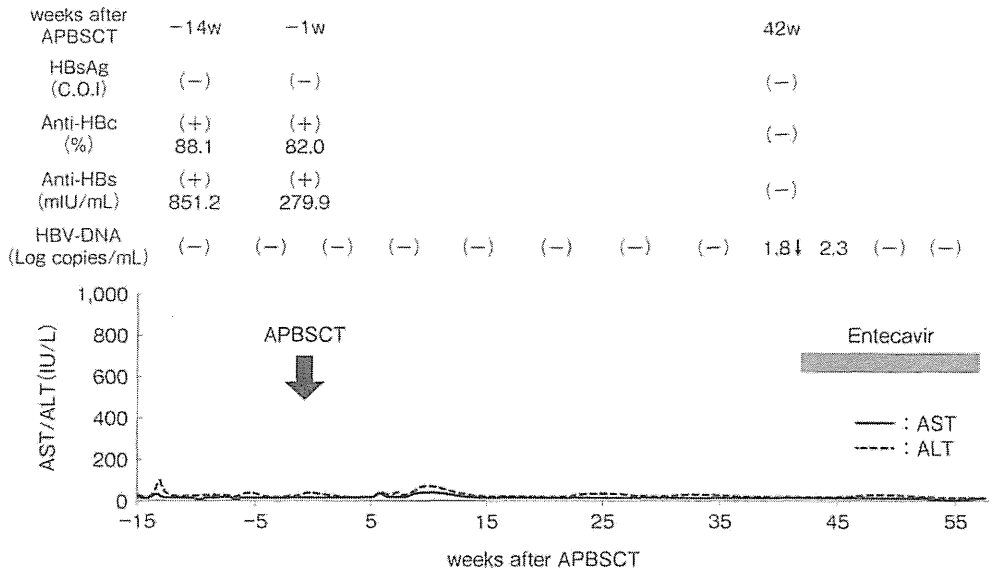

図 1　HBV再活性化例の臨床経過

61 歳女性，症候性骨髄腫に対し VAD 療法 3 コース後，大量エンドキサン(一般名シクロホスファミド)療法による自家末梢血幹細胞採取を施行．大量メルファラン療法による前処置を用いて自家末梢血幹細胞移植(APBSCT)を施行した．移植後 10 カ月の時点で HBV-DNA は 1.8 未満 Log copies/mL であるが，増幅シグナル陽性となり，翌月には 2.3Log copies/mL と上昇し，“再活性化”と診断した．

COI：cut off index，VAD：vincristine＋doxorubicin＋dexamethasone，APBSCT：autologous peripheral blood stem cell transplantation.

apy”が考えられる．

2009 年 1 月，厚生労働省研究班による免疫抑制・化学療法に伴う B 型肝炎対策ガイドラインが発表された[20]．その後，2011 年 9 月に若干の改訂がなされたが，欧米のガイドラインに比較し，HBV 既往感染例への対策がより具体的に記載されている(図 2)[20,21]．詳細はガイドラインに譲るが，HBs 抗原陽性例に対する化学療法時には，原則として抗ウイルス薬の予防投与を行う(図 2)．一方，HBV 既往感染例に対しては HBV-DNA モニタリングを行い，陽性化した時点で抗ウイルス薬を開始する．なお，図 2 は鹿児島大学の坪内博仁教授のご厚意により掲載させていただいた．

HBV再活性化対策における診療上の注意点

癌化学療法および免疫抑制療法開始前のスクリーニング検査として，HBs 抗原だけでなく HBc 抗体および HBs 抗体の測定が重要であり，いずれか陽性の場合には HBV-DNA を追加測定し，HBV 再活性化リスクを判断する．ただし，すでに初回治療が施行されている場合においては，癌化学療法・免疫抑制療法によって抗体価が低下し，既往感染と判別できない例が存在することに留意する必要がある[7,20]．

また，HBs 抗原陰性例の HBV 再活性化の大半が治療前 HBc 抗体陽性であるが，HBc 抗体陰性/HBs 抗体陽性(すなわち，HBs 抗体単独陽性)例からの HBV 再活性化が報告されていることから，HBc 抗体のみによる既往感染の判断には注意が必要である．この点については，HBV ワクチン接種歴の有無と合わせて判断することが重要である．

また，多発性骨髄腫における HBV 再活性化の特徴として自家造血幹細胞移植施行例が大半であるが，免疫の再構築が起こるため，移植後数年経過してからの HBV 再活性化に注意する必要がある[22,23]．とくに移植後合併症に対しステロイド投与を必要とした場合や，移植後再発例に対するサルベージ治療を施行した場合には HBV 再活性化リスクが高くなる可能性が示唆されるため，HBV-DNA モニタリングなどの対策を講じる必要のあることを改めて喚起したい．

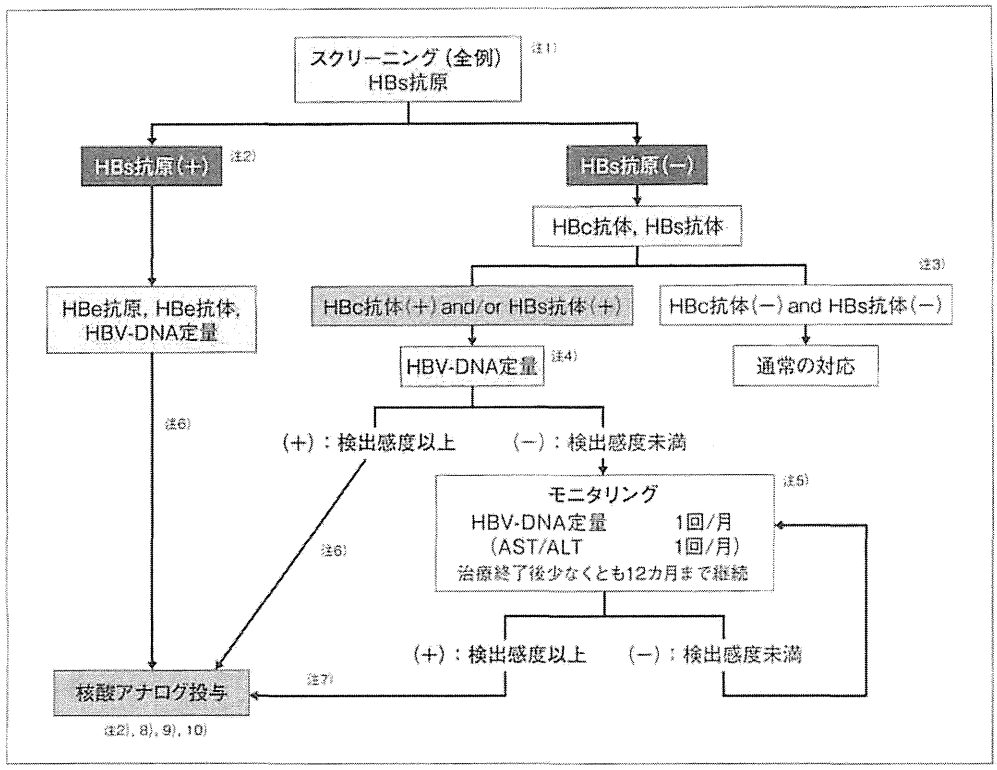

図 2　免疫抑制・化学療法により発症するB型肝炎対策ガイドライン（改訂版）[20]

血液悪性疾患に対する強力な免疫抑制・化学療法中あるいは終了後に HBs 抗原陽性あるいは HBs 抗原陰性例の一部に HBV 再活性化により B 型肝炎が発症し，そのなかには劇症化する症例があり，注意が必要である．その他の疾患においても治療による HBV 再活性化のリスクを考慮して対応する必要がある．また，ここで推奨する核酸アナログ予防投与のエビデンスはなく，劇症化予防効果を完全に保証するものではない．

注1：HBV キャリアおよび既感染者では，免疫抑制・化学療法時に HBV の再活性化が起こることがある．したがって，まず HBs 抗原を測定して HBV キャリアかどうかを確認する．HBs 抗原陰性の場合には，HBc 抗体および HBs 抗体を測定して，既感染者かどうかを確認する．HBs 抗原・HBc 抗体および HBs 抗体の測定は，高感度の測定法を用いて検査することが望ましい．

注2：HBs 抗原陽性例は肝専門医にコンサルトする．すべての症例で核酸アナログ投与にあたっては肝専門医にコンサルトすることが望ましい．

注3：初回治療時に HBc 抗体・HBs 抗体未測定の再治療例では抗体価が低下している場合があり，HBV-DNA 定量検査などによる精査が望ましい．

注4：PCR 法およびリアルタイム PCR 法により実施する．より検出感度の高いリアルタイム PCR 法が望ましい．

注5：リツキシマブ・ステロイド使用例，造血細胞移植例は HBV 再活性化の高リスクであり，注意が必要である．フルダラビンは強力な免疫抑制作用を有するが，HBV 再活性化のリスクは不明であり，今後注意が必要である．

注6：免疫抑制・化学療法を開始する前，できるだけ早期に投与を開始することが望ましい．

注7：免疫抑制・化学療法中は HBV-DNA 定量検査が検出感度以上になった時点でただちに投与を開始する．

注8：核酸アナログはエンテカビルの使用を推奨する．核酸アナログ投与中は原則として 1〜3 カ月に 1 回，HBV-DNA 定量検査を行う．

注9：下記の条件を満たす場合には核酸アナログ投与の終了を検討してよい．

・スクリーニング時に HBs 抗原（+）例では B 型慢性肝炎における核酸アナログ投与終了基準を満たす場合．

・スクリーニング時に HBc 抗体（+）and/or HBs 抗体（+）では，①免疫抑制・化学療法終了後，すくなくとも 12 カ月間は投与を継続すること，②この継続期間中に ALT（GPT）が正常化していること（ただし HBV 以外に ALT 異常の原因がある場合は除く），③この継続期間中に HBV-DNA が持続陰性化していること．

注10：核酸アナログ投与終了後 12 カ月間は現住に経過観察する．経過観察方法は各核酸アナログの使用上の注意に基づく．経過観察中に HBV-DNA 定量検査が検出感度以上になった時点でただちに投与を再開する．

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≪トピックス≫ リンパ腫治療時のB型肝炎ウイルス再活性化

楠本　茂　田中靖人*

要旨

- リンパ腫治療におけるB型肝炎ウイルス(HBV)再活性化への対策において重要な点は，化学療法前のリスク評価(スクリーニング検査)，および再活性化リスクに応じた対策を実施することである．
- HBV再活性化による肝障害が出現してから抗ウイルス薬を投与した場合に十分でない場合がある．
- 厚生労働省ガイドラインに従い，治療前HBs抗原陽性例においては，原則として抗ウイルス薬の予防投与(prophylaxis)を行う．
- HBV既往感染例(HBs抗原陰性例のうち，HBc抗体陽性and/or HBs抗体陽性)においては，HBV-DNAモニタリングによるpreemptive antiviral therapyを行う．

HBV再活性化のリスク

リンパ腫治療において，HBVの再活性化は以前より知られた合併症であり，その大半は治療前HBs抗原陽性例であった[1]．最近，抗CD20モノクローナル抗体(rituximab)の導入によって，治療前HBs抗原陰性例の一部(HBc抗体陽性and/or HBs抗体陽性)においてもHBV再活性化が起こり，重篤な経過をたどることがわかってきた[2~5]．

HBV再活性化の病態は，HBVの増殖と宿主の免疫応答のバランスに大きく影響される．リンパ腫治療前のベースライン時のHBV感染状態および治療による免疫抑制の程度が重要な危険因子となると考えられている．前者はHBV-DNA量，HBs抗原，HBe抗原，HBc抗体およびHBs抗体が重要とされる．一方，後者にはステロイド併用化学療法，rituximab＋ステロイド併用化学療法，造血幹細胞移植療法(同種＞自家)などがある．

これらの報告をもとにHBV再活性化のリスク分類を示す(Fig. 1)．HBs抗原陽性例は，従来HBV再活性化ハイリスク群と認識されており，24～53%のリスクが報告されている[6,7]．一方，HBV既往感染例(HBs抗原陰性例のうち，HBc抗体陽性and/or HBs抗体陽性)における再活性化は，自家もしくは同種造血幹細胞移植例など一部の症例に限られていた．Huiらは，244例のHBs

キーワード：B型肝炎ウイルス，再活性化，癌化学療法．

* S. Kusumoto(講師)(腫瘍・免疫内科学)，Y. Tanaka(教授)(病態医科学(ウイルス学))：名古屋市立大学．

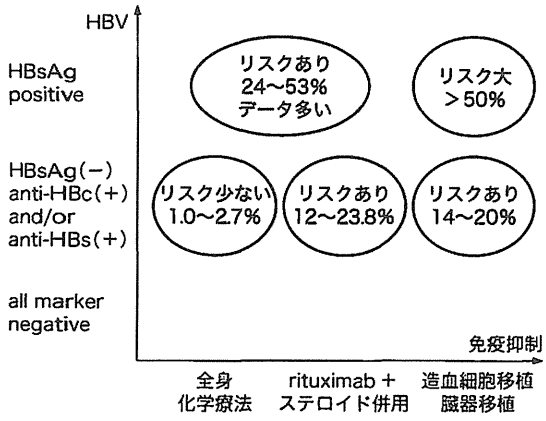

Fig. 1. HBV 再活性化のリスク分類

抗原陰性の悪性リンパ腫例に対し，癌化学療法を施行し，3.3%(8 例)が再活性化による肝炎を発症したことを報告した[3]．8 例全例が HBc 抗体陽性あるいは HBs 抗体陽性であった(1 例は HBs 抗体単独陽性)．また，rituximab＋ステロイド併用化学療法が危険因子であることを多変量解析ではじめて証明した(12.2% vs. 1.0%)．Yeo らは，80 例の HBs 抗原陰性悪性リンパ腫(びまん性大細胞型 B 細胞性リンパ腫)に対し，R-CHOP-like あるいは CHOP-like レジメンを施行し，6.25%(5 例)の再活性化が発症したことを報告した[4]．HBV 既往感染例かつ R-CHOP 施行例に限ると，23.8%(21 例中 5 例)の再活性化頻度であった．

HBV 再活性化対策のためのスクリーニング検査と注意点

HBV 再活性化による肝炎・肝障害が出現してから，抗ウイルス薬を投与開始した場合には間に合わない(劇症肝炎によって死亡する)可能性がある[6,8]．したがって，肝炎が出現してから治療介入するのではなく，あらかじめハイリスク群を同定し，肝炎が出現する前に抗ウイルス療法を開始する必要がある．

厚生労働省ガイドラインにおいて，癌化学療法前のスクリーニング検査として HBs 抗原，HBc 抗体，HBs 抗体の重要性が明記されている[9](Fig. 2)．具体的には，まず HBs 抗原検査を行い，陰性であった場合には，HBc 抗体および HBs 抗体を測定する．いずれかが陽性であった場合には，HBV 既往感染あるいは occult HBV を鑑別するために HBV-DNA 定量検査を行う．HBs 抗原陰性例のうち，HBV-DNA 陽性の場合は"occult HBV 感染"と判定し，HBs 抗原陽性と同様に HBV 再活性化対策を行う必要がある．

なお，いずれの検査においても感度の高い検査方法(HBs 抗原：CLIA 法，HBV-DNA 定量検査：リアルタイム PCR 法)で行うことが望ましい．また，すでに化学療法が施行されている例においては，HBc 抗体および HBs 抗体の力価が低下している場合があり，HBV 既往感染の判定がむずかしくなることに留意すべきである．

また，HBs 抗体単独陽性例で，かつ HBV ワクチン接種歴が明らかな場合には HBV 再活性化リスクはないと判断し，通常の対応とする．

HBs 抗原陽性例への対策と問題点

厚生労働省ガイドラインに従い，HBs 抗原陽性例への対策として，"抗ウイルス薬の予防投与(prophylaxis)"を行う[9](Fig. 2)．抗ウイルス薬として entecavir を用いる．

抗ウイルス薬の投与期間については，質の高いエビデンスは限られている．HBs 抗原陽性例においては，できるだけ早期に抗ウイルス薬を開始し，化学療法開始時のウイルス量が検出感度未満であることが望ましい．また，抗ウイルス薬の中止規準についても明確なエビデンスはないが，① 化学療法後少なくとも 12ヵ月間は予防投与を行う，および② HBV-DNA 定量検査が検出感度未満であることが必要と考えられる．さらに，中止時に HBs 抗原陰性であることが望ましい．

重要な点は，抗ウイルス薬中止後においても，HBV-DNA 定量検査を継続して行うことである．中止後少なくとも 1 年間は HBV-DNA モニタリングを行うことが望ましい．

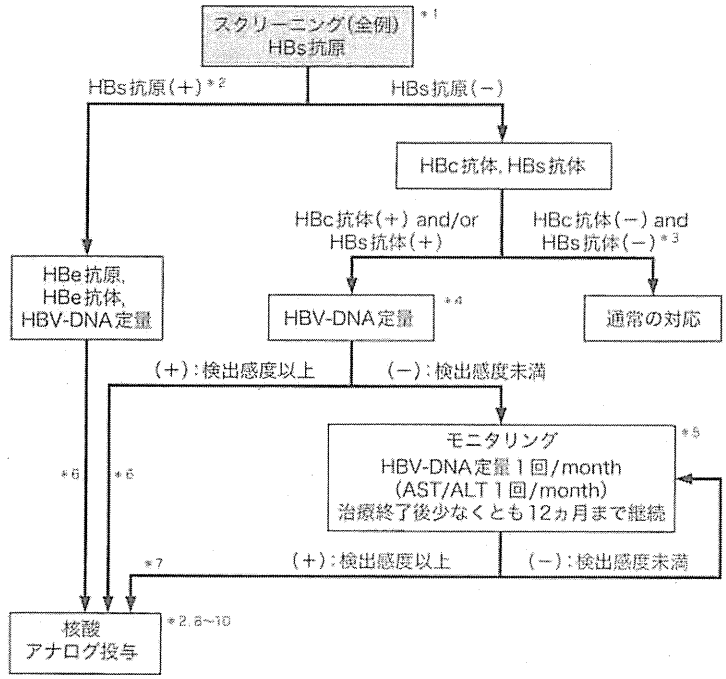

Fig. 2. 免疫抑制・化学療法により発症する B 型肝炎対策ガイドライン(改訂版)

血液悪性疾患に対する強力な免疫抑制・化学療法中あるいは終了後に HBs 抗原陽性あるいは HBs 抗原陰性例の一部に HBV 再活性化により B 型肝炎が発症し，その中には劇症化する症例があり，注意が必要である．その他の疾患においても治療による HBV 再活性化のリスクを考慮して対応する必要がある．また，ここで推奨する核酸アナログ予防投与のエビデンスはなく，劇症化予防効果を完全に保証するものではない．

＊1) HBV キャリアおよび既感染者では，免疫抑制・化学療法時に HBV の再活性化が起こることがある．したがって，まず HBs 抗原を測定して，HBV キャリアかどうか確認する．HBs 抗原陰性の場合には，HBc 抗体および HBs 抗体を測定して，既感染者かどうか確認する．HBs 抗原・HBc 抗体および HBs 抗体の測定は，高感度の測定法を用いて検査することが望ましい．

＊2) HBs 抗原陽性例は肝臓専門医にコンサルトする．すべての症例で核酸アナログ投与にあたっては肝臓専門医にコンサルトすることが望ましい．

＊3) 初回治療時に HBc 抗体，HBs 抗体未測定の再治療例では抗体価が低下している場合があり，HBV-DNA 定量検査などによる精査が望ましい．

＊4) PCR 法およびリアルタイム PCR 法により実施する．より検出感度の高いリアルタイム PCR 法が望ましい．

＊5) rituximab・ステロイド使用例，造血細胞移植例は HBV 再活性化の高リスクであり，注意が必要である．fludarabine は強力な免疫抑制作用を有するが，HBV 再活性化のリスクは不明であり，今後注意が必要である．

＊6) 免疫抑制・化学療法を開始する前，できるだけ早期に投与を開始することが望ましい．

＊7) 免疫抑制・化学療法中は HBV-DNA 定量検査が検出感度以上になった時点で直ちに投与を開始する．

＊8) 核酸アナログは entecavir の使用を推奨する．核酸アナログ投与中は原則として 1〜3ヵ月に 1 回，HBV-DNA 定量検査を行う．

＊9) 下記の条件を満たす場合には核酸アナログ投与の終了を検討してよい．
スクリーニング時に HBs 抗原(+)例では B 型慢性肝炎における核酸アナログ投与終了基準を満たす場合．スクリーニング時に HBc 抗体(+)and/or HBs 抗体(+)例では，① 免疫抑制・化学療法終了後，少なくとも 12ヵ月間は投与を継続すること．② この継続期間中に ALT(GPT)が正常化していること(ただし HBV 以外に ALT 異常の原因がある場合は除く)．③ この継続期間中に HBV-DNA が持続陰性化していること．

＊10) 核酸アナログ投与終了後 12ヵ月間は厳重に経過観察する．経過観察方法は各核酸アナログの使用上の注意に基づく．経過観察中に HBV-DNA 定量検査が検出感度以上になった時点で直ちに投与を再開する．

(2011 年 9 月 26 日改訂)
[文献 9) より引用]

HBV 既往感染例への対策と問題点❍

厚生労働省ガイドラインに従い，月 1 回の HBV-DNA モニタリングを行い，HBV-DNA を検出した時点で抗ウイルス薬を開始する preemptive therapy を行う[9] (Fig. 2).

先述した Hui らの報告によると，再活性化による肝炎が発症する前に平均 18.5 週(最短で 12 週)先行して血中に HBV-DNA の上昇を認めた[3].

また，本邦における rituximab 投与例かつ HBs 抗原陰性 50 例のデータ(全薬工業社内資料)では，rituximab もしくは化学療法最終から肝炎発症までの期間中央値は約 2ヵ月であり，遅発例は 8.5ヵ月が最長であった[5]．その他，これまでの HBs 抗原陰性例からの再活性化例における遅発例は化学療法終了後 1 年が最長であった[10]．以上より，HBV-DNA モニタリング期間は治療終了後少なくとも 1 年間とするのが妥当と考えられた.

最近，台湾のグループは HBV-DNA モニタリング(月 1 回)による多施設共同前方視的研究を学会報告した[11]．HBV-DNA のカットオフ値は 3 log コピー/m*l* で，HBV 再活性化の定義はベースラインから 10 倍以上の HBV-DNA の上昇とした．その結果，9.3%(14 例)で HBV 再活性化を認め，うち 5 例で肝障害を認めた．さらに 2 例では，HBV 再活性化に関連する重篤な肝障害(基準値上限の 10 倍以上の ALT 上昇)を発症した．これらの結果は，より高感度な HBV-DNA モニタリング(カットオフ値は少なくとも 2 Log コピー/m*l*)が必要であることを示唆している.

現在，本邦において厚生労働省研究班(肝炎等克服緊急対策研究事業：H20-肝炎-若手-014，H23-肝炎-若手-008)により rituximab＋ステロイド併用悪性リンパ腫治療中の HBV-DNA モニタリングの有用性を検証するための多施設共同臨床研究(UMIN000001299)が進行中である.

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Hepatitis B Virus Reactivation during Treatment with Multi-Tyrosine Kinase Inhibitor for Hepatocellular Carcinoma

Satoshi Shiba[a] Shunsuke Kondo[a] Hideki Ueno[a]
Chigusa Morizane[a] Masafumi Ikeda[b] Takuji Okusaka[a]

[a]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, and [b]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital East, Chiba, Japan

Key Words
Hepatitis B virus reactivation · Hepatocellular carcinoma · Multi-tyrosine kinase inhibitor

Abstract
Hepatitis B virus (HBV) reactivation is well documented in individuals with cancer who receive certain cytotoxic or immunosuppressive therapies including rituximab treatment. As a general rule, the risk is greatest upon withdrawal of chemotherapy. The risk ranges from approximately 20 to 50% among HBsAg-positive carriers. A 67-year-old man was diagnosed with inoperable multiple hepatocellular carcinoma accompanied by an increase in alpha-fetoprotein and protein induced by vitamin K absence or antagonist II level. Eighteen weeks after starting on the oral multi-tyrosine kinase inhibitor TSU-68, laboratory investigations showed a substantial increase in serum transaminase levels (AST: 302 IU/l; ALT: 324 IU/l) and an elevation of the HBV-DNA level (6.9 log copies/ml). The diagnosis was that the cause of the acute hepatitis was HBV reactivation and we immediately administered entecavir. Two months after the initiation of daily entecavir treatment, laboratory findings showed that the serum levels of transaminases and ALP had improved (AST: 18 IU/l; ALT: 10 IU/l; ALP: 197 U/l). When the HBV markers were examined 4 months later, they were altered: HBeAg was negative and HBeAb was positive. Entecavir treatment was discontinued after 6 months. Although reactivation with rituximab has been reported, reactivation with a tyrosine kinase inhibitor is extremely unusual in a patient who is HBsAg negative but anti-HBc positive. This is the first report describing HBV reactivation with an increasing HBV-DNA level in a HBsAg-negative/HBcAb-positive/HBsAb-positive patient who was treated with TSU-68 for hepatocellular carcinoma.

Shunsuke Kondo
Hepatobiliary and Pancreatic Oncology Division
National Cancer Center Hospital
5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045 (Japan)
E-Mail shkondo@ncc.go.jp

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Introduction

Hepatitis B virus (HBV) reactivation is well documented in individuals with cancer who receive certain cytotoxic or immunosuppressive therapies including rituximab treatment. As a general rule, the risk is greatest upon withdrawal of chemotherapy. The risk ranges from approximately 20 to 50% among hepatitis B surface antigen (HBsAg)-positive carriers. While any chemotherapy regimen can potentially lead to a reactivation of HBV replication, the risk may be decreased with steroid-free chemotherapy, implicating the use of glucocorticoids as a risk factor in lymphoma. In patients who are HBsAg negative but hepatitis B core antibody (HBcAb) positive, reactivation with rituximab has been reported.

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the third leading cause of cancer-related death [1]. Almost 80% of all cases are due to an underlying HBV and hepatitis C virus (HCV) infection. For advanced HCC patients, sorafenib, an inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2), c-Kit, and raf, has been demonstrated to be active and tolerable [2]. Scientific studies on the molecular pathogenesis of HCC have led to the active development of new drugs. TSU-68 is an orally administered, small-molecule, multiple receptor tyrosine kinase inhibitor that targets VEGFR-2, platelet-derived growth factor receptor, and fibroblast growth factor receptor [3]. Since it is a potent anti-angiogenic agent, TSU-68 is also expected to be effective against HCC.

This is the first report describing HBV reactivation in an HBsAg-negative/HBcAb-positive/hepatitis B surface antibody (HBsAb)-positive patient who was treated with the oral multi-tyrosine kinase inhibitor (multi-TKI) TSU-68 for HCC.

Case Report

A 67-year-old man was diagnosed with inoperable multiple HCC accompanied by an increase in alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II level. Although the patient had neither undergone a blood transfusion nor been tattooed and although he did not drink alcohol or use illicit drugs, he had acquired acute hepatitis with no known cause at 30 years of age and had been treated for chronic hepatitis C with interferon-alpha at 58 years of age. When he was diagnosed with HCC, HBsAg, HCV antibody, and HCV-RNA were negative. HBsAb, HBcAb, and HBV-DNA levels were not assessed at the time of diagnosis. His family history of HBV included the following point of interest: his daughter was an HBV carrier. There was no information regarding his late wife's HBV status, as his wife had died almost a decade before.

Transcatheter arterial chemoembolization (TACE) was performed twice upon presentation. Once the patient showed reduction of tumor vascularity on angiography after TACE, he was registered for a phase II clinical trial with the new molecular agent TSU-68, which was administered as an adjuvant chemotherapy after TACE in accordance with the protocol used in the clinical trial. At the beginning of the adjuvant chemotherapy, serum transaminase levels were stabilized within the normal range (aspartate aminotransferase [AST]: 30 IU/l [normal: ≤33 IU/l]; alanine aminotransferase [ALT]: 32 IU/l [normal: ≤42 IU/l]). Eighteen weeks after starting on the novel treatment, laboratory investigations showed a substantial increase in serum transaminase levels (AST: 302 IU/l; ALT: 324 IU/l; fig. 1). The inhibitor was discontinued immediately. Computed tomography showed that the HCC was not exacerbated, and the serum AFP level was normal. Initiating a treatment with ammonium glycyrrhizate did not ameliorate the hepatocellular injury, and a gradual increase in transaminase levels was noted. The HBV markers were positive for HBsAg, HBcAb, and hepatitis B e antigen (HBeAg), and the quantity of HBV-DNA was 6.9 log copies/ml. HCV antibody and HCV-RNA were negative; the serum markers related to other hepatitis infections such as hepatitis A virus,

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cytomegalovirus, Epstein-Barr virus, and herpes virus were negative. The drug lymphocyte stimulation test yielded a negative result for TSU-68.

Using stored serums, we tested HBsAb, HBcAb, and HBV-DNA levels prior to the initiation of TSU-68; the sample was found to be HBsAb positive and HBcAb positive, with an HBV-DNA level of 2.1 log copies/ml. In addition, molecular analysis showed that the HBV genotype was C, with no HBV mutation in the pre-core or core promoter region. We therefore concluded that the cause of the acute hepatitis was HBV reactivation. We immediately administered entecavir at a dose of 0.5 mg once daily. Two months after starting the daily entecavir treatment, laboratory findings showed that the serum levels of transaminases and alkaline phosphatase (ALP) had improved (AST: 18 IU/l; ALT: 10 IU/l; ALP: 197 U/l). When the HBV markers were examined 4 months later, they were altered: HBeAg was negative and hepatitis B e antibody was positive. Entecavir treatment was discontinued after 6 months, but we continued to observe the patient and carefully monitor his liver function and HCC. One year after commencing the treatment for HBV reactivation, HBsAg was negative, HBsAb was positive, and the quantity of HBV-DNA was undetectable by real-time polymerase chain reaction. After the withdrawal of entecavir, no evidence of increased liver damage or disease progression has been noted during follow-up up to today.

Discussion

To the best of our knowledge, this is the first report describing HBV reactivation in an HBsAg-negative/HBcAb-positive/HBsAb-positive patient who was treated with the multi-TKI TSU-68 for HCC in a clinical trial.

Hepatic flare causes an elevation in serum transaminase levels, with the proposed definition of hepatic flare constituting an abrupt increase in serum ALT level to 3–5 times higher than the normal range [4]. HBV flares are usually preceded by an increase in serum HBV-DNA levels. However, because the increase in serum ALT level lags behind the increase in HBV-DNA level, serum HBV-DNA levels may be declining or undetectable when patients with flares are initially evaluated. Thus, HBV reactivation is closely related to the increased quantity of HBV-DNA. In the present patient, who was HBsAg negative, HBsAb positive, and HBcAb positive, serum ALT level increased to more than 7 times the upper limit of the normal range, suggesting a hepatitis flare; the simultaneous increase in the quantity of HBV-DNA allowed us to diagnose HBV reactivation.

HBV reactivation is known to occur often in individuals with chronic HBV infection. In patients with cancer who are HBsAg positive, especially in those with leukemia and lymphoma, the administration of corticosteroids and rituximab during a hematopoietic cell transplantation therapy has been noted to influence HBV reactivation [5]. Recently, it has been reported that the use of rituximab results in HBV reactivation in individuals who are HBsAg negative/HBcAb positive or HBsAb positive. This finding suggests that HBsAg-positive patients, as well as HBsAg-negative/HBcAb-positive or HBsAb-positive patients, have a high risk of HBV reactivation [6]. The guidelines issued by the American Association for the Study of Liver Diseases and the American Society of Clinical Oncology Provisional Clinical Opinion recommend that persons receiving cytotoxic or immunosuppressive therapy should be tested for serologic markers of HBV infection so that prophylactic antiviral therapy can be administered to prevent reactivation in HBsAg-positive patients [7].

Apart from rituximab, other drugs that induce HBV reactivation include infliximab, which targets tumor necrosis factor and is used for the treatment of rheumatoid

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arthritis and inflammatory bowel disease [8], and alemtuzumab, which is a humanized monoclonal antibody directed against CD52 that is used for the treatment of chronic lymphocytic leukemia [9]. However, few reports have described small-molecule inhibitors, such as the histone deacetylase inhibitor [10] that is used for T-cell lymphoma and imatinib, which is used for chronic myeloid leukemia. We believe that this report is unique in that it describes HBV reactivation during the administration of a novel multi-TKI in a patient who did not have any hematopoietic disease and who was HBsAg negative, HBsAb positive, and HBcAb positive. In the SHARP trial for advanced HCC, the multi-TKI sorafenib led to liver dysfunction, which resulted in 5% of the patients discontinuing treatment, but no reports have described an association between such liver dysfunction and HBV reactivation [11]. Although liver dysfunction and an elevation of AST and ALT was noted in 29% of the patients with HCC in a phase II study of TSU-68 which was also administered to our patient [12], our case highlights the possibility that HBV reactivation may be latent in such patients.

HBV genotype influences clinical outcomes, serum quantitative HBV-DNA levels, fulminant hepatitis, and mutational patterns in the pre-core and core promoter regions [13]. In the patient we presented, the HBV genotype was C, but the serum HBV-DNA level at the time of initiating treatment with TSU-68 was not high, and no HBV mutations were observed in the pre-core or core promoter region. These findings lead us to surmise that HBV genotype directly influences HBV reactivation associated with chemotherapy. On the other hand, it should also be noted that no depletion of neutrophils or lymphocytes occurred in our patient. The inhibition of tyrosine kinase may be relevant to the replication of HBV, although it remains unclear how tyrosine kinase inhibition induces HBV reactivation.

Preemptive therapy with lamivudine for HBsAg-positive patients undergoing chemotherapy reduces the risk of HBV reactivation and HBV-associated morbidity and mortality [14]. Monotherapy with entecavir in adult patients with chronic HBV infection is safe, tolerable, and lowers serum HBV-DNA levels to a greater extent than lamivudine [15]. A clinical trial assessing entecavir as preventive therapy for HBV reactivation associated with rituximab treatment is currently underway. It is unclear whether preventive antiviral therapy for patients receiving multi-TKIs is effective, and the risk of developing HBV reactivation during such treatment warrants further investigation.

In conclusion, the risk of HBV reactivation associated with multi-TKIs, especially those that inhibit angiogenesis and cell growth, remains unclear. In clinical trials of such new agents, it is difficult to predict the time point at which HBV reactivation occurs following the administration of new molecular agents. Risk classification of chronic HBV infection and preemptive therapy may prevent HBV reactivation and contribute to the development of novel anticancer treatments in this patient population.

Disclosure Statement

The authors declare that they have no potential conflicts of interest to disclose.

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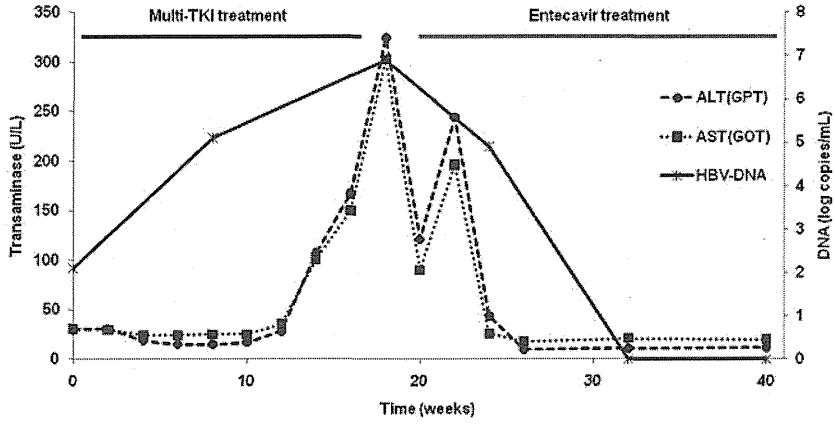

Fig. 1. Changes in serum transaminase levels and HBV-DNA level.

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Digestive Diseases

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Characteristic Pattern of Reactivation of Hepatitis B Virus during Chemotherapy for Solid Cancers

Satoru Hagiwara[a] Toshiharu Sakurai[a] Shinichi Nishina[b] Kaoru Tanaka[b] Masafumi Ikeda[d] Kazuomi Ueshima[a] Yasunori Minami[a] Tatsuo Inoue[a] Norihisa Yada[a] Satoshi Kitai[a] Masahiro Takita[a] Tomoyuki Nagai[a] Sousuke Hayaishi[a] Tadaaki Arizumi[a] Ah-Mee Park[c] Hiroshi Munakata[c] Naoshi Nishida[a] Masatoshi Kudo[a]

Departments of [a]Gastroenterology and Hepatology, [b]Medical Oncology, and [c]Biochemistry, Kinki University School of Medicine, Osaka, and [d]Division of Hepatobiliary and Pancreatic Oncology, National Cancer Hospital East, Chiba, Japan

Key Words
Hepatitis B virus reactivation · Solid cancer · Chemotherapy

Abstract
Objective: A number of studies have reported reactivation of hepatitis B during intensive immunosuppressive therapy such as cases of hematological malignancy, whereas little has been reported for characteristics of reactivation triggered by chemotherapy for solid cancer. ***Methods:*** A total of 130 patients underwent chemotherapy for treatments of common solid cancer between May 2011 and May 2012 at Kinki University Hospital. Among them, 27 patients were suspected for a past infection of hepatitis B virus (HBV), showing positive for hepatitis B core antibody or surface antibody but negative for hepatitis B surface antigen, and were eligible for this study. ***Results:*** Hepatitis B reactivation was observed in 2 of 27 cases (7.4%). The duration between the start of chemotherapy and increase of serum HBV load was 30 days in both cases. ***Conclusions:*** We reported the 2 cases of hepatitis B reactivation receiving chemotherapy for solid cancer in terms of patterns and characteristics of reactivation. Accumulation of such cases will help in clarifying the clinical importance of hepatitis B reactivation during treatment of solid malignancies.

Introduction

Recently, reactivation of hepatitis B virus (HBV) has widely attracted attention among physicians of several specialties, such as hepatologists, clinical oncologists, etc. Because several novel anticancer drugs have come into being recently, effective immunosuppression is potentially attributed to an increase of the reactivation rate of hepatitis B as a consequence of accelerated viral replication [1–3]. Generally, reactivation of hepatitis B can be observed in two populations: asymptomatic hepatitis surface antigen (HBsAg)-positive carriers and HBsAg-negative subjects with a past history of HBV infection.

About 85% of HBV carriers become asymptomatic with stable clinical manifestations due to spontaneously reduced viral replication. However, it is well known that

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Naoshi Nishida, MD, PhD
Department of Gastroenterology and Hepatology
Kinki University School of Medicine, 377-2 Ohno-Higashi
Osaka-Sayama, Osaka 589-8511 (Japan)
E-Mail naoshi@med.kindai.ac.jp

Table 1. Characteristics of patients treated with chemotherapy

Characteristics	Patients, n
Total number of patients	27
Gender	
Male	20
Female	7
Age, years	
Median	66
Range	47–80
Viral markers	
Positive for both HBcAb and HBsAb	23
Positive only for HBcAb	4
Positive only for HBsAb	0
Combination with CDDP	
Yes	17
No	10

the virus remains even in asymptomatic carriers, which causes an increase of replication during or even after systemic chemotherapy as well as immunosuppressive therapy [4]. If systemic chemotherapy or administration of immunosuppressants is stopped even in asymptomatic HBV carriers, severe hepatitis should emerge as a consequence of immune reactivation, which should be an underlying mechanism of reactivation of hepatitis B in asymptomatic carriers. According to recent reports, reactivation is observed in 20–50% of HBV carriers who received intensive cancer chemotherapy or immunotherapy and, importantly, it triggered a fulminant hepatitis in a considerable number of cases [5–7].

Previously it was thought that HBV was completely eliminated from the host with a past history of infection. However, it has been found that HBV is present as cccDNA in hepatocytes and HBV DNA persistently replicates even in those subjects with a past history of acute hepatitis B showing positive for hepatitis B core antibody (HBcAb) as well as hepatitis B surface antibody (HBsAb) [8]. This type of reactivation triggered by chemotherapy and immunosuppressant in subjects with a past infection is called 'de novo hepatitis B'.

Hui et al. [1] examined de novo hepatitis B in 244 HBsAg-negative cases with malignant lymphoma in a cohort manner. They reported that the median period from the elevation of HBV DNA to the onset of hepatitis was 18.5 weeks. Therefore, administration of analogue agents soon after HBV DNA becomes positive would prevent the onset of hepatitis in patients with a past infection. On the basis of this knowledge, prophylactic administration of nucleotide analogue was recommended for asymptomatic carriers in Japan, while HBV DNA should be measured once a month in subjects with a past infection and analogue agents should be administered when HBV DNA becomes positive.

So far, a number of studies have reported the characteristics of reactivation in cases who received intensive chemotherapy and immunosuppressive therapy, such as cases of hematological malignancy. On the contrary, little has been known as to the frequency and characteristics of reactivation during chemotherapy for common solid cancer. We speculate that a unique character of reactivation might exist during the therapy of a common solid tumor because the immunosuppressive effect should be different from those of hematological malignancy. This is an intensive report of reactivation of hepatitis B in cases of de novo hepatitis B who received systemic chemotherapy for common solid cancer.

Materials and Methods

Patient Characteristics and Study Design

A total of 27 cancer patients with a median age of 66 (47–66) years were enrolled in this study, which was approved by the ethical committee of Kinki University Hospital. The inclusion criteria were: (1) patients with a solid malignant tumor undergoing chemotherapy for the first time; (2) HBsAg-negative patients positive for either HBcAb or HBsAb, and (3) patients who gave written informed consent. The exclusion criteria were: (1) patients who underwent or were scheduled to undergo hemodialysis; (2) patients with hepatitis C virus (HCV) antibody-positive; (3) patients positive only for HBsAb with a history of HBV vaccination, and (4) patients who were judged by a physician as ineligible for enrolling in this clinical study. Serum HBsAg, HBsAb, HBeAg, and HBeAb were measured by CLIA with the Architect kit (Abbott Japan). Serum HBV-DNA level was quantified by real-time fluorescent probe PCR (Accugene; Abbott Japan) with a lower limit of quantification at 1.5 log copies/ml. Negative for serum HBV-DNA was confirmed before chemotherapy, and serum HBV-DNA was measured periodically once a month during chemotherapy to monitor HBV reactivation. Monitoring was continued for 12 months after the end of chemotherapy. In cases with HBV reactivation, a nucleotide analogue of entecavir (ETV) was administered. HBV reactivation was defined as a positive signal for amplification of HBV-DNA.

Results

Patient Characteristics

Tables 1 and 2 show the characteristics of the patients treated with chemotherapy. Among a total of 27 patients, 20 were males and 7 were females with a median age of

Table 2. Detailed characteristics and outcomes of patients treated with chemotherapy

Case No.	Age	Gender	Cancer origin	HBsAg	HBcAb S/CO	HBsAb mIU/ml	Regimen	Reactivation	Period until reactivation days	Combination with radiation	Follow-up days
1	60	M	Lung	–	908 (+)	4.1 (+)	CBDCA+PTX	–		+	390
2	71	M	Lung	–	0 (–)	1.9 (+)	CDDP+ETOP	–		–	372
3	47	F	Breast	–	170 (+)	3.2 (+)	AC	–		–	376
4	65	M	Pharynx, esophagus	–	0 (–)	11.8 (+)	CDDP+5-FU	+	30	+	361
5	66	M	Lung	–	45 (+)	4.8 (+)	CDDP+VNR	–		–	361
6	69	M	Lung	–	26 (+)	4.2 (+)	CBDCA+PTX	–		+	354
7	61	F	Esophagus, stomach	–	25 (+)	7.9 (+)	CDDP+5-FU	–		+	361
8	65	M	Pharynx	–	>1,000 (+)	2.6 (+)	CDDP	–		+	345
9	47	F	Breast	–	>1,000 (+)	9.1 (+)	TXT+CPA	–		–	298
10	71	M	Pharynx	–	>1,000 (+)	9.2 (+)	CDDP	–		+	302
11	80	F	Lung	–	44 (+)	4.7 (+)	CBDCA+PTX	–		+	265
12	70	F	Esophagus	–	317 (+)	11.0 (+)	CDGP+5-FU	–		+	202
13	64	F	Breast	–	402 (+)	9.7 (+)	PTX+trastuzumab	–		–	201
14	69	M	Pharynx	–	117 (+)	3.9 (+)	CDDP	–		+	190
15	75	M	Esophagus	–	793 (+)	9.3 (+)	CDDP+5-FU	–		+	170
16	80	M	Esophagus	–	24 (+)	10.5 (+)	CDGP+5-FU	–		+	146
17	72	M	Esophagus	–	320 (+)	9.9 (+)	CDDP+5-FU	–		+	115
18	67	M	Esophagus	–	4 (–)	9.7 (+)	CDDP+capecitabine	–		–	126
19	60	M	Pharynx	–	>1,000 (+)	9.9 (+)	CDDP	–		+	113
20	63	M	Pharynx	–	315 (+)	9.6 (+)	CDDP	–		+	108
21	67	M	Lung	–	68 (+)	10.7 (+)	CDDP+TXT	+	30	–	107
22	65	M	Pharynx	–	81 (+)	10.6 (+)	CDDP+5-FU	–		–	92
23	71	M	Gallbladder	–	5 (–)	9.4 (+)	GEM+low-dose CDDP	–		–	91
24	75	M	Esophagus	–	78 (+)	2.7 (+)	CDDP+5-FU	–		+	74
25	63	M	Lung	–	82 (+)	5.5 (+)	CBDCA+PTX	–		–	77
26	62	F	Esophagus	–	93 (+)	9.6 (+)	CDDP+5-FU	–		–	71
27	61	M	Lung	–	78 (+)	11.2 (+)	CDDP+ETOP	–		+	38

66 years. The profile of serological markers of HBV was as follows: 23 cases were positive for both HBcAb and HBsAb and 4 were positive for only HBcAb, while no case was positive for HBsAb alone. 17 cases were treated using a combination with CDDP, while 10 were treated using a regimen without including CDDP. The origins of cancer were: 9 cases of esophageal cancers, 8 lung cancers, 7 pharyngeal cancers, 3 breast cancers, and 1 gastric and gallbladder cancer, respectively. The median follow-up period after chemotherapy was 190 days, ranging from 38 to 390 days. Among 27 cases, HBV reactivation was observed in 2 cases (7.4%) (cases 4 and 21; table 2). The period before HBV reactivation was 30 days in both cases.

Clinical Course in Cases with HBV Reactivation

Case 4 (fig. 1). A 65-year-old male had synchronous double cancers of the pharynx and esophagus. He received the combination therapy of 5-fluorouracil (5-FU) and cisplatin (CDDP) (CDDP 70 mg/m^2, 5-FU 700 mg/m^2) and underwent radiation simultaneously for a total dose of 60 Gy. Viral markers before chemotherapy were: HBsAg (–), HBcAb 11.8 S/CO (+), and HBsAb (–). One month after the start of chemotherapy, blood tests showed positivity for HBV-DNA at 1.8 log copies/ml and reactivation of hepatitis B was diagnosed. After the administration of ETV, HBV-DNA became negative persistently. Flare-up of hepatitis with elevation of serum ALT in association with appearance of serum HBV-DNA was not observed. Chemotherapy and radiation therapy for cancers were completed without discontinuation or cessation.

Case 21 (fig. 2). A 67-year-old male was suffering from lung cancer and started receiving chemotherapy with CDDP at 80 mg/m^2 and docetaxel (DTX) at 80 mg/m^2 on March 13, 2012. Viral markers before chemotherapy were: HBsAg (–), HBcAb 10.7 S/CO (+), and HBsAb (–). One month after the beginning of chemotherapy, blood examinations revealed a serum HBV-DNA level of <1.5

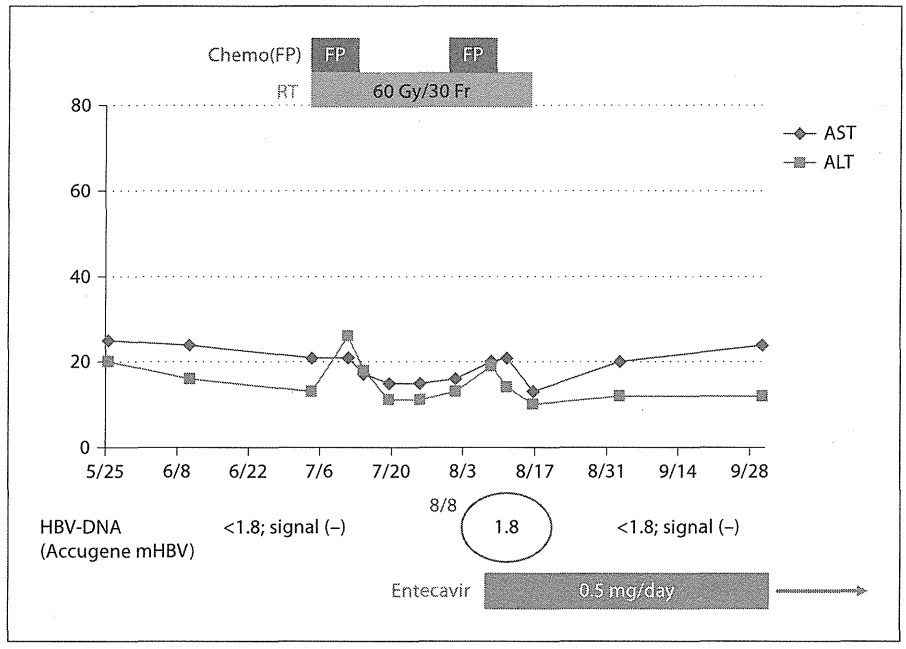

Fig. 1. Clinical course (case 4). A combination of FP (CDDP at 70 mg/m^2 and 5-FU at 700 mg/m^2) and radiation was started. One month after the beginning of chemotherapy, blood tests showed positive HBV DNA at 1.8 log copies/ml.

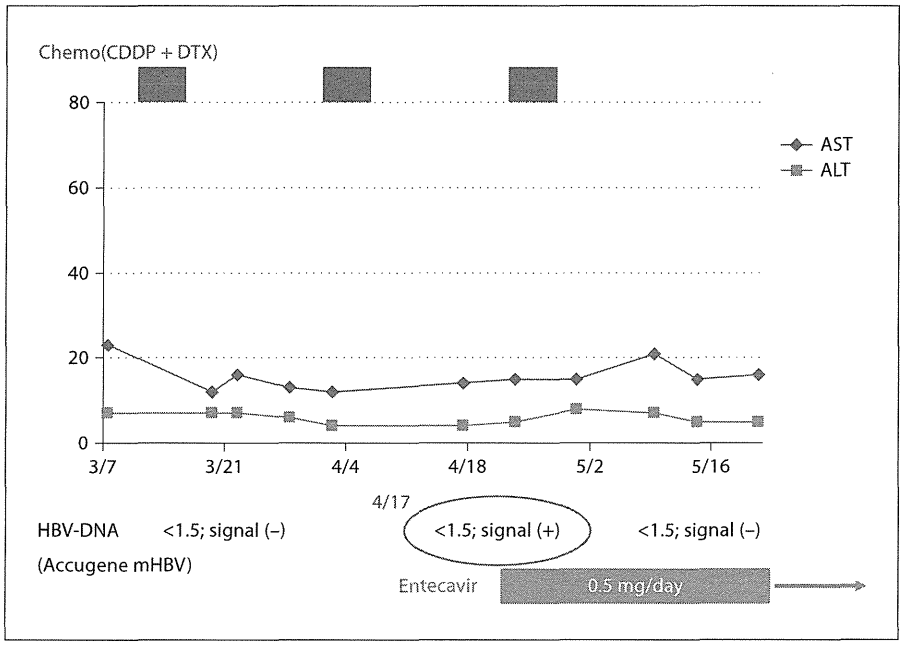

Fig. 2. Clinical course (case 21). CDDP at 80 mg/m^2 and DTX at 80 mg/m^2 were started. One month after the beginning of chemotherapy, blood tests showed HBV DNA at <1.5 log copies/ml but signals were detected.

log copies/ml, but signals of amplification of HBV-DNA were detected which led to the diagnosis of HBV reactivation. ETV was administered and amplification signals have been persistently undetectable since then. No flare-up of ALT at the time of detection of HBV-DNA was observed. Chemotherapy for cancer was completed without discontinuation or cessation.

Discussion

Hui et al. [1] reported the frequency of de novo hepatitis B, or reappearance of HBV-DNA among the patients with a past history of hepatitis B positive for HBcAb and/or positive for HBsAb, in a cohort of 244 cases of HBsAg-negative malignant lymphoma. According to the report,

de novo hepatitis B appeared in 8 cases (3.3%). In particular, it appeared in 12.2% of the cases treated by combination chemotherapy of rituximab and steroid and 1.0% by chemotherapy without the combination, which suggested that receiving combination chemotherapy of rituximab and steroid was a remarkable risk for the onset of de novo hepatitis B.

In 2009, Yeo et al. [9] reported reactivation of hepatitis B in 5 (6.25%) of 80 HBsAg-negative cases with malignant lymphoma who received systemic chemotherapy. In all the 5 cases who showed reactivation, HBcAb was positive and HBsAb was negative before chemotherapy. Uemoto et al. [10] also examined de novo hepatitis B in cases who underwent a living donor liver transplant, and de novo hepatitis B was observed in 94% of the recipients after liver transplantation if the donors showed a past history of HBV infection. These reports indicate the importance of the presence of an undetectable level of HBV in hepatocytes on the pathogenesis of de novo hepatitis B under the immunosuppressant condition.

So far, a number of studies have reported de novo hepatitis B in the treatment of hematological disorders and transplant. On the other hand, this type of hepatitis has rarely been reported in cases receiving chemotherapy for common solid cancer. However, according to the increase of solid cancers and developing new agents for this type of tumor, it is of great importance to know the real frequencies and characteristics of de novo hepatitis B for this type of common disease. In the present study, HBV reactivation was observed in 2 cases (7.4%), which should be a considerable frequency and thus needs paying attention to.

According to the 2 cases we experienced, we noticed that both cases showed: (1) negative HBsAb (CLIA); (2) HBcAb (CLIA) at a high titer $\geq$10 (S/CO); (3) regimens containing CDDP, and (4) HBV reactivation in a relatively short term after the beginning of chemotherapy with a low HBV-DNA load after reactivation.

A decreased titer of neutralizing antibody (or HBsAb) was reported as a risk factor for de novo hepatitis B [9, 11, 12], and HBsAb was negative in the 2 cases of the present study. Furthermore, according to previous reports, HBV reactivation was more frequent in asymptomatic HBsAg-positive HBV carriers than HBsAg-negative carriers [13–15]. However, HBsAg was negative but HBcAb showed a high titer in the present cases, which suggested the possibility that HBsAg became negative due to a persistent viral decrease in asymptomatic HBV carriers.

A number of drugs have been reported to reactivate HBV-DNA [16, 17]. In addition to rituximab for malignant lymphoma, it has been reported that TNF-α antagonists, such as infliximab, for rheumatoid arthritis and Crohn's disease and glucocorticoid monotherapy may also trigger the reactivation of HBV. On the contrary, although HBV reactivation by CDDP was reported previously, it was relatively rare compared to the other immunosuppressive agents [16]. In the 2 cases of the present study, both received CDDP for the treatment of a solid tumor. So far, it is believed that CDDP does not carry direct immunosuppressive activity and it is unclear how much of the induction of reactivation is a result of administrating CDDP. Actually, 15 of 25 cases without reactivation of hepatitis B also received CDDP. However, as both the de novo hepatitis B cases underwent a combination therapy including CDDP, the additive effect might exist for induction of HBV replication. This should be worth paying attention to because CDDP is a key agent for the treatment of common solid cancers. However, it seemed that low viral load at the time of reactivation might be another characteristic in the de novo hepatitis B of a common solid tumor compared to those among hematological malignancies. It could be possible that different immunosuppressive potentials of regimens for malignancies might attribute to the difference of viral load at the time of reactivation.

HBV reactivation is often observed in cases receiving chemotherapy and bone marrow transplant for hematological disorders, but the frequency in cases receiving chemotherapy for solid cancer and the characteristics of HBV reactivation have yet to be elucidated. In conclusion, although only in a few cases, we reported the characteristics of HBV reactivation in cases receiving chemotherapy for solid cancer. Further accumulation of such cases should be clinically important because a growing number of patients have received systemic anticancer therapy for a solid tumor along with the development of new agents and regimens.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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Review Articles

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Reactivation of Hepatitis B Virus in Patients Receiving Chemotherapy

Masafumi Ikeda*

Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

*For reprints and all correspondence: Masafumi Ikeda, Division of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, 277-8577, Japan. E-mail: masikeda@east.ncc.go.jp

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In patients undergoing chemotherapy for the treatment of malignant disease, the reactivation of hepatitis B virus in hepatitis B surface antigen-positive patients has been frequently reported. However, activation has also been reported in hepatitis B surface antigen-negative patients who test positive for hepatitis B core antibody and/or hepatitis B surface antibody, who were thought to have had transient infections and to have been cured. Reactivation has often been reported in patients receiving rituximab-containing regimens and has attracted a lot of attention in recent years. In Japan, 1–3% of patients undergoing chemotherapy are hepatitis B surface antigen-positive, and ~20–25% of patients are hepatitis B surface antigen-negative with hepatitis B core antibody and/or hepatitis B surface antibody positivity; therefore, about one out of every four patients undergoing chemotherapy may be at risk for the reactivation of hepatitis B virus. In most of the guidelines for hepatitis B virus reactivation, the prophylactic administration of an antiviral drug in hepatitis B surface antigen-positive patients is recommended, and periodic monitoring of hepatitis B virus DNA and the deferred pre-emptive administration of an antiviral drug after conversion to hepatitis B virus DNA positivity are recommended in hepatitis B surface antigen-negative patients who are hepatitis B core antibody-positive and/or hepatitis B surface antibody-positive when chemotherapy has been scheduled. However, numerous issues regarding hepatitis B virus reactivation, including the frequency, the types of anticancer drugs, the cancers that facilitate hepatitis B virus reactivation and the optimal method of management, etc., have not been fully clarified. A variety of well-designed prospective studies are currently under way in both Japan and abroad, and strong evidence of hepatitis B virus reactivation following chemotherapy is anticipated in the future.

Key words: hepatitis B virus – reactivation – chemotherapy – HBV DNA – entecavir

INTRODUCTION

Liver dysfunction is caused by a variety of anticancer drugs and their metabolites. Among these liver dysfunctions, a rapid increase in the growth of hepatitis viruses sometimes occurs, which can lead to fatal liver damage in patients who harbor hepatitis viruses and are receiving chemotherapy. The rapid growth of hepatitis viruses is classified as the reactivation of viral hepatitis. The reactivation of hepatitis C virus leading to severe hepatitis is certainly less common than that of hepatitis B virus (HBV), and the associations with chemotherapy have not been sufficiently elucidated (1). However, the reactivation of HBV has often been reported in patients undergoing chemotherapy (1–4), especially those with malignant lymphoma who are receiving combination chemotherapy involving rituximab (5–7). Reports of the reactivation of HBV after treatment with other molecularly

targeted drugs have also been recently increasing (8,9). The reactivation of HBV has frequently been found in hepatitis B surface antigen (HBsAg)-positive patients. In recent years, however, the reactivation of HBV has been reported even in HBsAg-negative patients who are positive for hepatitis B core antibody (HBcAb) or hepatitis B surface antibody (HBsAb) and who were thought to have had transient infections and to have been cured (1–7). Thus, caution regarding the reactivation of hepatitis viruses following chemotherapy is warranted.

Case Description of HBV Reactivation (Fig. 1)

The patient was a 76-year-old woman with malignant lymphoma. Before chemotherapy, she was HBsAg-negative, HBcAb-positive and HBsAb-positive and her liver function was normal (aspartate aminotransferase [AST], 31 U/L; alanine aminotransferase [ALT], 15 U/L; total-bilirubin [T-Bil], 1.2 mg/dl). She had undergone cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) therapy combined with rituximab for 7 months without receiving antiviral therapy for HBV or HBV DNA monitoring. A complete remission of the malignant lymphoma was achieved, and the chemotherapy was terminated. At the time, her liver function was within the normal range (AST, 25 U/L; ALT, 11 U/L; T-Bil, 0.7 mg/dl). Seven months after the termination of the chemotherapy, severe liver dysfunction suddenly occurred (AST, 438 U/L; ALT, 326 U/L; T-Bil, 1.2 mg/dl). At the time of the severe liver dysfunction, the HBsAg status became positive, and the HBV DNA level increased to 9.7 log copies/ml. She was diagnosed as having HBV reactivation following the administration of CHOP therapy with rituximab. Even though an oral antiviral drug (entecavir) was hastily prescribed, the patient's liver function deteriorated further (AST, 4118 U/L; ALT, 1899 U/L; T-Bil, 17.4 mg/dl), and she developed hepatic failure and died. A complete remission of her malignant lymphoma had been achieved and a cure had been expected, but her death as a result of HBV reactivation was an extremely sorrowful outcome. In the present case, the patient's liver dysfunction might have likely been prevented if proper management for HBV reactivation had been performed.

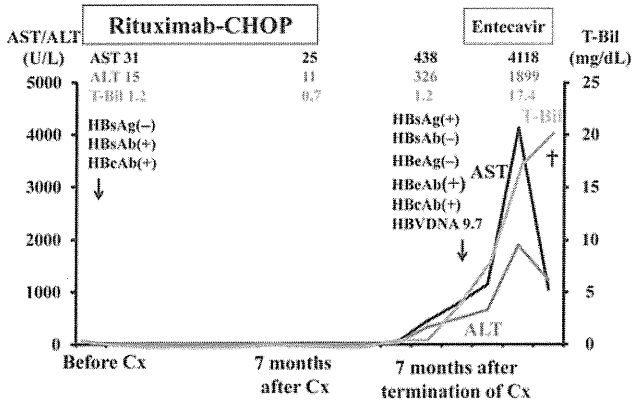

Figure 1. Clinical course of a hepatitis B surface antigen (HBsAg)-negative, HBcAb and HBsAb-positive patient who developed hepatitis B reactivation. The patient was a 76-year-old female and had undergone rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone therapy therapy for malignant lymphoma. Seven months after the commencement of the chemotherapy, a complete remission of the malignant lymphoma was achieved, and the chemotherapy was terminated. Seven months after the termination of the chemotherapy, the reactivation of hepatitis B reactivation suddenly occurred, and she developed hepatic failure and died, despite a treatment of an oral antiviral drug (entecavir). Cx, chemotherapy.

HBV Reactivation

HBV can sometimes be transmitted from mother to child during the immunotolerant period of infancy and early childhood. When infection occurs during this period, the recipient of the virus often becomes an asymptomatic carrier; in some patients, however, chronic hepatitis or liver cirrhosis may develop. In this state, patients are usually HBsAg-positive and HBV DNA is detected in their serum. When the immune response is suppressed by chemotherapy, HBV is reactivated and liver dysfunction is induced, sometimes progressing to a fulminant and fatal stage (10).

After reaching adulthood, HBV can sometimes be transmitted through unhygienic procedures, such as sharing psychostimulant substances, narcotic needles or tattooing, through blood transfusion or through sexual contact. In many patients who become infected after reaching adulthood, the infection is transient and the patient improves after having developed acute hepatitis. Under such circumstances, the HBsAg status usually becomes negative, the HBcAb or HBsAb status becomes positive and HBV DNA cannot be detected in the patient's serum. Previously, HBV was thought to have been completely eradicated from the body in such patients (10). However, Rehermann et al. reported that HBV continued to be present in the liver or peripheral mononuclear cells even after the improvement in liver function following a transient infection (11). Moreover, when HBV remains latent in the liver or peripheral mononuclear cells for a long time, it can begin to proliferate once again if the immune response is suppressed by chemotherapy, and HBV reactivation sometimes occurs as a result of immunocompetent cells attacking liver cells infected with HBV once the immune suppression recovers after the completion of chemotherapy (1–7).

Thus, the risk of HBV reactivation must clearly be considered not only in asymptomatic carriers and chronic hepatitis patients, but also in patients who have been transiently infected and in whom the virus was thought to have been eradicated. Such HBV reactivation has generally been defined as follows (3,4):

1. HBsAg-positive patients
   - A 10-fold or greater increase in HBV DNA
   - Hepatitis B e antigen (HBeAg) becomes positive in HBeAg-negative patients