Hepatitis B Virus Reactivation Associated with Chemotherapy in
Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and is one of the
commonest causes of cancer morbidity and mortality in China and the Far East. Only 10% of the patients
could be considered for curative surgical resection at presentation. For the remaining 90% of the patients, the
prognosis is poor with a median survival in the range of 4 months. Palliative chemotherapy could be offered
for patients with unresectable tumours. Unfortunately, severe toxicities have been associated with
chemotherapy, in particular, hepatic dysfunction. In parts of Asia including Southern China, 85% of the HCC
patients have chronic hepatitis B virus (HBV) infection. It is well recognized that for chronic carriers of
HBV undergoing cytotoxic chemotherapy, hepatic dysfunction occurs more frequently than non-HBV carriers,
and this has mainly been attributed to the development of HBV reactivation.

The diagnosis of HBV reactivation has become better defined over the past decade. In early reports, the
diagnosis of HBV reactivation was based on the measurement of HBsAg and HBsAb titres. Wands et al.
described the condition in two separate clinical scenarios. For patients who were HBsAg positive, there was an
increase in HBsAg titre during HBV reactivation. Among those who were initially HBsAg negative/HBsAb
positive, the titre of HBsAb declined dramatically with the reappearance of HBsAg during immunosuppressive
therapy. With the introduction of quantification of HBV DNA, HBV reactivation is now characterized by raised
levels of serum HBV DNA, abnormal liver function tests and clinical hepatitis of varying severity.

Clinical Features

Most of the earlier reports on HBV reactivation have been on patients with hematological malignancies, in
which viral reactivation has been reported in over 40% of those undergoing chemotherapy. Increasingly,
HBV reactivation has been reported in patients other than those with hematological malignancies, and the
reported incidence has been consistently over 20% among HBsAg seropositive cancer patients receiving
cytotoxic chemotherapy. While HBV reactivation may spontaneously resolve in some, the occurrence of this
condition invariably leads to delay in chemotherapy schedules, and premature termination of the cytotoxic
treatment in the more severe cases, which effectively compromises an individual’s prognosis of cancer. Further,
in the most severe form, HBV reactivation leads to fatal hepatic failure.

Patients with unresectable HCC treated with chemotherapy in this geographical locality present a clinical
challenge based on the following aspects. On one hand, the HBV carriage rate among HCC patients, often with
co-existing cirrhosis, is disproportionately higher than other cancer population. On the other hand, the anthracyclines, a group of cytotoxic agents that has been commonly used in this disease, is also commonly associated with the viral condition\textsuperscript{[3,14]. Thus, studies have conducted to investigate HBV reactivation in this patient population.

For those who undergone locoregional transarterial chemotherapy, Nagamatsu et al. has reported that 25% of the 33 patients studied developed hepatic damage; however, the causes of hepatitis were not specified in this study\textsuperscript{[15]. In another study on 146 HCC patients reported by Jang et al\textsuperscript{[16}, 83 patients underwent transarterial chemo-lipoidalization with cisplatin and/or epirubicin, while another 63 patients underwent other forms of palliative anti-cancer therapy that were less immunosuppressive and included percutaneous ethanol injection therapy, surgical resection and conservative management. Transarterial chemo-lipoidalization was found to correlate with a significantly higher incidence of hepatitis attributed to HBV reactivation (21.7% vs 1.6%)\textsuperscript{[16].

For HCC patients undergoing systemic cytotoxic chemotherapy, Yeo et al. reported a study on HBsAg-positive patients with unresectable tumours\textsuperscript{[17]}. One of the following two systemic chemotherapeutic regimens was used: combination cisplatin, interferon, doxorubicin and fluorouracil (PIAF) or single agent doxorubicin. Patients were followed up during chemotherapy and until 8 weeks after the cytotoxic treatment. The results revealed that of the 102 patients studied, 59 (58%) developed hepatitis. Thirty-seven of these patients (63%) had hepatitis attributable to HBV reactivation. Ten patients (17%) had hepatitis attributable to chronic active hepatitis B infection, i.e. they were found to have raised HBV DNA but the extent of rise did not reach the stipulated definition of HBV reactivation. For the remaining 12 patients, hepatitis was attributable to the use of cytotoxic chemotherapy. When compared with the patients who did not develop viral reactivation, the clinical course of hepatitis was significantly more severe in the patients who developed reactivation: 62% developed severe hepatitis, 86% had their chemotherapy interrupted and 30% died as a result of hepatic failure. Despite a significant reactivation-associated morbidity and mortality among the patients, the median survival of these patients were not significantly from those who did not reactivated, reflecting the general poor prognosis of HCC patients who had unresectable disease.

**Associated Factors**

Several risk factors in association with HBV reactivation had been reported in (non-HCC) cancer patients undergoing cytotoxic chemotherapy. In earlier reports, data on hepatic complications during cytotoxic chemotherapy in HBV seropositive cancer patients were mainly assessment on the risk factors associated with the occurrence of hepatitis, rather than that of HBV reactivation per se. The inclusion of various causes of hepatitis into the risk analyses would create difficulties in differentiating factors that were directly related to HBV reactivation from that associated with other causes. While over 40% of hepatitis could be attributed to HBV reactivation, hepatitis during chemotherapy have been reported to be due to chronic active hepatitis B infection, hepatitis C infection, malignant liver infiltration, hepatotoxicity from the use of chemotherapeutic agents and use of herbal remedies\textsuperscript{[12].

More recent studies have reports on risk factors in association with HBV reactivation. Factors that have been suggested include male sex\textsuperscript{[11,12]}, younger age\textsuperscript{[12]}, detectable HBV DNA, and the presence of lymphoma or breast cancer\textsuperscript{[11-12,18,19]. While HBeAg positivity has also been reported to be a factor\textsuperscript{[11,12], HBeAg negative/anti-HBe positive has also been associated with increased risk in certain patient population, and this has been attributed
to the presence of the pre-core/core promoter HBV mutant (i.e. HBeAg negative/anti-HBe positive)\textsuperscript{[8,30]} The use of certain cytotoxic drugs such as anthracyclines and corticosteroids has also been associated with the condition\textsuperscript{[12,19,21]} A recent study on 138 cancer patients undergoing chemotherapy has described a mathematical model to enable risk calculation in an individual for the developing HBV reactivation whilst undergoing chemotherapy\textsuperscript{[19]}.

In studies that specifically assess HCC population, HBeAg positivity and an elevated baseline (pre-treatment) alanine transaminase have been found to be the factors associated with the exacerbation of viral reactivation and/or hepatic damage\textsuperscript{[15-17]} Interestingly, with systemic chemotherapy, the incorporation of conventional interferon with cytotoxics into the systemic therapy has not been shown to lower the incidence of HBV reactivation\textsuperscript{[17]} This could have been associated with the lower efficacy of the agent in Asian chronic HBV infection with a response rate about 10%\textsuperscript{[22]}, and the sub-therapeutic dosage of interferon used in comparison to that for the treatment of chronic HBV infection.

It has to be noted that the incidence of HBV reactivation appears to correlate with the intensity of immunosuppression of the anti-cancer therapy. Based on indirect evidence, HCC patients undergoing different modalities of anti-cancer therapy developed viral reactivation at different frequencies, ranging from 40% among those who underwent systemic chemotherapy, to 25% who received locoregional transarterial chemotherapy and 2% who underwent non-immunosuppressive anti-cancer therapy\textsuperscript{[15-17]}.

**Management**

Previously, supportive therapy and discontinuation of the implicated cytotoxic chemotherapy had been the mainstay of treatment.

The anti-viral agent, lamivudine, had been reported to be effective in controlling viral replication during HBV reactivation in patients who had previously received immunosuppressive therapy\textsuperscript{[22-23]} However, despite using lamivudine as a therapeutic measure, HBV-associated mortality has been reported in up to 20% of those who were treated. This has been suggested to be related to a delay in initiating the anti-viral treatment.

On the other hand, for those patients who recovered from HBV reactivation with lamivudine, the occurrence of the condition causes significant disruption, and may sometimes, premature termination of the cytotoxic therapy. Thus, preventing the occurrence of the condition may provide a more practical approach in managing patients who required chemotherapy. One of the preventative measures that had been suggested has been the omitting of corticosteroids (an agent often associated with the condition) in the cytotoxic regimen; however, results have not been satisfactory\textsuperscript{[26-28]} The use of lamivudine at the time of starting chemotherapy has been found to effectively reduce the occurrence of viral reactivation and its associated morbidity\textsuperscript{[29-31]} Specifically, such an approach has been reported to be effective in a small group of HCC patients undergoing locoregional transarterial chemotherapy\textsuperscript{[31]}.

**Conclusion**

Hepatitis is a common occurrence in HBsAg seropositive HCC patients undergoing cytotoxic chemotherapy. The underlying causes are mainly HBV-related, with 65% attributable to HBV reactivation, and another 15% related to chronic active hepatitis B. Further, it is difficult to exclude HBV-related chronic liver disease as a contributing factor in the remaining 20% of patients who developed hepatotoxicity that was attributable to
cytotoxic agents. The overall poor prognosis of patients with unresectable HCC could be a combination of high chemo-resistant nature of this malignancy, poor hepatic reserve in association with extensive hepatic parenchymal tumor involvement and co-existing chronic liver disease in particular, cirrhosis and active viral hepatitis. Prophylactic use of lamivudine has shown to minimize the hepatic damage related to chemotherapy-related HBV reactivation. Thus, further studies into optimizing treatment for this patient population with novel anti-cancer agents and supportive therapy including anti-virals are required.

References

20. W Yeo, S Zhong, PKS Chan, WM Ho, HM Wong, ASK Chan, PJ Johnson. Sequence variations of precore/core and precore promoter


HEPATITIS B VIRUS REACTIVATION ASSOCIATED WITH CHEMOTHERAPY IN HEPATOCELLULAR CARCINOMA

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• Background
• Definition
• Clinical Features
• Associated Factors
• Treatment
• Prevention

Hepatocellular carcinoma (HCC)

• one of the most common malignancies worldwide
• one of the commonest causes of cancer morbidity and mortality in China and the Far East
• Only 10% could be considered for curative surgical resection at presentation.
• For the remaining 90%, the prognosis is poor
  – median survival ~ 4 months
  – Palliative chemotherapy offered

• chemotherapy is associated with severe toxicities,
  → hepatic dysfunction
• In parts of Asia including Southern China, 85% of the HCC patients have chronic hepatitis B virus (HBV) infection
• For chronic HBV carriers undergoing chemotherapy hepatic dysfunction occurs more frequently, well recognized to be attributable to HBV reactivation

Lok, Am J Gastroenterol 1987
Ho, Pathology 1981
Gabbrielli, Lancet 1975
Nakamura, Cancer 1988
Kumaga, Ann Oncol 1997

• Frequently reported in patients with hematological malignancies, and increasingly recognized in those with solid tumors
**Clinical Picture**

3rd - 4th cycle of standard chemotherapeutic regimen
↓
raised transaminases
↓
raised bilirubin
↓
patient deteriorates

**Mechanism**

HBV carrier
↓
immuno-suppression
enhanced viral replication
(raised HBV-DNA)
↓
withdrawal of immuno-suppression
enhanced hepatocyte killing
by cytotoxic T cells
↓
hepatitis

**Profiles and ALT and HBV DNA in a patient undergoing chemotherapy**

![Graph showing HBV DNA and ALT levels](chart.png)

**Definition**

**Diagnosis**

- Hepatitis (↑ ALT)
- ↑ HBV-DNA
  - exclusion of other causes

* 85 patients with haematological malignancies (17 HBsAg+ and 40 HBsAb+)

Walls, Gastroenterology 1975
Definitions

- **Hepatitis**: $3 \times \text{ALT} > 58 \text{ IU/L}$ or $\text{ALT} > 100 \text{ IU/L}$
- **HBV reactivation**: $10 \times \text{HBV DNA} \text{ levels}$ or $\text{HBV DNA} \text{ level} > 1000 \times 10^6 \text{ g.e.} / \text{ml}$ in the absence of clinical or laboratory features of acute infection with HAV, HCV, delta virus or other systemic infections.
- **Degree of severity of hepatitis**

<table>
<thead>
<tr>
<th>Degree of severity of hepatitis</th>
<th>ALT levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild</td>
<td>$\leq 2 \times \text{UNL}$</td>
</tr>
<tr>
<td>moderate</td>
<td>$2 \times \text{UNL} &lt; \text{ALT} \leq 5 \times \text{UNL}$</td>
</tr>
<tr>
<td>severe</td>
<td>$\geq 5 \times \text{UNL}$</td>
</tr>
</tbody>
</table>

UNL = upper normal limit of ALT = 58 IU/L

Spot HBV DNA measurement with ALT-HBV reactivation >20%

In some cases, HBV DNA has become undetectable by the time hepatitis becomes evident......

Spot HBV DNA measurement with ALT-HBV reactivation >20%

Serial monitoring of HBV DNA with ALT-HBV reactivation >40%

Serial monitoring explain some causes of hepatitis in patients undergoing chemotherapy who would otherwise have been missed.

Clinical Features

**Patients with lymphoma:**

- HBV seropositive rate = 27%
  - Earlier reports: based on patients with hematological malignancies undergoing chemotherapy
  - Lok et al, with standard dose chemotherapy:
    - 70% developed raised transaminases
    - Amongst those who developed hepatitis
      - > 70% due to HBV reactivation:
        - 40% become jaundiced
        - 5% non-fatal hepatic failure
        - 5% liver related mortality
  - Incidence: > 40%

Lok, Gastroenterology 1991
Makamura, Cancer 1996
Kumagai, Ann Oncol 1997
HBV reactivation rate in various malignancies: HBV seropositive rate 10%

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>% hepatitis*</th>
<th>% attributable to HBV reactivation</th>
<th>% HBV reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes 2000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General cancer</td>
<td>45%</td>
<td>&gt;40%</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>Yes 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>60%</td>
<td>70%</td>
<td>40%</td>
</tr>
<tr>
<td>Yes in press</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal cancer</td>
<td>33%</td>
<td>85%</td>
<td>30%</td>
</tr>
</tbody>
</table>

* Other causes of hepatitis
- Chronic active HBV infection
- HCC infection
- Chemotherapy-induced liver damage
- Chemotherapeutic agents
- TCM
- Could not be determined

HCC patients treated with chemotherapy

A clinical challenge:
- High HBV carriage rate
  - up to 85%
  - Often with co-existing cirrhosis
- Commonly used agents - the anthracyclines
  - Commonly associated with viral condition

Thus, studies have conducted to investigate HBV reactivation in this patient population.

HCC patients - locoregional chemotherapy

<table>
<thead>
<tr>
<th>No. studied</th>
<th>% hepatitis*</th>
<th>% attributable to HBV reactivation</th>
<th>% HBV reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagamatsu</td>
<td>33</td>
<td>25%</td>
<td>Not specified</td>
</tr>
<tr>
<td>Jang 2004</td>
<td>63</td>
<td></td>
<td>22%</td>
</tr>
</tbody>
</table>

HCC patients - systemic chemotherapy

- 102 patients, one of these systemic chemotherapeutic regimens:
  - PIAF: cisplatin, interferon, doxorubicin and fluorouracil
  - Doc: single agent doxorubicin
- Patients were followed up during chemotherapy and until 8 weeks after the cytotoxic treatment.

= With systemic chemotherapy:
  - 59% developed hepatitis
  - Amongst those who developed hepatitis
    - 63% due to HBV reactivation
    - 17% attributable to chronic active HBV
    - 20% attributable to cytotoxics
  - Overall HBV reactivation rate = 36%
### Risk/Associated Factors

#### Several risk factors in association with HBV reactivation during cytotoxic chemotherapy had been reported:

- **Patient groups**
  - Lymphoma patients
  - Cancer patients non-HCC
  - HCC patients
- **Studies that assessed hepatitis vs HBV reactivation**
  - early vs recent reports

#### Causes of hepatitis during chemotherapy for HBV carriers

- 62% patients undergoing cytotoxic chemotherapy
  - HBsAg +ve
  - 548
  - hepatitis
  - 34
  - other causes
- Reactivation 44%
  - 3%
    - chronic active HBV infection
  - 3%
    - HCV infection
  - 6%
    - malignant liver infiltration
  - 32%
    - chemotherapeutic agents
  - 12%
    - TCM could not be determined

#### Factors in association with HBV reactivation:

- male sex
- younger age
- detectable HBV DNA
- HBeAg positivity
- HBeAg negative/anti-HBe positive
  - attributed to pre-core/core promotor HBV mutant
- lymphoma or breast cancer
- anthracyclines and corticosteroids

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**Table:**

<table>
<thead>
<tr>
<th></th>
<th>HBV reactivation group</th>
<th>Non-reactivation group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>37</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Severity of hepatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (30%)</td>
<td>20 (30%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (35%)</td>
<td>14 (27%)</td>
<td></td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>18 (49%)</td>
<td>10 (15%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Disruption in chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay of 2 to 8 days in between cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV reactivation/hepatitis</td>
<td>18 (49%)</td>
<td>54 (83%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>11 (29%)</td>
<td>27 (41%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Premature termination of chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV reactivation/hepatitis</td>
<td>3 (8%)</td>
<td>16 (25%)</td>
<td></td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>2 (5%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>5.97</td>
<td>5.51</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* Amongst those reactivated, 30% died as a result of hepatic failure

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**Graph:**

- Median survival of patients who did and did not develop reactivation

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**Note:**

- Despite a significant reactivation-associated morbidity and mortality, the median survival of was similar to those who did not reactivated
- reflecting the general poor prognosis of HCC patients who had unresectable disease
Pre-chemotherapy HBV DNA load

Comparison of serum HBV DNA level using real-time PCR assay between the reactivation and non-reactivation groups

<table>
<thead>
<tr>
<th>Reaction</th>
<th>N=16</th>
<th>Non - reaction</th>
<th>N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>2.9 x 10^7</td>
<td>2.9 x 10^7</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>8.2 x 10^5</td>
<td>8.2 x 10^5</td>
<td></td>
</tr>
</tbody>
</table>

Optimal cut-off between the two groups

A high HBV viral load prior to chemotherapy is a significant predictive factor for the development of HBV reactivation.

HBeAg status

- 28 patients – 14 developed HBV reactivation
- 14 who had no reactivation

- 12 HBeAg positive
- 16 HBeAg negative
- Anti-HBe positive
- 7 of 1896 mutation
- 6 of type HBV
- IFN not detected
- 8 DNA positive
- 11 reactivation (62%)
- 11 reactivation (57%)
- 11 reactivation (51%)

Conclusion

- Chronic HBV carriers who are HBeAg negative/anti-HBe positive with 1896 mutation may be more likely to develop HBV reactivation during antiviral therapy than those with the wild type virus.

Anthracyclines / Corticosteroids Vs Lymphoma / Breast cancer

- Common regimen
  - Breast cancer: AC+adriamycin+cytostatic+cytoxan, doxorubicin as pre-med
  - Lymphoma: CHOP, cyclophosphamide+adriamycin+vincristine+prednisolone

- Underlying associations:
  - Individual agents associated with HBV reactivation through specific mechanism
  - Degree of immunosuppression as consequence of combination therapy
  - CHOP
  - AC: 4% of Western patients but 77% Chinese

- Development of HBV reactivation: degree of immunosuppression of treatment
  - The type of malignancy per se

HBV reactivation correlate with intensity of immunosuppression?

- Indirect evidence

  - Intensive chemotherapy with BMT: higher incidence of HBV reactivation
  - Gastrointestinal malignancies (less immunosuppressive agents, e.g., fluorouracil and folinic acid): lower risk of developing viral reactivation

HBV reactivation correlate with intensity of immunosuppression?

- Indirect evidence from HCC patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>HBVR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-immunosuppressive anti-cancer therapy*</td>
<td>Jang 2004</td>
</tr>
<tr>
<td>Looseregional transantieral chemotherapy</td>
<td>Jang 2004</td>
</tr>
<tr>
<td>Nagamatsu 2004</td>
<td>33</td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>Yeo 2004</td>
</tr>
</tbody>
</table>

* including percutaneous ethanol injection therapy, surgical resection and conservative management

Risk factor analyses based on HCC patients

Factors associated with viral reactivation and/or hepatic damage:

- HBV positivity
- Elevated baseline (pre-treatment) ALT

- Interferon-containing cytotoxic regimen did not lower the incidence of HBV reactivation. Underlying reasons:
  - ?? lower efficacy of the agent in Asian chronic HBV infection with a response rate about 10%
  - ?? sub-therapeutic dosage of interferon used—e.g., in PIAF regimen—SMU/m2 daily for four days

Nagamatsu Hepato-Res 2003
Jang J Hepato 2004
Yeo Ann Oncol 2004
Lee Gastroenterology 1992
Risk calculation for HBV reactivation—mathematical model [19]

- Based on data from 138 cancer patients

\[
\log\left(\frac{P_R}{1 - P_R}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-3.608(0)</td>
<td>0.049</td>
<td>1.00 - 22.59</td>
</tr>
<tr>
<td>Lymphoma (0)</td>
<td>1.265(0)</td>
<td>0.044</td>
<td>0.92 - 1.71</td>
</tr>
<tr>
<td>Breast (0)</td>
<td>1.306(0)</td>
<td>0.045</td>
<td>0.90 - 1.91</td>
</tr>
<tr>
<td>Stomach (0)</td>
<td>0.800(0)</td>
<td>0.060</td>
<td>0.84 - 2.69</td>
</tr>
<tr>
<td>HIV (0)</td>
<td>2.123(0)</td>
<td>0.060</td>
<td>0.84 - 2.69</td>
</tr>
</tbody>
</table>

\(x_i = 1\) if present or 0 if absent
\(P_R\) = probability of HBV reactivation
\(P_{10} = 0.37\), a higher likelihood of developing HBV reactivation

Yeo, Br J Cancer 2004

For example:

- A patient with HCC is being considered for systemic chemotherapy
  - has detectable HBV DNA by PCR on baseline
  - Corticosteroids (dexamethasone) will be given as part of the anti-emet regimen

Then according to formula:

\[
\log\left(\frac{P_R}{1 - P_R}\right) = -3.6589 + 1.4086(0) + 1.4264(0) + 0.9939(0) + 2.1339(0)
\]

\(P_R = 0.18\), i.e. a lower likelihood of developing HBV reactivation

For example:

- A patient with HCC is being considered for systemic chemotherapy
  - no detectable HBV DNA by PCR on baseline
  - Corticosteroids (dexamethasone) will be given as part of the anti-emet regimen

Then according to formula:

\[
\log\left(\frac{P_R}{1 - P_R}\right) = -3.6589 + 1.4086(0) + 1.4264(0) + 0.9939(0) + 2.1339(0)
\]

\(P_R = 0.065\), i.e. a low likelihood of developing HBV reactivation

Advocated Treatment

- Aggressive supportive therapy
- Discontinuation of the implicated cytotoxic chemotherapy
- Interferon:
  - Kumagai et al. interferon controls hepatitis during chemotherapy
  - Note: interferon usage in chronic HBV infection has been associated with the possibility of fatal hepatic flares by augmenting immune-mediated destruction of hepatocytes—limitation to its use

Kumagai, Ann Oncol 1997
- Antivirals: lamivudine, famciclovir
  - claimed to be effective

Conventional monitoring of patients with chronic HBV during chemotherapy

...... unlikely to be an adequate management

However, even with lamivudine ......
Consequences of HBV reactivation

Hepatitis

Slow recovery

Subacute hepatic failure

Delayed administration may not be effective. ?? related to the progression to massive hepatic damage with insufficient regenerative compensation

However, even with prompt lamivudine ......
Consequences of HBV reactivation

Hepatitis

Slow recovery

Subacute hepatic failure

However, even with prompt lamivudine ......
Consequences of HBV reactivation

Hepatitis

Slow recovery

Subacute hepatic failure

Premature termination of chemotherapy

Delaying chemotherapy

Lamivudine
However, even with prompt lamivudine......

Consequences of HBV reactivation

- Hepatitis
- Slowness of recovery
- Premature termination of chemotherapy
- Delaying chemotherapy
- Subacute hepatic failure
- Impairing dose intensity

However, even with prompt lamivudine......

Consequences of HBV reactivation

- Hepatitis
- Slow recovery
- Premature termination of chemotherapy
- Delaying chemotherapy
- Subacute hepatic failure
- Impairing dose intensity

Therefore......

- Preventing the occurrence of the condition - a more practical approach in managing patients who required chemotherapy

Preventive Measures

1. Omitting corticosteroids in the cytotoxic regimen
   - Results have not been satisfactory......
   - Does not eliminate the condition- reactivation may still occur with other cytotoxic/immunosuppressive agents
   - Leads to suboptimal therapy and jeopardize the patient’s chance of cure

Omission of corticosteroid

50 NHL patients
HBsAg positive

25% "PACE" (Prednisolone, Epirubicin, Cyclophosphamide, Etoposide)

25% "ACE" (Prednisolone, Epirubicin, Cyclophosphamide, Etoposide)

Steroid free regimen

Follow-up for
- HBV reactivation
- Response to chemotherapy
- Overall survival

Cheng, Hepatology 2003

Development of HBV reactivation during systemic chemotherapy
Steroid-free regimen
- Significantly reduced incidence of HBV reactivation at 9 months: 73% vs. 36%

Overall survival of the patients
Steroid-free regimen
- Significant reduction in complete remission rate (46% vs. 35%)
- Significantly shorter overall survival

Cheng, Hepatology 2003
2. Continuous low dose steroids and a gradual tailing off of immunosuppressive cytotoxica have been suggested

- No conclusive evidence

3. Lamivudine Prophylaxis

Conventional monitoring of patients with chronic HBV during chemotherapy

- conventional approach in the diagnosis of HBV reactivation, i.e.
  1. initial monitoring with ALT

Prompt administration of the anti-viral, i.e. at the first instance when HBV DNA first starts to rise and prior to severe irreversible hepatic damage.
- Requires intense monitoring modality- ?? difficult to conduct in a busy clinic setting

?? How prompt is “prompt”
Proposed measures:

- HBV carrier to start CT
- Viral load suppression during immuno-suppression
- Hepatocyte killing withdrawal of immuno-suppression
- Hepatitis minimized by cytotoxic T cells minimized

Lau et al 1999- 8 bone marrow transplant patients received prophylactic anti-viral (lamivudine)
a trend towards a lower rate of hepatic complications during anti-cancer therapy

Lamivudine for the prevention of HBV reactivation

Objectives:
By using lamivudine at the time of starting chemotherapy:
1. To assess its efficacy in reducing the incidence of HBV reactivation.
2. To assess the severity of hepatitis during HBV reactivation.

- Comparison with historical controls

Vee et al, J Clin Oncol 2004

Treatment Regimen

<table>
<thead>
<tr>
<th>Week</th>
<th>start of CT</th>
<th>stop of CT</th>
<th>8/52 post-CT</th>
<th>16/52 post-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↓</td>
<td>↓</td>
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<td>↓</td>
</tr>
</tbody>
</table>

- Commence lamivudine*  
- Stop lamivudine

- *100 mg orally once a day, dose adjusted for renal insufficiency
- CBP, clotting profile, RFT, LFT and HBV DNA level monitored with clinical signs and symptoms every 10-14 days

PATIENTS

- 258 patients
  - HBsAg positive
  - Otherwise fit for chemotherapy
  - 65 patients with lamivudine
  - 193 patients no lamivudine

Exclusion criteria:
- Evidence of decompensated liver disease at screening
  - PT > 4 sec prolonged; albumin < 20 g/l; total bilirubin > 50 umol/l; history of non-malignant ascites; variceal haemorrhage; hepatic encephalopathy; ALT > 10 x UNL
- Other cases of chronic hepatitis: HCV, HBV, HCV, acute fulminant or autoimmune hepatitis
- Prior chronic anti-viral therapy with activity against HBV within the previous 6 months

RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Without lamivudine</th>
<th>With lamivudine</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of hepatitis</td>
<td>45%</td>
<td>18%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Incidence of severe hepatitis</td>
<td>19%</td>
<td>5%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Disruption in chemotherapy</td>
<td>35%</td>
<td>15%</td>
<td>0.0029</td>
</tr>
<tr>
<td>Incidence of HBV reactivation</td>
<td>25%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Mortality associated with HBV reactivation</td>
<td>11%</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Reason for failure of the approach:
- 1- poor compliance
- 1- ?? lamivudine-resistance YMDD mutant

Prospective Studies on the use of prophylactic lamivudine for HBV reactivation during conventional dose chemotherapy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patient population</th>
<th>Type of study</th>
<th>No. patients</th>
<th>* No. controls</th>
<th>Incidence of HBV reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose 2001</td>
<td>Hematological malignancies</td>
<td>Prospective</td>
<td>20</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>Liao 2004</td>
<td>Lymphoma</td>
<td>Prospective</td>
<td>11</td>
<td>53</td>
<td>6 vs 32%</td>
</tr>
<tr>
<td>Yee 2004</td>
<td>Various malignancies</td>
<td>Prospective</td>
<td>65</td>
<td>152</td>
<td>4% vs 35%</td>
</tr>
<tr>
<td>Yee 2004</td>
<td>Breast cancer</td>
<td>Prospective</td>
<td>31</td>
<td>66</td>
<td>6% vs 31%</td>
</tr>
<tr>
<td>Dai 2004</td>
<td>Breast cancer</td>
<td>Prospective</td>
<td>11</td>
<td>5</td>
<td>0 vs 54%</td>
</tr>
</tbody>
</table>

* Number

4. Interferon Prophylaxis

- Prior to the commencement of chemotherapy
  - 13 patients with non-Hodgkin's lymphoma received interferon at 3x10^6 IU thrice weekly.
  - Results showed that none of those patients developed viral reactivation during the followup period.
- Interferon-containing combination chemotherapy for patients with inoperable hepatocellular carcinoma does not avoid viral reactivation.

Conclusion

- Hepatitis is a common occurrence in HBsAg seropositive HCC patients undergoing cytotoxic chemotherapy.
- The underlying causes are mainly HBV-related
  - 65% attributable to HBV reactivation
  - 15% related to chronic active HBV
  - 25% of patients who developed hepatitis that was attributable to cytotoxic agents/TIM/other uns.
- The overall poor prognosis of patients with unresectable HCC is likely to be
  - High chemo-resistant nature of the malignancy
  - Poor hepatic reserve in association with extensive hepatic parenchymal tumor involvement and coexisting chronic liver disease in particular, cirrhosis and active viral hepatitis.
• Prophylactic lamivudine prior to commencing chemotherapy has been demonstrated to
  - minimize the hepatic damage
  - reduce the incidence of HBV reactivation in cancer patients undergoing cytotoxic chemotherapy

• Specifically, such an approach has been reported to be effective in a small group of HCC patients undergoing locoregional transarterial chemotherapy.

Nature, 2004

• Thus, further studies into optimizing treatment for this patient population with novel anti-cancer agents and supportive therapy including anti-virals are required.

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