, studies of previous influenza pandemics suggest that developing countries are disproportionately affected by influenza pandemics[11,12]. Data from 1918–1920 Spanish Influenza (H1N1) outbreaks suggest the current global influenza pandemic could result in global mortality of approximately 62 million, with 96% of the deaths occurring in the low- and middle-income populations of developing countries[12]. This prediction is supported by considerable numbers of human deaths in the early stages of the pandemic having occurred in Mexico, a middle-income developing country.

The factors underlying increased mortality in Mexico are not yet clear; however, among contributing factors are the delayed identification of the H1N1 virus (due to a lack of sophisticated laboratory facilities), the absence of early action to block the transmission cycle[13] and the virus's greater pathogenicity than the seasonal influenza virus[14,15].

Developing countries are characterized by limited access to medical care, undeveloped public health infrastructure, low socio-economic conditions, increased population density, insufficient public awareness and a high prevalence of existing infectious diseases (eg gastrointestinal and respiratory infections, HIV, tuberculosis, malaria, dengue fever and hepatitis). Various host-related factors, such as poor nutritional status, may also influence morbidity and mortality. The currently useful antiviral drugs (oseltamivir and zanamivir) are most available in developed countries such as the USA, Japan and the countries of the European Union[16]. Vaccines for the current virus are under development in developed countries, where they will be first available. Therefore, additional effort must be made to assist those in developing countries to combat the current pandemic.

Pandemic preparedness plans

The WHO urges all countries to develop and implement national pandemic preparedness plans to prevent, mitigate and minimize the effects of the pandemic (H1N1) 2009[17]. Effective plans for combating any catastrophic infectious disease (such as pandemic influenza) address five issues: (i) surveillance and laboratory services; (ii) communications; (iii) maintenance of community services; (iv) providing medical care; and (v) the supply and delivery of vaccines and drugs[18]. Social distancing also plays a crucial role in developing countries if one or more of these issues cannot be addressed.

In many developing countries preparedness for combating pandemics is inadequate. However, apart from attempting to follow the approach used in developed countries, inherent capacity in developing countries may assist. Many are regularly subject to natural disasters such as cyclones, floods, famine or earth quakes, and recovery from such events may offer resources useful in combating a pandemic. For example, Bangladesh has suffered from food insecurity for decades; however, that country now produces high-yield rice by planting 2–3 crops each year. Small pox has also been eradicated from this and other developing of countries, and polio vaccine coverage is at almost 100%. In such settings, public health programs have succeeded by integrating the skills of people from differing fields.

Table 1: Cases of pandemic (H1N1) 2009 worldwide[8]

WHO Regions	First case reported to WHO	Total	
		Case	Deaths
America	24 April 2009	87965	707
Europe	27 April 2009	16556	34
Western Pacific	28 April 2009	21577	30
South-East Asia	13 May 2009	7358	44
Eastern Mediterranean	3 June 2009	890	1
Africa	18 June 2009	157	0
Total	–	134503	816

Data source: reference 8.

To minimize the impact of the current pandemic (H1N1) 2009, immediate preparedness plans should be devised on the basis of local socio-economic conditions. However, some important issues common to most developing countries should be emphasized. The case fatality rate of a pandemic can be reduced substantially by improving the healthcare system. Essential basic supplies such as drugs, masks and gloves should be available to all hospitals and clinics. In case of scarcity, an alternative approach may be developed on the basis of local social realities. A good distribution system is essential and achievable. The gathering of people for festivals and religious meetings should be restricted, if necessary. Also, public health measures, including the provision of clear and timely information, should be undertaken to avoid the spread of panic.

Healthcare personnel require basic understanding of pandemic infection control. Field workers need to be briefed about the nature of the infection, such as the difference between this and the traditional influenza virus, and differing recommendations for management. Indeed, control of the pandemic (H1N1) 2009 is dependent on comprehensive approaches taken by staff of local departments of health, veterinary sciences and animal husbandry. Politicians and policy-makers should play coordinating roles. Information about influenza infection may be new to public health personnel who may be required to collect samples from patients and animals (in conjunction with veterinary workers). In the absence of private facilities, samples may need to be examined at central public health and veterinary laboratories in developing countries.

Public health and veterinary workers may also take the lead in convincing village populations to develop family emergency plans. Such a plan may involve storing food, prescription medicines, face masks, soap, alcohol for disinfection and other essential supplies. This underscores the importance of a larger nationwide mass-media campaign to boost public awareness. And international cooperation with developed countries will assist in establishing and allocating stockpiles of antivirals and other healthcare supplies. International cooperation can also help build capacity in terms of researchers and healthcare workers.

Conclusion

There is every reason for attention to appropriate pandemic preparedness plans in each developing country to prevent, mitigate and recover from this potentially dangerous strain of influenza. In addition, it is important to build capacity for early detection and outbreak control. Using local resources and capacities in each country as well as international collaboration will help achieve essential goals.

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Review Article

Chronic microbial infections: Manipulation of host immunity as interventional approach

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List of Abbreviations

ALT, alanine aminotransferase: anti-HBs, antibody to HBsAg: APC, Antigen-presenting cell: CHB, Chronic hepatitis B: cccDNA, covalently closed circular DNA: CTL, Cytotoxic T lymphocytes: DC, Dendritic cells: HBV, Hepatitis B virus: HBsAg, hepatitis B surface antigen: HCV, Hepatitis C virus: HBV-TM, HBV transgenic mouse, HIV, Human immune deficiency virus: HSV, Herpes simplex virus: HPV, Human papillomavirus: HBV-TM, HBV transgenic mouse: IL, Interleukin: IFN, Interferon Key words: Chronic viral infections, Immune responses, Antiviral agents, Dendritic cells, Immune therapy

Abstract

Chronic viral infections represent major challenges in contemporary medicine, virology and pharmacology. The virus-bearing hosts are commonly found in every parts of the world and it is extremely difficult to manage these patients. In addition, considerable numbers of these patients develop progressive diseases and severe complications. Finally, most of these patients act as permanent reservoirs of virus. Understandings of viral life cycle during the last decade of 20th century and the first decade of 21st century have allowed development of hundreds of antiviral agents for different diseases. But, the clinical efficacy of these drugs is not yet satisfactory. In addition, virologists have provided conclusive evidences suggesting that eradication of most chronic virus from infected hosts may an unachievable goal. In this context, it is essential to develop alternative, novel, and evidence-based therapeutic maneuver for these patients. Manipulation of host immune system may be one of these approaches. We would discuss about scopes, limitations, and strategies for manipulation for controlling of chronic viral infections.

The primary function of the host's immune system is to mount responses that protect the individual from various microbial infections including viruses. Host's immune responses also control the spread and virulence of the viruses [1]. This is applicable to viruses that cause acute infection. After entering the hosts, these viruses are localized in host's tissues, proliferate and induce antiviral immunity. These cellular events may cause damage and destruction of tissues and the host exhibit features of acute inflammatory diseases. However, the viruses are either almost completely eliminated from the hosts or adequately controlled in situ by host's immune systems. However, chronic infection is established by many viruses because the hosts induce improper and uncoordinated immune responses against these viruses. Most viruses cause persistent infection by evading the host immune surveillance mechanism. Both virus-related factors and host-dependent factors are primarily responsible for viral persistency in subjects with chronic viral infections.

Virus-related factors and persistent viral infection:

Different viruses adopt different mechanisms to establish persistent infections. For example, some viruses may hide in some tissues other than main organ of localization and replication. Thus, the virus can avoid surveillance mechanisms of host immune system [2]. Some viruses can cause latent infections in many tissues and remain inactive for long period of time with minimum levels of replication [3]. In addition, many viruses undergo mutations and avoid immune surveillance of the hosts. The viruses can also circulate as a population of closely-related, yet heterogeneous sequences: the quasispecies in many chronic viral carriers [4]. Some viruses develop different type of life cycle so that it can not be eradicated from the hosts [5].

Latent viral infection and viral persistence:

Evolutionary, microbial agents including viruses have evolved with host immune systems and accordingly are

well adapted to their hosts. Tropism to some specific tissues is part of natural life cycles of many viruses. But, most of the viruses also enter, replicate and integrate in tissues other than their main target organs. Viruses in these tissues can avoid immunological surveillance of the hosts. Latent viral infection may result in acute phase of the disease or more slowly progressive diseases or different types of diseases not resembling to original diseases [6]. Latent viruses can become productive under certain circumstances or in specific cell types. Epstein-Barr virus is latent in B cells and can be productive if released from pharyngeal epithelial cells [7]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are two important human viruses that cause chronic liver diseases such as chronic hepatitis and serious complications like liver cirrhosis and hepatocellular carcinoma. Although these two viruses are primarily hepatotrophic, they have also been detected from many tissues and cells including cells of the immune system such as peripheral blood mononuclear cells, T cells, B cells, macrophages, and dendritic cells [8]. Herpes simplex virus (HSV) usually infects the mucocutaneous surfaces and replicate inside the cells and cause cell death. Concurrently, virus is transported to neuronal cells nuclei in the ganglia innervating the mucocutameous zone of infection. The virus may replicate in this site and establish a clinically silent latent infection [9]. If the host becomes immunosuppressed, the virus may enter into a productive phase and may cause pathological lesions. Recent studies indicate that latent viral infection may be an a common features of most viruses.

Escape from immune surveillance by viral mutations

In order to escape from the host immune surveillance, several viruses undergo mutations so that they are not recognized by the immune systems. Different viruses adapt different mechanisms to achieve this. HCV replicate at an enormous rate of 1012 virions/day by the action of its RNA-dependent RNA polymerase that lacks a proof reading function. This favors formation of variant viruses by cellular and humoral immune responses. Analogous to other RNA virus, HCV circulates in an infected individual as a population of closely related, yet heterogeneous sequences, the quasispecies [10, 11]. The progressive evolution of viral diversity in the hypervariable region of E2 of the HCV has been associated with chronically-evolving hepatitis, whereas, stasis is associated with a self-limited course. However, it is possible that viral escape may be the result rather than cause of viral persistence. Human immune deficiency virus (HIV)-1 also adopts genetic variations to escape attack by host's immune system. The nucleoside misincorporation rate of HIV-1 is of order of 10-4 per site per replication cycle [12]. This virus can undergo frequent recombination between two single stranded positive sense RNA genomes that are present in each virus particle. In addition, internal deletions occur frequently during retrovirus replication. All these allow the mutant strains to escape recognition by the cytotoxic T cell (CTL) responses of the host. In case of human papillomavirus (HPV), infections with multiple HPV types may be responsible for HPV persistence. Infection of individuals with HPV 16 and another type of HPV result in longer duration of detectable HPV 16 than did infection with HPV 16 alone [13]. In comparison to retroviruses, the rate of mutations is comparatively low in DNA viruses such as the HBV. However, the HBV undergoes mutations at different regions of the HBV. It has been estimated that 1010 incorrect nucleotides are incorporated into viral particles every day in a HBV-infected individual. This provides a potential reservoir of genomic variants [14].

Altered life cycle of the HBV and viral persistence

Once a person is infected with the HBV, that individual harbors the virus for the rest of his or her life. The HBV adopts a special type of replication cycle. After interaction of the HBV with cellular receptor on the hepatocyte's membrane, the HBV particle fuses with the membrane, and releases the nucleocapsid into the cytoplasm. The viral envelope proteins are shed during this process and the nucleocapsid migrate to the host nucleus where it is transformed into a supercoiled covalently closed circular DNA molecule (cccDNA). The initial formation of cccDNA from incoming virions cannot be prevented using potent nucleoside analogs inhibiting the viral polymerase and plus strand DNA synthesis [15]. The half life of HBV DNA in the hepatocytes is long compared to that in the blood. Reactivation of viral replication from cccDNA supply new HBV virions that infect fresh hepatocytes. Although, altered life cycle of HBV has been cited here, this may be detected in other viruses as well.

Host-related factors and chronic viral infections

The description provided above indicate that chronic viral infection is established in a host due to several virus-related factors such as presence of latent virus, mutation at the immunogenic epitopes of the viruses, presence of viral quasispecies and exceptional nature of replication of the viruses. In addition, viruses may directly cause functional impairment of host's immune system. Induction of an effective immune response after viral infection is dependent on several factors. Different types of cells of the immune system must act in a coordinated manner for the induction of virus-spe-

cific immune response [16-18]. After the entry to the hosts, the viruses or their antigens must be recognized by the host's antigen-presenting cells (APCs). Different types of immunocytes and parenchymal cells possess APC-like functions. Among these, antigen-presenting dendritic cells (DC) are most potent APC and able to induce both innate and adaptive immune responses. DCs are also endowed with immune regulatory capacities. DC first recognizes the virus at the tissue of infiltration or localization of the viruses. After recognition, the virus is internalized in the DCs by various receptors. The virus is cleaved at the endosomal compartments of DCs into immunogenic epitopes, which then migrate to MHC compartments of DCs and finally to the surface of the DCs. DCs undergo maturation due to internalization and processing of viruses. Maturating DCs then migrate to lymphoid tissues to present antigen to clonally-selected lymphocytes. This lead to the production of virus-specific CD4+ T cells, CD8+ T cells including CTL and antibody-forming B cells including plasma cells. Virus-specific T cells migrate to the tissue of localization of the viruses and destroy the virus-infected cells by cytopathic mechanisms or block the replication of virus by noncytopathic manners. Antibody produced by virus-specific plasma cells neutralizes the free viruses. If the magnitude of virus-specific immune responses is strong and coordinated, it will ultimately result in clearance or down regulation of viral replication. An efficient antiviral immune responses can be induced if all the cellular events related to virus/host interactions such as (1) viral recognition (2) viral internalization (3) intracellular migration of viral antigens (4) maturation of DCs after processing of viral antigens (5) migration of DCs expressing antigenic peptides of the virus (6) presentation and formation of virus-specific T and B cells (7) migration of antiviral T cells to virus-infected tissues and (8) production of neutralizing antibodies proceed in a systemic and coordinated manner. However, several studies have shown that the virus down regulate the functions of DCs by various techniques. Viruses such as HIV-1, HCV and HBV infect the DCs and down regulate their capacities to induce virus-specific immunity by destroying DCs, reducing their T cell stimulatory capacities and interfering with their ability to produce various cytokines. Moreover, virus-specific CTL, and CD4+ T cells also show impaired migration to tissues of localization of the viruses. Finally, some viruses down regulate the functions of effecter cells of immune systems. High viral load inhibit or down regulate the functional capacities of CTLs. In addition to DCs, many viruses have been detected in T cells and B cells and the functions of these cells are also compromised by these viruses [18].

Disease patterns during chronic viral infections

Patients chronically infected with different viruses may remain asymptomatic or may develop features of different diseases. The nature of the pathological processes also shows diversities. Again, chronic viral carriers may remain asymptomatic initially for many years and then develop features of different diseases. Some times, the diseases are progressive in nature and serious complications of those diseases are developed. This is especially manifested in cases of chronic infections by non cytopathic viruses like hepatitis viruses. The causes underlying these are not well understood. However, several investigations have pointed that inadequate and uncoordinated immune responses in chronic viral carriers play roles not only for viral persistence but also for diseases progression.

Therapy of chronic viral infections

Therapy against chronic viral infections is a major challenge for all disciplines of medicines and sciences. Several questions regarding purpose of therapy and nature of therapy have remained unanswered. The final goal of treatment of chronic viral carriers is to eradicate the viruses and down regulate the disease processes. The eradication of the viruses from chronic viral carriers should be achieved before irreversible damages of the hosts occur. Accordingly, several antiviral agents have been developed to destroy the viruses from chronic viral carriers. An ideal antiviral agent should have the following criteria: (1) capable of destroying all types of viruses including latent viruses from all tissues, (3) able to destroy the mutant viruses and viral quasispecies, (3) should be effective against intracellular viruses including modified forms of viruses such as the cccDNA forms of the viruses. Unfortunately, antiviral drugs with these properties are not available at present. However, newer antiviral drugs are coming to the markets. Many of these drugs have been developed to tackle some particular viruses after developing insights about the life cycle of those viruses. Several antiviral agents are used in combination in some patients with chronic viral infections. However, adequate therapeutic effects are not detected in most cases. It is elusive whether it is possible to develop ideal antiviral drugs for chronic viral carriers? In this perspective, we will discuss about some agents that are not endowed with direct antiviral properties, but possess antiviral capacities. Already some of these agents are used in clinics and there are ample opportunities to develop newer and more potent agents in future. Indeed, many of these agents may also be used with antiviral drugs to have a synergist effect against chronic viral infections.

ably be one of the most challenging targets for the development of therapeutic vaccination. The outcome of HIV infection is precisely a progressive destruction of the immune cells that could have a key role in viral control. Most of the current strategies for an HIV vaccine concentrate on the induction of a CD8+ T-cell response. However, it has been shown recently that a single point mutation can allow a viral escape and development of disease. Therefore, a broader immune response, including a CD4+ T cell and a strong antibody response is likely to be needed, both for prophylactic and therapeutic vaccination.The world is encountering different emerging viruses with potential devastating properties. Bird flu viruses are becoming a major public health challenges. In addition to viruses, many bacterial infections may shatter the ongoing public heath delivery system. Malaria and tuberculosis are two such bacterial infections. Due to emergence of mutant types of strains of these bacteria, it has become difficult to treat these patients by antibiotics. Although, manipulation of host immunity has not been started by immune modulators during bacterial infections, a new strategy of anti-bacterial therapy can be developed by on the basis of this concept. Modulation of host immunity is a traditional approach of management of infectious diseases. The endeavor started with eating nutritious food, taking adequate rest, using of traditional biological response modifier. Now, modulation of host immunity during chronic microbial infections is a reality. Development of proper strategies remains to be addressed.

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Conflict of interest

There is no conflict of interest about this article.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Regular surveillance by imaging for early detection and better prognosis of hepatocellular carcinoma in patients infected with hepatitis C virus

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Abstract
Purpose This study evaluated the usefulness of regular check-ups by ultrasonography and contrast-enhanced imaging for early detection of hepatocellular carcinoma (HCC) in a retrospective analysis.
Patients and methods From April 2001 to March 2007, 240 consecutive patients with HCC who were infected with hepatitis C virus (HCV) were divided into three groups. Patients diagnosed with HCC by repeated imaging constituted Group A (surveillance group). Group B comprised patients in whom HCC was detected during scheduled doctor visits for liver disease or other diseases such as diabetes. Group C comprised non-screened patients.
Results The prevalence of solitary tumors decreased from Group A through Group B to Group C (66, 48 and 24%, respectively, $P < 0.001$). The proportion of patients in stages I and II decreased from 83% (103/124) in Group A to 53% (42/79) in Group B and 24% (9/37) in Group C ($P < 0.001$). The proportion of patients who were treated with curative procedures, such as resection or ablation, was highest at 80% (99/124) in Group A, and lower at 53% (42/79) in Group B and 27% (10/37) in Group C ($P < 0.001$). The cumulative survival rate was better in Group A than B ($P < 0.05$), and in Group B than C ($P < 0.001$). Periodical medical check-ups without imaging did not necessarily detect early-stage disease, even when HCC-related markers including des-γ-carboxy prothrombin were tested.
Conclusions Regular surveillance with ultrasonography and contrast-enhanced imaging is useful for detecting early-stage HCC and increase chances for curative treatments in patients with HCV-related chronic liver disease.

Keywords Hepatocellular carcinoma · Early detection · Curative procedures · Survival rates · Surveillance

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1], and patients with HCC continue to suffer an unsatisfactory prognosis. Surveillance for HCC should aim at decreasing mortality, and early detection is vital for therapeutic success. Serum levels of alpha-fetoprotein (AFP) and ultrasonography are widely accepted screening tests for early diagnosis of HCC [2–11].