型肝炎1,000例と比較すると、劇症肝炎発症率は27% vs 7%、劇症肝炎死亡率は100% vs 44%であり、臨床経過が大きく異なることが明らかとなった。また本報告でも、HBs抗原陰性例においてHBVが再活性化する症例のあることが示された。

2 海外におけるリツキシマブ投与例におけるHBV再活性化の報告

リツキシマブ投与時のHBV再活性化に関しては、香港や台湾からの報告が大部分を占めており、前述したHuiらの論文[3]が最もまとまった報告である。なお、海外報告を参考にする場合、HBV感染率は各国で大きく異なることを念頭におく必要がある。

HBs抗原、HBc抗体およびHBs抗体各々の陽性率を比較すると、香港ではHBs抗原は12%、HBc抗体またはHBs抗体陽性率は71～79%であった(**表3**)[3)11)18)]。一方、名古屋市立大学病院の輸血前検査データでは、2005～2006年の2年間3,874検体において、HBs抗原陽性例は1.5%、HBc抗体(および/)またはHBs抗体陽性例は約23%であった[19]。

以上のように、悪性リンパ腫の治療におけるリツキシマブ+ステロイド併用化学療法がHBV再活性化のリスクファクターであることを示唆するHuiらの報告により、従来、HBV再活性化のリスクが低いと認識されてきたHBs抗原陰性例のうち、HBc抗体またはHBs抗体陽性例においても、リスク分類を見直す必要が生じている(**図2**、363頁)。これら症例をHBV再活性化ハイリスク群とした場合、該当する症例数は従来の10倍以上に増加することとなる。

続いて、これらHBV再活性化ハイリスク群に対する対策について、現時点でのエビデンスをまとめ、今後の方向について述べてみたい。

表3 HBs抗原、HBc抗体、HBs抗体陽性率(香港・日本)

	Hong Kong	Hong Kong	Japan (Nagoya)
HBs抗原(+)	12%[11] (78/626)		1.5%[19] (56/3,874)
Anti-HBc(+)	76%[18] (94/124)	62%[3] (152/244)	20%[19] (764/3,874)
Anti-HBs(+)	65%[18] (81/124)	58%[3] (142/244)	22%[19] (822/3,874)
Anti-HBc(+) and/or Anti-HBs(+)	79%[18] (98/124)	71%[3] (173/244)	23.2%[19] (899/3,874)

(文献3)11)18)19)による)

4 HBV再活性化による肝炎・肝障害への対策

HBV再活性化による肝炎発症後に、抗ウイルス薬を投与した場合には治療が間に合わない可能性がある。

Yeoらは、32例のHBV再活性化肝炎に対してラミブジン投与を行ったところ、5例(16%)は死亡、22例は全身化学療法を中止もしくは中断せざるを得なかったことを報告した[15]。そのうち、症状のあるHBV再活性化の死亡率は4～41%と高率であった。また、本邦においても通常の急性B型肝炎と比較して、HBV再活性化による肝炎では劇症化率

が高く、死亡率も高いことが報告されている[17]。したがって、肝障害が出現してから治療介入するのではなく、あらかじめリスク群を同定し、肝炎・肝障害が出現する前に治療を行う必要があるといえる。

現時点での対策として、①抗ウイルス薬の予防投与、②HBV-DNA モニタリングにより陽性化した時点で抗ウイルス薬を投与する“preemptive therapy”がある。当院での取り組みも含めて、HBs 抗原陽性および陰性に分け、対策法と問題点について述べる。

1 HBs 抗原陽性例：抗ウイルス薬の予防投与が原則

全身化学療法における HBV 再活性化の問題は“古くて新しい”問題であり、HBs 抗原陽性例はハイリスク群と認識されてきた。予防投与をしない場合には HBV 再活性化の頻度は 24～53%と報告されている。

香港・台湾を中心としたグループより、これまでに抗ウイルス薬予防投与の臨床試験が施行され、抗ウイルス薬予防投与の有効性に関する多くのデータがある。

Lau らは、全身化学療法予定の HBs 抗原陽性リンパ腫 30 例を対象とし、ラミブジン予防投与(化学療法前から化学療法後 6 週間まで)の有無により二群に割り付けるランダム化比較試験の結果を報告した。HBV 再活性化の頻度は 0% vs 53%と有意に予防投与群において低かった[4]。また、Yeo らは、全身化学療法予定の HBs 抗原陽性の悪性腫瘍 65 例を対象とし、ラミブジン予防投与(化学療法前 1 週間から化学療法終了後 8 週間まで)を行う第Ⅱ相試験の結果を 193 例のヒストリカル・コントロールと比較して報告した[15]。HBV 再活性化の頻度は 4.6% vs 24.4%とラミブジンの予防効果が示された。一方で、ラミブジン投与中にもかかわらず、化学療法中に HBV 再活性化が 3 例(4.6%)に認められたことは留意すべきである。

以上より、HBs 抗原陽性例においては、抗ウイルス薬の予防投与を行うことが原則と考えられる(**図 3、4**)。

また、われわれは、HBs 抗原陽性あるいは HBV-DNA 陽性を「HBV キャリア・慢性 B 型肝炎」として抗ウイルス薬予防投与の対象と考えており、ハイリスク群の同定を目的とし、治療前に HBs 抗原だけでなく、HBc 抗体、HBs 抗体および HBV-DNA の測定を行っている[19]。

抗ウイルス薬の予防投与期間に関するエビデンスはない。治療前 1～2 週間から開始し、治療後は少なくとも 6ヵ月間を目安として予防投与を行っている。また、投与中止前に HBV-DNA が陰性化していることが前提であるが、中止後も HBV-DNA モニタリングは必要と考えられる。

また、抗ウイルス薬の選択については、厚生労働省班会議が提示した平成 18 年度の B 型慢性肝炎ガイドライン[20]によると、35 歳以上の場合はエンテカビル(バラクルード®)をファーストラインに推奨している(**表 4**)。ラミブジン(ゼフィックス®、エピビル®)においては、慢性 B 型肝炎を対象とした臨床試験において、1 年間で耐性が出現する症例が 24%

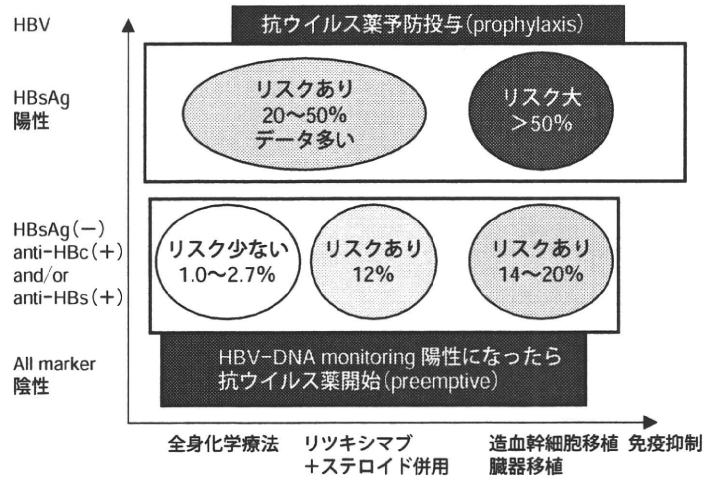

図 3◉HBV 再活性化ハイリスク群への対策(名古屋市立大学)

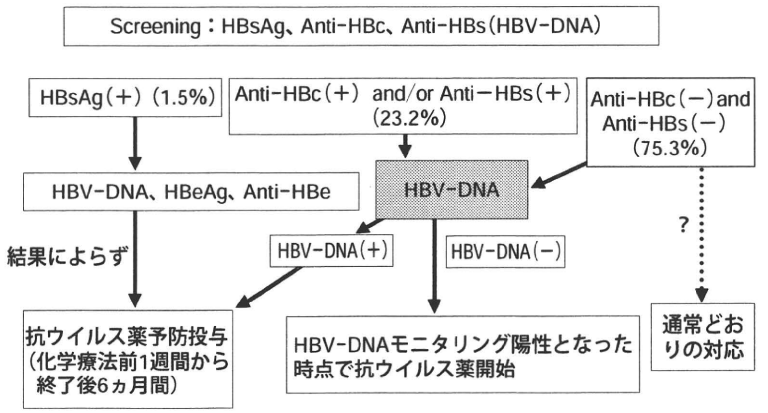

図 4◉HBV 再活性化対策のフローチャート(名古屋市立大学)

表 4◉B 型慢性肝炎患者に対する治療ガイドライン

	HBV DNA	≧7LGE/ml (10⁷copies/ml)	<7LGE/ml (10⁷copies/ml)
35 歳未満	HBe 抗原陽性	IFN 長期間欠	IFN 長期間欠
	HBe 抗原陰性	経過観察(進行例はラミブジン、エンテカビル)	経過観察(進行例はラミブジン、エンテカビル)
35 歳以上	HBe 抗原陽性	①エンテカビル(ラミブジン) ②IFN 長期間欠	エンテカビル(ラミブジン)
	HBe 抗原陰性	エンテカビル(ラミブジン)	エンテカビル(ラミブジン)

【ガイドラインの補足】
抗ウイルス療法は、ALT 値が正常値の 1.5 倍以上を持続する場合に考慮する。
ラミブジン耐性ウイルスによる肝炎に対しては、アデホビル(またはエンテカビル)の投与が有効である。
肝病変進行例(組織所見が F3 以上)では、エンテカビル(ラミブジン)の投与を考慮する。
＊平成 17 年度ガイドラインにおいて、抗ウイルス療法として IFN とラミブジンを中心とした治療法を提示したが、平成 18 年度ガイドラインでは、核酸アナログ製剤をラミブジンからエンテカビルに変更している。
(厚生労働省班会議による平成 18 年度「B 型慢性肝炎の治療ガイドライン」より抜粋，一部追記)

あることが報告されており、予防投与中の耐性化による再燃に注意する必要がある。エンテカビルにおいても長期投与による耐性化の可能性はあるため、薬剤投与の適応および期間については、臨床試験による検討が必要である。われわれは、治療中止のための血清マーカーとして「HB コア関連抗原」に注目しており、この抗原が陰性またはかなり低い値であれば、安全に治療を中止できるとするデータがある[21]。

2 HBs 抗原陰性例：HBV-DNA モニタリングによる臨床試験の必要性

HBs 抗原陰性例におけるデータは極めて限られており、標準的な対策方法は確立していない。これまでの報告からリツキシマブ＋ステロイド併用化学療法が HBV 再活性化のリスクファクターであること、本邦において HBs 抗原陰性ハイリスク群(HBc 抗体あるいは HBs 抗体陽性)が 20～25％存在することがわかった。重要な点は HBV 感染率が各国で異なるため、本邦におけるデータを集約し質の高いエビデンスをつくる必要性がある。

HBs 抗原陰性ハイリスク群への対策を考えるうえで、HBV 再活性化イベントと時間差についてのデータが参考になる。前述した Hui らの報告[3]では、化学療法終了後から肝炎発症までの期間の中央値は 33.5 週(range 12～40 週)であり、先行する HBV-DNA 検出から肝炎発症までの期間の中央値は 18.5 週(range 12～28 週)であった(**図 5**)。すなわち、HBV-DNA は肝障害に先行して上昇し、上昇後 2～3ヵ月以上経過してから肝機能障害が起こるため、HBV-DNA が陽性(現在保険収載されている PCR 法にて 400copies/m*l* 以上)となった時点で治療介入しても十分に抗ウイルス効果が期待できる。

以上のような理由から、当院では HBV-DNA モニタリングにより陽性化した時点で抗ウイルス薬を投与する“preemptive therapy”による対策を行っている(**図 3、4**)[19]。治療中は“2ヵ月に 1 回”、HBV-DNA が上昇する可能性が高い化学療法終了後から 1 年間は“1ヵ月に 1 回”の頻度で HBV-DNA を測定し、その後はリスクに応じて HBV-DNA モニタリングを中止するか継続するかを検討している(**表 5**)。これら HBV-DNA モニタリングにおいても、その頻度や期間においてはデータが十分とはいえず、よくデザインされた前方視的臨床試験が必要である。

一方、抗ウイルス薬予防投与については検討すべき選択肢であるが、エビデンスが皆無であり、現時点では耐性化や費用対効果の問題がある。

また、ステロイドを併用しないことにより HBV 再活性化割合が低下することが予想されるが、治療効果においてネガティブな点を考慮する必要がある。Cheng らは、HBs 抗原陽性悪性リンパ腫を対象としたランダム化比較試験ではあるが、PSL 併用の有無で二群に層別化し、ステロイドを併用しない群において、統計学的有意差をもって HBV 再活性化割合は低かったことを報告した。一方でステロイドを併用しない群において寛解割合および生存割合も低い傾向にあった(有意差なし)ことを報告している[8]。

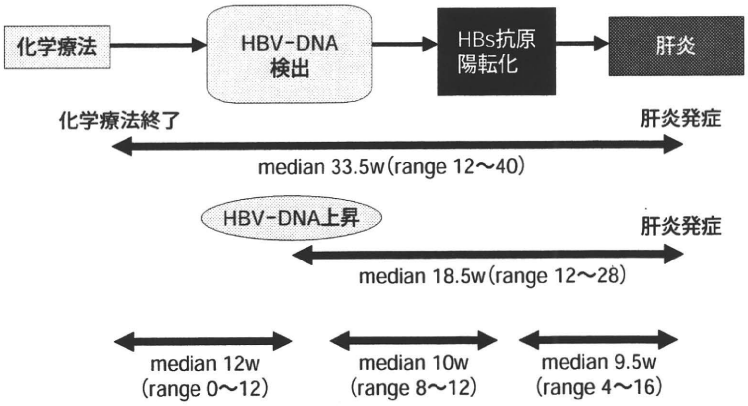

図 5 HBs 抗原陰性例での HBV 再活性化イベントと時間差

(Hui CK, Cheung WW, Zhang HY, et al : Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology 131 : 59-68, 2006 による)

表 5 HBV-DNA モニタリングにおける化学療法前後に行う検査(名古屋市立大学)

	HBs 抗原	Anti-HBc	Anti-HBs	HBV-DNA	AST/ALT
治療前	○	○	○	○	○
治療中 2ヵ月ごと				○	○
終了時	○		○ 抗体価低下例は要注意	○	○
終了後 毎月〜12ヵ月				○	○

→ HBV-DNA(PCR 法)陽性(>400copies/ml)時点でエンテカビル投与(予防投与は行わない)

注意点 HBs 抗原陰性例、HBV-DNA 陰性例においては、HBV-DNA モニタリング、抗ウイルス薬予防投与いずれも現時点では保険適応はない。

●おわりに

悪性リンパ腫治療中の HBV 再活性化のリスク分類を見直す必要があること、HBs 抗原陽性および陰性ハイリスク群における対策と問題点について述べた。欧米に比べ、同ウイルスの既感染患者が比較的多いアジアにおいて、再活性化ハイリスク群の同定および肝炎発症予防の標準的対策法を確立することは急務の課題である。

(楠本　茂、田中靖人)

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＜特別寄稿＞

免疫抑制・化学療法により発症するB型肝炎対策 —厚生労働省「難治性の肝・胆道疾患に関する調査研究」班 劇症肝炎分科会および「肝硬変を含めたウイルス性肝疾患の 治療の標準化に関する研究」班合同報告—

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索引用語：　劇症肝炎　HBV再活性化　*de novo* B型肝炎　核酸アナログ製剤　リツキシマブ

近年，化学療法，免疫療法，移植療法の進歩に伴い，多様な抗癌剤や免疫抑制剤を使用する機会が増加している．以前よりB型肝炎ウイルス（HBV）キャリアに合併した悪性腫瘍患者に対し，ステロイドを併用した化学療法を施行した場合，HBVの急激な増殖すなわちHBVの再活性化（reactivation）により致死的な重症肝炎が発症することが知られていた[1,2]．HBV遺伝子にはglucocorticoid enhancement elementが存在するため[3]，ステロイドにより直接的にウイルス複製が助長されるだけでなく，化学療法による免疫抑制や治療終了後に生じる免疫学的な均衡の破綻により，HBVの増殖とともに広範な感染肝細胞の破壊を伴う重症肝炎が惹起される．このようなHBVキャリアに対する化学療法時にはラミブジンなどの核酸アナログを予防投与してHBV再活性化を避けることが必要である[4]．

一方，HBs抗原陰性でHBc抗体ないしHBs抗体陽性例は従来HBV既往感染とされ，臨床的には治癒の状態と考えられてきた．しかしこのような既往感染例でも肝臓や末梢血単核球中では低レベルながらHBV-DNAの複製が長期間持続することが明らかになっている[5~7]．最近，移植後やB細胞表面抗原CD20に対する抗体であるリツキシマブなど強力な免疫抑制剤の使用により，このような既往感染例からもHBV再活性化により重症肝炎が発症することが報告され，de novo B型肝炎と呼ばれている[8~10]．厚生労働省「肝硬変を含めたウイルス性肝疾患の治療の標準化に関する研究」班の全国調査によりこのようなde novo B型肝炎は通常のB型肝炎

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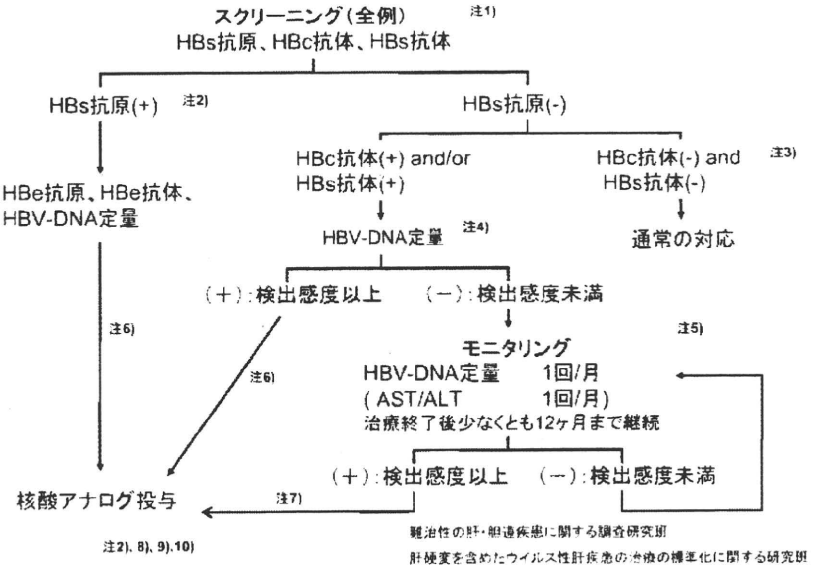

Fig. 1　免疫抑制・化学療法により発症するB型肝炎対策ガイドライン*

補足

*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．

注1）CLIA法で測定することが望ましい．

注2）HBs抗原陽性例は肝臓専門医にコンサルトすること．全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のが望ましい．

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．フルタ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のが望ましい．

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直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．

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良い．
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．(但し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．

に比して劇症化する頻度が高率で，死亡率も高いことが明らかになった[11-13]．また，厚生労働省「難治性の肝・胆道疾患に関する調査研究」班で実施している劇症肝炎・遅発性肝不全（LOHF）の全国調査でもここ数年，特に悪性リンパ腫に対しリツキシマブとステロイドを併用したR-CHOP治療例からの劇症化やde novo B型肝炎が増加傾向にあり，予後不良であった[10,15]．以上のような経緯から，早急なHBV再活性化対策が必要となり，両研究班が合同でワーキンググループを立ち上げ，Fig. 1に示すガイドラインを作成した．

ガイドラインの要旨は以下のとおりである．まずHBV再活性化リスク群の同定を目的にスクリーニング検査として，全ての症例にHBs抗原およびHBc抗体，HBs抗体を測定する．HBs抗原が陽性の場合はさらにHBe抗原，HBe抗体，HBV-DNA定量検査を実施する．HBs抗原陽性例では，無症候性キャリアだけではなく，慢

性肝炎，肝硬変例が含まれる可能性があるので肝臓専門医にコンサルトする必要がある．HBs抗原陽性例での再活性化のリスクは大きいので，基本的に核酸アナログの予防投与を実施する．但し，HBV再活性化のリスクが少ない悪性疾患以外の若年HBe抗原陽性無症候性キャリアに対するステロイド治療例などでは，核酸アナログ予防投与の有効性に関するエビデンスはなく経過観察など他の選択肢があり，適応は慎重に判断する必要がある．HBs抗原陰性でHBc抗体，HBs抗体いずれも陰性の場合は通常の対応とする．HBs抗原陰性でHBc抗体ないしHBs抗体が陽性，すなわち感染既往例と判断される場合は更にHBV-DNA定量検査を実施し，HBV-DNAが陽性の場合は核酸アナログの予防投与を行う．一方，HBV-DNAが陰性の場合はHBV-DNAを毎月モニタリングしながら，陽性化した時点で直ちに核酸アナログを投与する．特にリツキシマブ・ステロイド使用例，造血細胞移植例は再活性化のリスクが高いので慎重な対応が必要である．核酸アナログ予防投与例の投与中止時期に関する明確なエビデンスはないが，HBs抗原陰性，HBc抗体ないしHBs抗体陽性例では免疫抑制・化学療法終了後も12カ月間は投与を継続し，この継続期間中に一定の基準を満たせば投与終了も可能とした．以下にガイドライン作成にあたり論点になった事項を補足する．①スクリーニングにあたってはHBs抗原だけではなくHBc抗体，HBs抗体をできるだけ感度の高い検査法で実施する必要がある．HBs抗原陰性でHBc抗体，HBs抗体いずれも陰性の場合でも，患者が既に免疫抑制状態にある場合には抗体が検出されないことがあり，HBV-DNA定量検査まで測定することが望ましい．②B型キャリア例の急性増悪では発症後早期の核酸アナログ治療が有効であるが，HBV再活性化による劇症化例は発症後の核酸アナログ治療では予後不良であり，発症前の予防投与が必要である．しかし既往感染例でのHBV再活性化率は明らかでなく，また本邦におけるHBc抗体ないしHBs抗体陽性の既往感染例の頻度は高率であることより，全ての症例に核酸アナログの予防投与を実施するのは医療経済的にも困難である．Huiらの報告[5]ではHBs抗原陰性例のHBV再活性化では，HBV-DNAが陽性化し，肝炎が発症するまでに12～28週（平均18.5週）を要しており，したがってHBV-DNAをPCR法またはリアルタイムPCR法で毎月モニタリングし，検出感度以上になった時点で直ちに核酸アナログを投与しても肝炎の重症化は予防可能と推測される．③核酸アナログ製剤はB型慢性肝炎の治療ガイドライン[17]に準拠して，エンテカビル投与を推奨している．しかし，投与期間が長期に及ばない場合など，より安価なラミブジンへの代用も検討の余地がある．④核酸アナログ投与終了に関する明確な基準はない．HBs抗原陽性例では使用する各核酸アナログの投与終了基準に準ずる．HBs抗原陰性，HBc抗体ないしHBs抗体陽性例では免疫抑制・化学療法終了後も12カ月間は投与を継続し，この継続期間中にALTの正常化とHBV-DNAの持続陰性化が見られる場合は投与終了の検討も可能である．但し，HBV以外にALT異常の原因がある場合はALTの正常化は必須ではない．また，核酸アナログ予防投与終了後のHBV再活性化例の報告もあり，投与終了後も更に12カ月間は厳重な経過観察が必要である[18]．

本ガイドライン作成にあたってはワーキンググループ委員の他，名古屋市立大学腫瘍・免疫内科学および鹿児島大学大学院消化器疾患・生活習慣病学血液内科グループの協力および助言を得た．今後は本ガイドラインを血液内科をはじめとする関係領域に周知させていくとともに，各分野と協力して本ガイドラインの有効性を検証していくことが重要である．

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Prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection —Joint report of the Intractable Liver Diseases Study Group of Japan and the Japanese Study Group of the Standard Antiviral Therapy for Viral Hepatitis—

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Key words: fulminant hepatitis　HBV reactivation　*de novo* hepatitis B　nucleoside analog　rituximab

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CLINICAL REVIEW

History and prevention of de novo hepatitis B virus-related hepatitis in Japan and the world

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Abstract Hepatitis B virus (HBV) replication has been shown to persist at low levels in the liver for decades, even in patients with resolved HBV infection. In these cases, reactivation of HBV and ensuing hepatitis during or after cytotoxic or immunosuppressive therapy is now recognized as de novo HBV-related hepatitis. The occurrence of de novo HBV-related hepatitis has become more frequent after the introduction of rituximab for the treatment of hematological disorders, such as malignant lymphomas. More alarmingly, reactivation can lead to fatal fulminant hepatic failure, indicating a need to establish guidelines to prevent the occurrence of de novo HBV-related hepatitis. It is possible that lamivudine prophylaxis and close surveillance of serum HBV DNA are effective in this regard. However, such measures are currently not available to hepatitis B surface antigen (HBsAg)-negative patients in Japan. A preliminary guideline for preventing HBV reactivation during and after cytotoxic or immunosuppressive therapies was made in 2008 by two collaborative study groups from the Japanese Ministry of Health, Labour, and Welfare, including measures not only for HBV carriers, but also for patients with resolved HBV infection. Since this recommendation is a tentative one, further testing and improvements are being planned.

Keywords Hepatitis B virus · De novo hepatitis · Reactivation · Immunosuppression · Prevention

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History and prevention

Approximately 3 billion people have been exposed to the hepatitis B virus (HBV), and there are an estimated 350 million chronic carriers worldwide [1–3]. The clearance of circulating hepatitis B surface antigen (HBsAg) and appearance of antibody to HBsAg (anti-HBs) with normalization of liver function were generally considered as evidence of complete clearance of HBV from hosts until the early 1990s. Since then, it has been shown that HBV replication persists at low levels in the liver and peripheral blood mononuclear cells for decades, even in HBsAg-negative patients with resolved HBV infection [4–6]. In such patients, HBV replication is suppressed by immune responses to HBV, including specific cytotoxic T lymphocyte (CTL)-mediated responses [4].

HBV reactivation in patients with resolved infection is being reported in increasing numbers because the number of people undergoing strong immunosuppressive therapy is increasing worldwide, especially patients with malignant neoplasms, autoimmune disorders, and following transplantation for prevention of rejection. In those patients with resolved HBV infection, reactivation of HBV and ensuing hepatitis is recognized as de novo HBV-related hepatitis, which sometimes leads to fulminant hepatic failure (FHF) and is thus becoming an alarming, well-recognized complication of immunosuppressive therapy that needs further attention [7–9].

Wands et al. [10] reported that reseroconversion from anti-HBs to HBsAg was observed in 5 (13%) of 40 patients with myeloproliferative or lymphoproliferative disorders who received cytotoxic chemotherapy in 1975. This might have been the first report suggesting an association between HBV reactivation and chemotherapy in patients who showed the serological markers of resolved HBV infection.

However, the clinical significance of these phenomena was not clear at that time because our knowledge regarding occult HBV infection was limited. In 1991, Lok et al. reported a prospective study on hepatitis associated with HBV reactivation in patients with malignant lymphoma who received cytotoxic chemotherapy [11]. In their study, HBV reactivation and resulting hepatitis was common in patients who were HBV carriers, but rare (2%) in patients with resolved HBV infection. On the other hand, de novo HBV hepatitis was relatively frequent (14–50%) in patients with hematological disorders who received allogenic bone marrow transplantation [12–16]. This difference in frequency could be attributed to the difference in extent of immunosuppression between the treatments; generally, immune responses are suppressed more profoundly in patients with allogenic bone marrow transplantation than in those with ordinary cytotoxic chemotherapy.

The recent occurrence of HBV reactivation hepatitis in the treatment of hematological disorders, such as malignant lymphomas, has drawn the attention of both hepatologists and hematologists [7, 9]. It is considered to be caused mainly by the introduction of rituximab, which is used mainly for the treatment of B-cell-type malignant lymphomas. Accordingly, the US Food and Drug Administration reported a possible relationship between FHF and rituximab use in October 2004. Rituximab is a genetically engineered chimeric murine/human monoclonal antibody against the CD20 antigen found on the surface of normal and malignant B lymphomas and is used alone or in combination with cytotoxic chemotherapeutic drugs [17, 18]. Dervite et al. [19] first reported a possible relationship between HBV reactivation and rituximab use in a patient with resolved HBV infection in 2001. Following that report, several cases of de novo HBV-related hepatitis after treatment with rituximab that proved fatal were reported [20–24]. B cells may act as antigen-presenting cells and prime CTL responses in HBV infection. Rituximab induces profound and durable B cell depletion to an extent of 0% CD20-positive cells, thus possibly enabling reactivation of CTL-suppressed HBV replication to occur.

Hui et al. [25] evaluated the risk of developing de novo HBV-related hepatitis after chemotherapy in Hong Kong. They prospectively followed 244 patients with lymphomas who were negative for HBsAg for a median period of 12.4 months. In their report, eight (3.3%) patients developed de novo HBV-related hepatitis. These eight patients were presumed to have occult HBV infection because they were found to be positive for at least one anti-HBs and for anti-HBc. Of these patients, three developed FHF, one of whom died. Multivariate analysis showed that de novo hepatitis was independently associated with higher risk of FHF, with a relative risk of 29.9. A risk factor for developing de novo hepatitis was the use of a rituximab plus steroid-containing regime. In addition, elevation of HBV DNA, HBsAg, and alanine aminotransaminase (ALT) values were seen after finishing chemotherapy. Since a 100-fold increase in serum HBV DNA preceded the onset of de novo hepatitis by a median period of 18.5 (range 12–28) weeks, Hui recommended close surveillance for such an increase so that antiviral therapy could be initiated as quickly as possible. On the other hand, Liu et al. suggested the possibility that short-term lamivudine prophylaxis during chemotherapy for patients with occult HBV infection is more cost effective than close surveillance of serum HBV DNA [26]. Further studies are required to clarify this matter.

De novo HBV-related hepatitis after orthotopic liver transplantation was first reported by Douglas et al. in 1993 [27]. Uemoto et al. [28] clarified that HBV strains found in a donor liver before transplantation were the same as those found in a corresponding recipient who developed de novo hepatitis by comparing nucleotide sequences in the HBV genome. Rokuhara et al. [29] also showed that those two strains of HBV were identical by determining the full nucleotide sequence of the HBV genome. According to reports so far, the incidence of de novo hepatitis ranges from 33% to 94% when livers are transplanted from donors with anti-HBc, and from 0% to 0.5% when livers are transplanted from donors without [27–32] indicating that de novo HBV-related hepatitis in liver transplantation recipients is closely associated with occult HBV infection in donor livers. Since the occurrence of de novo hepatitis is quite frequent when donors show serological markers of resolved HBV infection, it may be prevented by the administration of hepatitis B immunoglobulins and nucleot(s)ide analogues in combination [33].

The state of de novo HBV-related hepatitis in Japan was surveyed in 2005 by a group directed by Dr. Kumada (Toranomon Hospital) from the Ministry of Health, Labour, and Welfare of Japan (study for standardization of treatment of viral liver diseases including liver cirrhosis) [34]. In this retrospective study, a total of 55 patients with de novo HBV-related hepatitis were seen between January 2000 and December 2004 in 90 hospitals. During the same period, approximately 1,000 patients with typical acute hepatitis B were diagnosed in those hospitals. Among the 55 patients with de novo HBV-related hepatitis, 27% developed FHF, compared with only 7% of patients with acute hepatitis B. It is noteworthy that mortality was as high as 100% in patients with de novo hepatitis who developed FHF [8]. Taken together, it is evident that de novo HBV-related hepatitis with a strong tendency to develop into FHF with high mortality is an important issue that needs to be addressed.

There seem to be no official guidelines for preventing de novo HBV-related hepatitis occurring during or after cytotoxic or immunosuppressive therapy in the world. The American Association for the Study of Liver Diseases has

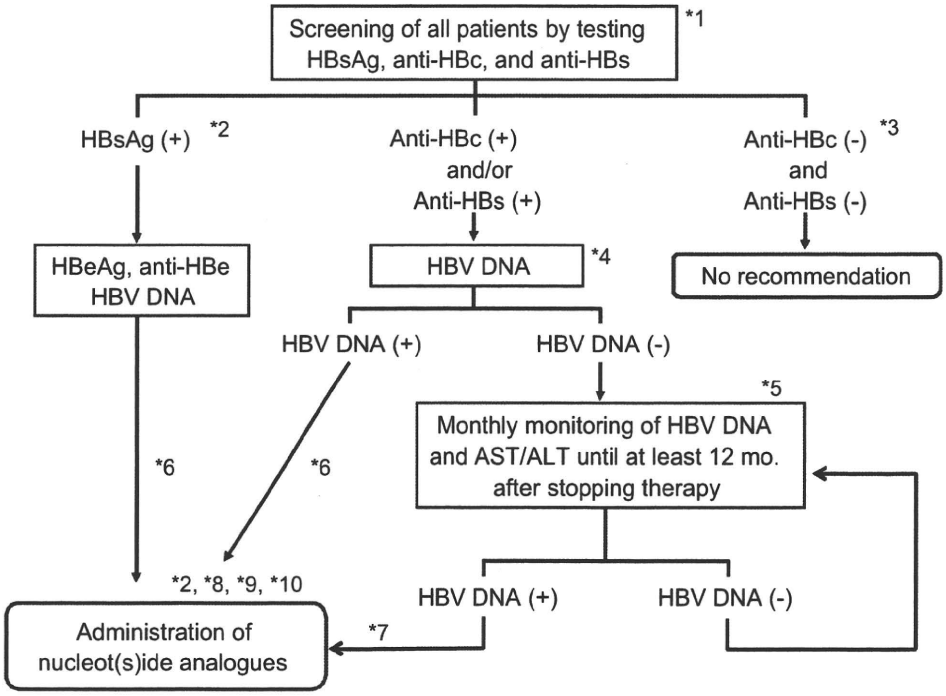

Fig. 1 Recommendation for preventing hepatitis B due to reactivation of HBV during and after immunosuppressive or cytotoxic therapies. The prophylactic administration of nucleot(s)ide analogues recommended here is not completely based on evidence, and thus does not necessarily guarantee the prevention of fulminant hepatic failure. *1 Measurement using chemiluminescence immunosorbent assay is recommended. *2 Consultation with a hepatologist is recommended. *3 It is possible that anti-HBc and anti-HBs becomes undetectable during immunosuppressive or cytotoxic therapies. Additional measurement of HBV DNA is recommended in these cases. *4 HBV DNA is recommended to be tested by methods having the highest sensitivity available. *5 A high risk of developing de novo HBV-related hepatitis should be noted in patients who receive a rituximab plus steroids regime or in those who underwent hematopoietic cell transplantation. Fuldarabine can suppress immune responses profoundly and thus its use requires attention; however, its potential for causing reactivation of HBV is currently unknown. *6 Administration of nucleot(s)ide analogues is recommended as early as possible before starting immunosuppressive or cytotoxic therapies. *7 Administration of nucleot(s)ide analogues is recommended as soon as possible when HBV DNA becomes detectable during immunosuppressive or cytotoxic therapies. *8 Entecavir is recommended among nucleot(s)ide analogues. *9 In HBV-carrier patients, discontinuation of nucleot(s)ide analogues can be considered when patients meet the conditions shown in the guidelines for the treatment of hepatitis B patients prepared by Dr. Kumada and the Ministry of Health, Labour, and Welfare of Japan in 2008. In patients with resolved HBV infection at screening, discontinuation of nucleot(s)ide analogues can be considered when patients meet all of the following conditions: (1) the period after discontinuing immunosuppressive or cytotoxic therapies is at least 12 months, (2) ALT levels are within normal range during this period, and (3) HBV DNA levels are under detection limits during this period. *10 Patients should be followed carefully for 12 months after discontinuing nucleot(s)ide analogues. If serum HBV DNA becomes detectable during the follow-up period, administration of nucleot(s)ide analogues should be recommenced as soon as possible

published the antiviral prophylaxis for HBV carriers, but not for patients with resolved HBV infection [35]. It is possible that nucleot(s)ide analogue prophylaxis and close surveillance of serum HBV DNA are effective to prevent occurrence of de novo HBV-related hepatitis [25, 26]. However, such measures are currently not available to HBsAg-negative patients in Japan. The incidence of de novo HBV-related hepatitis is expected to increase in the future with the advent of stronger immunosuppressive and cytotoxic drugs, such as rituximab. As de novo hepatitis sometimes causes fatal FHF that cannot be controlled with nucleot(s)ide analogues after the onset of hepatitis, guidelines to prevent the occurrence of reactivation are needed.

A preliminary recommendation for preventing HBV reactivation during and after cytotoxic or immunosuppressive therapies was prepared in 2008 by two study groups from the Ministry of Health, Labour, and Welfare of Japan in collaboration: the study group for the standardization of treatment of viral liver diseases including liver cirrhosis directed by Dr. Kumada (Toranomon Hospital), and the study group for intractable liver and biliary tract diseases directed by Dr. Tsubouchi (Kagoshima University). This recommendation includes measures not only for HBV carriers, but also for patients with resolved HBV infection, as shown in Fig. 1. Although the guideline is tentative and may need future amendments, it nonetheless represents a first step in addressing the increasing global problem of de novo HBV-related hepatitis.

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BRIEF REPORT

Mortality Secondary to Fulminant Hepatic Failure in Patients with Prior Resolution of Hepatitis B Virus Infection in Japan

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Hepatitis B virus (HBV) reactivation in patients with resolved HBV infection was found in 23 (4%) of 552 newly hepatitis B surface antigen–positive patients in Japan. Because one-fourth of cases develop into fulminant hepatic failure and mortality is 100%, management of HBV reactivation in patients with resolved HBV infection should be discussed.

Reactivation of hepatitis B virus (HBV) is becoming a well-recognized complication in patients with chronic HBV infection who are undergoing cytotoxic chemotherapy or immunosuppressive therapy [1–5]. HBV reactivation has a variety of manifestations, ranging from subclinical increases in transaminase activity to severe and potentially fatal fulminant hepatic failure (FHF). Because clinical studies have demonstrated that lamivudine therapy reduces the rate of HBV reactivation and mortality [6–9], prophylactic antiviral therapy is advised for HBV carriers at the onset of chemotherapy [10].

The clearance of hepatitis B surface antigen (HBsAg) and the appearance of antibody to HBsAg, with normalization of liver function, is generally accepted as evidence of clinical and serologic recovery from acute hepatitis B. However, HBV replication has been shown to persist at low levels in the liver for decades [11–13], which may explain the recent increase in the rate of HBV reactivation in patients with resolved infection during or after chemotherapy and transplantation [1, 5, 14–16]. Although reactivation led to FHF and even death in some cases [17–22], the incidence of and mortality associated with HBV reactivation have not been fully clarified in this context. Recently, a prospective study [23] from Hong Kong revealed that 3.3% of HBsAg-negative patients developed HBV reactivation after chemotherapy. In Japan, because ~20% of individuals are positive for at least 1 HBV marker [24], HBV reactivation during or after immunosuppressive treatment may become a critical issue in the near future. Thus, we investigated the mortality associated with and prevalence and clinical significance of HBV reactivation in Japanese patients with resolved HBV infection in a multicenter, cross-sectional study.

Methods. In 2005, we sent a questionnaire to 230 hospitals certified by the Japan Society of Hepatology; this included questions about patients who had become newly positive for serum HBsAg from January 2000 through December 2004 [25]. A total of 1239 patients were registered by 93 hospitals (40%). Of those patients, 55 were recorded as having experienced HBV reactivation after having resolved HBV infection, and the remaining 1184 patients were classified as having acute hepatitis B. Sixty-three (68%) of 93 hospitals responded to a second survey and provided information on 552 patients enrolled in this study; 23 of these patients developed HBV reactivation, and 529 had acute hepatitis B.

HBV reactivation was defined (according to a slight modification of the report by Hui et al. [23]) as a decrease in the level of antibody to HBsAg that was associated with the reappearance of HBsAg, a 3-fold elevation of serum alanine aminotransferase (ALT) level above normal, and detection of HBV DNA in serum during or after chemotherapy. The diagnoses of acute hepatitis B and FHF were defined as reported elsewhere [26]. Patients with other liver diseases were excluded. Serum HBV markers were determined as reported elsewhere [26]. Serum levels of HBV DNA were determined with use of Amplicor HBV Monitor kits (Roche Diagnostics) at each hospital when the patients were admitted. HBV genotypes were determined with use of the PCR-invader method, with genotype-specific probes [27]. This study was approved by the ethics committees of appropriate institutional review boards. Informed consent was obtained from each patient in accordance with the Helsinki Declaration.

The Mann-Whitney U test was used to analyze continuous variables. The χ^2 test with Yate's correction was used for analysis of categorical data. In cases in which the number of patients was <5, Fisher's exact test was used. $P \leq .05$ was considered to

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be statistically significant. Statistical analyses were performed using SPSS, version 15.0J (SPSS).

Results. We first compared the demographic, clinical, and virologic features of the 23 patients who experienced HBV reactivation with those of the 529 patients with acute hepatitis B (table 1). The reactivation group had a significantly higher median age and median serum HBV DNA level ($P < .001$) and significantly lower peak ALT and albumin levels ($P < .001$). Although HBV genotype was not determined for one-half of the patients with acute hepatitis B, marked differences in the distribution of genotypes were seen; HBV type A occurred less frequently ($P = .003$) among patients with HBV reactivation than among those with acute hepatitis. However, HBV type B occurred more frequently among patients with HBV reactivation ($P < .001$).

FHF was more common among patients with HBV reactivation than among those with acute hepatitis ($P = .048$). Of the 23 cases of HBV reactivation, 6 (26%) resulted in liver-related death, 11 (48%) resolved, and 6 (26%) led to chronic hepatitis B. In contrast, of the 529 cases of acute hepatitis B, 490 (93%) were self-limited, 16 (3%) became chronic, and 21 (4%) resulted in death. These results revealed that liver-related mortality was significantly higher in the group with HBV reactivation than in the group with acute hepatitis ($P < .001$).

We then compared the clinical features of FHF between the groups (table 2). Patients with HBV reactivation had a higher median age, significantly lower peak ALT levels ($P = .006$), higher HBV DNA levels ($P = .035$), and higher mortality ($P = .031$) than did patients with acute hepatitis B.

Malignant lymphoma–associated morbidity was significantly higher among patients with HBV reactivation who developed FHF than among those who did not develop FHF (table 3). A rituximab-containing treatment regimen was administered to all patients who experienced FHF, compared with only 4 (22%) of 18 patients who did not experience FHF ($P = .004$). Lamivudine was administered to 16 (89%) of 18 patients who did not experience FHF and to all patients who experienced FHF at 7 and 20 days after hospital admission, respectively; this suggests that lamivudine treatment could not prevent FHF after HBV reactivation. Eventually, liver-related mortality occurred exclusively in patients who experienced FHF. There were no statistically significant differences between the 2 subgroups regarding HBV markers.

Discussion. Although a prospective study by Hui et al. [23] revealed that the incidence of HBV reactivation among HBsAg-negative patients after chemotherapy was 3.3%, there are no data available on HBV reactivation in Japan. In our nationwide cross-sectional study, a total of 552 newly HBsAg-positive patients were registered from 63 tertiary care hospitals. Overall, HBV reactivation was found in 4% of patients with resolved infection after chemotherapy. Serum and liver samples were not available before chemotherapy for most of these patients; therefore, we were unable to prove specifically whether reactivation was a result of occult or acute HBV infection. However,

Table 1. Demographic and clinical characteristics of patients with hepatitis B virus (HBV) reactivation, compared with those of patients with acute hepatitis B.

Characteristic	Patients with HBV reactivation	Patients with acute hepatitis B	*P*
Age, median years (95% CI)	63 (39–83)	33 (19–64)	<.001
Male sex	14/23 (61)	374/529 (71)	NS
Peak ALT level, median IU/L (95% CI)	929 (137–2441)	2300 (299–6626)	<.001
Peak bilirubin level, median mg/dL (95% CI)	10.3 (0.3–58.6)	6.4 (1.0–23.7)	NS
Lowest albumin level, median g/dL (95% CI)	3.2 (2.1–3.7)	3.6 (2.7–4.2)	<.001
Most prolonged PT%, median % (95% CI)	65.0 (10.2–121.4)	75.0 (11.0–103.1)	NS
HBV DNA level, median log copies/mL (95% CI)	7.5 (4.0 to >7.6)	5.5 (2.6 to >7.6)	<.001
Genotype			
A	0/19 (0)	57/232 (25)	.003
B	8/19 (42)	27/232 (12)	<.001
C	11/19 (58)	141/232 (61)	NS
Other	0/19 (0)	7/232 (3)	
Treatment			
Lamivudine	20/23 (87)	118/529 (22)	<.001
IFN	5/23 (22)	12/529 (2)	<.001
Fulminant hepatic failure	5/23 (22)	45/529 (9)	.048
Liver-related death	6/23 (26)	21/529 (4)	<.001

NOTE. Data no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; NS, not statistically significant; PT, prothrombin time.

Table 2. Demographic and clinical characteristics of patients with hepatitis B virus (HBV) reactivation who experienced fulminant hepatic failure (FHF), compared with those of patients with acute hepatitis B who experienced FHF.

Characteristic	Patients with FHF		*P*
	With HBV reactivation	With acute hepatitis B	
Age, median years (95% CI)	63 (47–64)	48 (18–72)	.029
Male sex	3/5 (60)	26/45 (58)	NS
Peak ALT level, median IU/L (95% CI)	907 (359–1823)	5995 (589–11,858)	.006
Peak bilirubin level, median mg/dL (95% CI)	20.8 (10.2–45.7)	9.9 (4.9–30.5)	.099
Lowest albumin level, median g/dL (95% CI)	2.6 (2.1–3.0)	2.9 (1.9–3.9)	NS
Most prolonged PT%, median % (95% CI)	22.0 (8.7–32.3)	16.0 (0.2–37.0)	NS
HBV DNA level, median log copies/mL (95% CI)	7.6 (5.6 to >7.6)	5.7 (2.6 to >7.6)	.035
Genotype			
A	0/5 (0)	2/16 (13)	NS
B	1/5 (20)	3/16 (19)	NS
C	4/5 (80)	11/16 (69)	NS
Received lamivudine treatment	5/5 (100)	29/45 (81)	NS
Liver-related death	5/5 (100)	21/45 (47)	.031

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; NS, not statistically significant; PT, prothrombin time.

because all patients were negative for HBsAg and positive for antibody to hepatitis B core antigen before treatment, we presumed that reactivation was occult in nature.

In our study, patients who experienced HBV reactivation were significantly older and had lower serum albumin levels, compared with patients with acute hepatitis B. The immune status of many patients may have been further decreased by cytotoxic chemotherapy. Approximately 20% of the patients who experienced HBV reactivation developed FHF. Surprisingly, mortality was 100%, implying that FHF in these cases is severe. Both the prevalence of and mortality associated with FHF were significantly higher among patients who experienced HBV reactivation than among those with acute HBV infection. Although the group with HBV reactivation also had lower albumin levels at the onset of lamivudine therapy, the development of FHF could not be predicted from this study. Thus, it is crucial to prevent FHF in patients with HBV reactivation with use of agents other than—or complimentary to—lamivudine. Unfortunately, preemptive therapy is not recommended because of the difficulties in detecting reactivation. Hui et al. [23] recommended monthly testing of HBV DNA levels and immediate antiviral therapy when levels are 100-fold the levels before chemotherapy. However, this strategy is still controversial [28, 29] and needs testing in a randomized study.

A recent study revealed that HBV type Bj and G1896A mutations were independently associated with a fulminant outcome in patients with acute HBV infection [30]. However, HBV genotype, serum HBV DNA level, or mutations in G1896A or A1762T/G1764A did not influence the development of FHF in patients who experienced HBV reactivation in this study. HBV reactivation in patients infected with HBV genotype A was also not found in this study, which may be explained by the fact that this genotype occurs in only 1.7% of patients with chronic hepatitis B in Japan [31].

Because our study and other studies [23] have confirmed that HBV reactivation can be fatal, we need to emphasize greater testing of HBV markers, including antibody to hepatitis B core antigen, antibody to HBsAg, and HBV DNA levels before administration of chemotherapy, especially therapy containing rituximab. Patients with resolved HBV infection should be routinely monitored for liver function and HBV DNA levels, and antiviral therapy should be administered immediately when evidence of HBV reactivation is found.

In conclusion, HBV reactivation is found in 4% of newly HBsAg-positive patients with resolved HBV infection in Japan. One-fourth of cases of HBV reactivation develop into FHF, and mortality is extremely high. Because our study was unable to distinguish HBV reactivation from occult HBV infection and could not clarify whether antiviral therapy was effective, a prospective study is being planned to clarify the mechanism of HBV reactivation and the benefits of antiviral therapy.

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Table 3. Demographic and clinical characteristics of patients with hepatitis B virus (HBV) reactivation who did and did not experience fulminant hepatic failure (FHF).

Characteristic	Patients with HBV reactivation		
	Experienced FHF (n = 5)	Did not experience FHF (n = 18)	P
Age, median years (95% CI)	63 (47–64)	63 (39–78)	NS
Male sex	3 (60)	11 (61)	NS
Peak ALT level, median IU/L (95% CI)	907 (359–1823)	1016 (124–2524)	NS
Peak bilirubin level, median mg/dL (95% CI)	20.8 (10.2–45.7)	7.6 (0.3–24.9)	.094
Lowest albumin level, median g/dL (95% CI)	2.6 (2.1–3.0)	3.3 (2.2–3.6)	.015
Most prolonged PT%, median % (95% CI)	22.0 (8.7–32.3)	77.5 (18.0–101.8)	<.001
ALT level,[a] median IU/L (95% CI)	176 (83–1035)	266 (58–1690)	NS
Bilirubin level,[a] median mg/dL (95% CI)	0.7 (0.4–7.2)	0.7 (0.3–13.6)	NS
Albumin level,[a] median g/dL (95% CI)	3.4 (2.5–3.5)	3.9 (2.8–4.5)	.035
PT%,[a] median % (95% CI)	42.2 (16.4–46.4)	83.7 (38.7–123.5)	NS
HBV DNA level, median log copies/mL (95% CI)	7.6 (5.6 to >7.6)	7.5 (4.0 to >7.6)	NS
Genotype			
Bj	1 (20)	7/14 (50)	NS
C	4 (80)	7/14 (50)	NS
Mutation			
G1896A	4 (80)	5/12 (42)	NS
A1762T/G1764A	2 (40)	2/12 (17)	NS
Non-Hodgkin lymphoma	5 (100)	8 (44)	.046
Received a rituximab-containing treatment regimen	5 (100)	4 (22)	.004
Treatment			
Lamivudine	5 (100)	16 (89)	NS
IFN	1 (20)	4 (22)	NS
Liver-related death	5 (100)	1 (6)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; NS, not statistically significant; PT, prothrombin time.

[a] Laboratory data are from the start of lamivudine therapy.

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