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化療導致B肝病毒活化的預防與治療

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摘　要

B型肝炎帶原之癌症患者，於化療(chemotherapy)期間除了面臨癌症所受的痛苦之外，又必須承擔B肝病毒活化(hepatitis B virus reactivation)所帶來的危機。在此，提出如何預防與治療B肝病毒的活化；並分析導致B肝病毒活化之各種危險因子。依實證醫學之建議：預防性、先給予干安能(preemptive lamivudine)，可以明顯減少B肝病毒之活化，避免失償性肝炎，減少中斷化療的機會。因此，在化療前，建議開始給藥；直到化療結束後，至少再延續3個月的干安能(lamivudine)。停藥前後，必須再三評估其免疫、造血功能(CBC/DC)是否恢復，並檢查ALT＆HBV-DNA濃度。至於YMDD突變與停藥後的反彈性肝炎(lamivudine withdrawal hepatitis)，只要提高警覺並定期追蹤檢查即可。由於台灣爲B型肝炎盛行區，成人需化療患者有10-15%爲B型肝炎帶原者，因此於化療前都應該檢測HBsAg，以提高警覺並避免療程中肝炎復發。

關鍵詞：B肝病毒活化(Hepatitis B virus reactivation)
干安能(Lamivudine)
預防性、先給予干安能(Preemptive lamivudine)
化療(Chemotherapy)

導論

B型肝炎帶原之癌症患者，於化療期間除了面臨癌症所受的痛苦之外，又必須承擔B肝病毒活化所帶來的危機。在台灣由於B型肝炎盛行，成人癌症患者有10-15%爲帶原者，尤值得特別注意。一般而言，在化療期間，B肝病毒活化的機率爲24-78%[1-14]；一旦B肝病毒活化，導致失償性肝炎、肝衰竭的機率爲4-63%。因此，本文特別討論化療前如何對B型肝炎之篩檢、評估，化療後B肝病毒活化之機轉，盛行率與發作時間；並分析導致B肝病毒活化危險因子，如：癌症種類、化療藥物種類，HBV-DNA濃度、HBeAg、前核突變(precore/core promoter mutation)、年紀、性別等因素。依實證醫學之結論，建議：凡是HBsAg(+)或HBV-DNA(+)之患者必須於化療前一週開始，預防性、先給予干安能(preemptive lamivudine)。但治療太久怕

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YMDD突變，太早停藥又怕停藥後產生的反彈性肝炎 (withdrawal hepatitis)，此兩個問題一向是臨床醫師所困擾與猶豫的事。因此，該治療多久？該何時停藥？如何追蹤檢查？本文將探討之。最後，在結論中提出建議與注意事項，以期使整個化療能順利進行，不再受B肝病毒活化所困擾。

化療前B肝之篩檢

化療前每個病人都應檢查HBsAg ，Anti-HBc

一、若HBsAg (-) /Anti-HBc (-)：應無B肝之疑慮。

二、若HBsAg (+) /Anti-HBc (+)：B肝帶原者，必須再加作HBeAg 、HBV-DNA

(1) 若HBeAg (+) / HBV-DNA (+)：Wild type HBV 。

(2) 若HBeAg (-) / HBV-DNA (+)：必須高度懷疑前核突變 (precore/core promoter mutation)

三、若HBsAg (-) /Anti-HBc (+)：必須視爲潛在性的B肝帶原者 (occult HBV)必須再加作HBV-DNA ，Anti-HBs 。

(1) 若HBV-DNA (+)，此時不論Anti-HBs (+)或(-)，仍需視爲B肝帶原者，建議化療前，先給予干安能 (preemptive lamivudine) [1,15-19] 。

(2) 若HBV-DNA (-) 且Anti-HBs (+)，不必先給予預防性的干安能。但B肝病毒可能潛伏在肝細胞或週邊血液的單核球內 (peripheral mononuclear cell)。因此，必須提高警覺，化療有可能使潛在性的B肝病毒活化，建議在化療後的第2個月開始，重新檢查HBV-DNA[1] ，以早期偵測到B肝病毒活化之現象，及時給予干安能[20-28] 。

B肝病毒活化之定義與機轉

一、化療後B肝病毒活化之定義：

化療後產生肝炎的原因，除了B肝病毒活化 (44%)[4] 以外，其他原因包括：化療藥物本身造成的肝毒性(32%)、敗血症、肝轉移浸潤、多發性器官衰竭等。B肝病毒活化定義爲[4,29-31] ：HBV-DNA濃度上升爲化療前的10倍以上，或HBV-DNA由化療前的陰性轉變爲陽性，或HBV-DNA ≧ 1000×10^6 copies/ml 。

一般而言，HBV-DNA大量複製後，約1-2週(median ，中位數；range ：0-11週) 才有可能造成ALT的上升[29,32] ，導致臨床上的肝炎發作 (ALT 上升大於化療前的2-3倍，或ALT ≧100 IU/L)。因此建議：若不給予預防性干安能 (pre-emptive lamivudine)，必須定期(每2-4週) 檢測HBV-DNA濃度，可以早期偵測到B肝病毒的活化，其盛行率由24% (單獨以ALT爲指標) 變成41% (合併ALT + HBV-DNA)[14] 。

二、化療導致B肝病毒活化之機轉[9,11,12]

給予化療或免疫抑制劑後 (如類固醇、器官移植後之抗排斥藥物)，因爲抑制免疫力使B肝病毒大量複製，並感染更多的肝細胞。當兩次化療之間，免疫力逐漸恢復時，Cytotoxic-T-lymphocyte會去攻擊被B肝病毒感染的肝細胞，造成發炎、壞死。因此，理論上，越強的免疫抑制劑會造成更多的B肝病毒活化、複製，突然停藥會造成更嚴重的肝炎。

化療後B肝病毒活化之盛行率與預後

一、化療後B肝病毒活化之盛行率

化療會導致B肝病毒活化，早在1975年就證實[33,34] ，其盛行率約24-78%[1-14] 。

造成統計差異的原因如下：

(一) B肝病毒活化之定義不盡相同

早期論文 (1995年以前)，均以ALT上升大於化療前的2-3倍或ALT ≧100 IU/L 爲準則，但B肝病毒活化、複製不一定會產生臨床上的肝炎。因此，若以HBV-DNA上升爲診斷標準，其盛行率較高。所以眞正的定義應該分成：

1.化療後的肝炎，包括：B肝病毒活化，化療藥物本身的肝毒性、敗血症、肝轉移、多發性器官衰竭、其他藥物的肝毒性等。

2.B肝病毒活化但不產生臨床上的肝炎。

3.B肝病毒活化，且產生臨床上的肝炎(ALT上升大於化療前的2-3倍或ALT ≧100 IU/L)。

4.B肝病毒活化且產生黃疸、失償性、猛暴性肝炎、肝衰竭。

(二) 腫瘤的種類

以血液腫瘤、骨隨移植病人最高。

(三)化療前HBV-DNA濃度、HBeAg(+)、前核突變(precore/core promoter)。

(四)化療藥物種類

二、化療後B肝病毒活化之發生時間

一般而言，常發生於化療後第2-3或4次化療時。(median，中位數：16週；range：4-36週)[1,8,9,35-37]。但根據台灣本土之研究，對於淋巴癌之患者，有一半的病人在第一次化療後之二星期內，就產生早期之B肝病毒活化。有可能是藥物本身就能直接刺激病毒的大量複製[11,61,62]。

三、化療後B肝病毒活化之預後

(一)B肝病毒活化後，進一步造成黃疸性肝炎之機率爲10-63%[1,2,5,6,38-41]。

(二)B肝病毒活化後，產生猛暴性肝炎、肝衰竭死亡之機率爲4-60%[1,2,5,6,13,14,19,20,31,38-45]。

化療後導致B肝病毒活化之危險因子

以實證醫學而論，只要HBsAg(+)或HBV-DNA(+)就應該在化療前一週先給予干安能，而不需要評估其危險因子，才決定是否要用干安能。但基於學術立場，在此討論各種危險因子：

一、癌症種類

一般而言，以血液腫瘤、骨髓移植最易導致B肝病毒活化，其盛行率約24-78%[4,7,30,46,47]。但solid tumor也不少[4,48,49]，尤其以乳癌之化療最常見，導致B肝病毒活化之機率爲10-55%[8,14,32,50,51]。其他如肺癌之化療(尤其是small cell)約30%[4]。

二、化療前HBV-DNA濃度

化療前之HBV-DNA濃度＞10^4 copies/ml時，不僅較易導致B肝病毒活化[51,59,60]，也容易在停止干安能後，產生反彈性肝炎[19,24,51-57](withdrawal hepatitis)。

三、化療藥物的種類

(一) Steroid [1,5,11,19,41,58]

類固醇除了會抑制免疫功能外，又可能直接造成B肝病毒之活化[11,61,62]。只有少數研究認爲類固醇並非危險因子[7,12,29,30]。

(二) Anthracyclines [4,7,19,30,32]

Doxorubicin，Epirubicin，Daunorubicin，Idarubicin。

(三) 治療性的單株核體[18,63-73]

如Rituximab(Anti-CD20)，Alemtuzmab(Anti-CD52)與Infliximab(Anti-TNF)。這些藥物會造成更長期、持續性的抑制免疫力，使B肝病毒活化的時間更慢(非一般的中位數：16週)，較易被忽略且會造成更嚴重的肝炎。因此，對於occult HBV患者或骨髓移植患者，化療後更需使用較長的干安能(至少再延續6-12個月)。

四、HBeAg(+)[10,28,73]

HBeAg(+)常被當成B肝病毒的活躍度，其HBV-DNA濃度也相對比較高，因此產生B肝病毒活化之機率也較高，但文獻上仍未有定論。

五、器官移植

器官移植後，必須長期使用抗排斥藥物，因此常造成B肝病毒活化，導致猛暴性肝炎、肝衰竭，到最後白忙一場。以肝移植而言，建議終身使用干安能。以骨髓、週邊血液幹細胞移植而言，建議長期使用干安能，直到免疫、造血功能恢復後，至少再延長一年且HBV-DNA(-)才可考慮停藥[9,12,19,59,60,74]。至於腎移植後，因B肝病毒活化導致死亡，約佔換腎死亡原因之37-57%。因此，換腎前若先給予預防性的干安能，可使B肝帶原者之存活率等同於HBsAg(-)之換腎病人[75-80]。

B肝病毒活化之預防與治療

一、化療前先給予干安能(Preemptive lamivudine)

如前所述，化療後B肝病毒活化之機率爲24-78%，進一步產生黃疸性肝炎爲10-63%，肝衰竭爲4-60%。因此，在化療前一週先給予干安能，能明顯降低B肝病毒活化，使化療順利完成；但是否會降低整體的死亡率則仍待更進一步的研究。至於先給予干安能，仍可能產生B肝病毒的活化，其機率爲0-8.7%[7,9,19,60,81]，但只會導致相當輕微的肝炎，不致於使化療中斷。

二、援救性治療(Rescue therapy)

B肝病毒活化後，再加上免疫力的恢復，可能造成大量的肝細胞壞死。一旦發現B肝病毒活化，即使在三天內儘快給予援救性治療(干安能)，即使在1-2週內能使HBV-DNA＜10^4 copies/ml，有

時仍無法彌補已造成的肝臟損傷、肝衰竭，其死亡率約14-75%[4,29,36,39,73,82,83]。因此，若不先給予干安能，最好定期(每2-4週)檢測ALT & HBV--DNA濃度[14,29]；但臨床上仍以監測ALT爲實際可行的方式，一旦ALT升高，立即給予干安能。至於使用干安能合併另一種抗病毒藥物(如Adefovir或Entecavir)，甚至給予類固醇以減輕免疫反應，這種援救性治療是否可改善死亡率仍有待更進一步研究。

預防性治療之疑慮

對於HBsAg(+)或HBV-DNA(+)之化療患者，預防性先給予干安能已成共識，但臨床上如何使用仍是大家所困擾之事。

一、何時開始給藥？

大多數認爲化療前一週給藥即可，少數建議化療前2-3週[69]，但不要在化療當天才給藥。

二、何時停藥？

整個化療階段均不能終止干安能之治療，直到化療結束後，免疫、造血功能恢復正常(如CBC/DC，platelet)，必須再延續干安能1-12個月的治療，才可以考慮停藥。亞太肝臟醫學會(APASL)只建議至少延續3個月，其他歐美醫學會的意見是至少6-12個月[1,19,37,44,69,85-87]，但仍需依病人情況而定。停藥後，要注意反彈性肝炎(withdrawal hepatitis)之可能性，B肝病毒再活化的危險因子如下：

(一)化療前HBV-DNA ＞10^4 copies/ml[52]。

(二)前核突變(precore/core promoter mutation)

(三)化療後，雖然已再延續干安能1-12個月的治療，但停藥時HBV-DNA ＞10^4 copies/ml或HBeAg(+)。

(四)使用治療性單株抗體(如Rituximab)。

(五)骨髓&週邊血液幹細胞移植之患者。

三、如何追蹤檢查？

(一)對於預防性、先給予干安能之化療患者

建議於每次化療前，除了檢查CBC/DC、血小板以外，仍必須加入ALT、Bilirubin、PT。干安能持續使用6-9個月以上，必須檢測HBV-DNA濃度，以早期偵測YMDD突變。停藥時，務必確認免疫、造血功能恢復正常。停藥後一年內，建議至少每三個月定期檢查ALT、CBC/DC，HBV-DNA。

(二)對於不給予預防性干安能之化療患者

化療期間以ALT無法早期發現B肝病毒之活化，最好每4星期監測HBV-DNA才能早期發現[29]；但是這些HBV-DNA的檢測費用，實在不符合經濟效益；目前仍以監測ALT爲實際可行的方式。

結論與建議

一、癌症患者必須面對很多難關，爲了使化療能順利完成，我們能作的事就是給予足夠的營養，避免感染，避免B肝病毒活化。因此，只要HBsAg(+)或HBV-DNA(+)，就應該於化療前(一週)，先給予干能。並且持續給藥到化療後，至少再延續3個月。

二、化療前先給予干安能(preemptive)或援救性治療(rescue therapy)有何差別？目前僅有少數的隨機前瞻性研究，成果仍不夠明確，仍有待大規模的隨機前瞻性研究。另外新的抗HBV藥物(如Entecavir、Adefovir)，亦待進一步探討。

三、化療前每個病人都應檢查HBsAg，Anti-HBc

對B肝之篩檢，千萬不要忘了Anti-HBc的重要性，只要Anti-HBc(+)，必須視爲潛在性的B肝帶原者。只要HBV-DNA(+)，就必須給予干安能；若HBV-DNA(-)，HBsAg(-)且Anti-HBs(+)，仍建議於化療後的第二個月，開始監測HBV-DNA是否呈現陽性反應。

四、健保法規尚未採納目前準則，而以治療復發爲主，將來宜爭取納入預防性用藥：

根據健保給付規定(2006年11月1日)

(一)慢性B型肝炎帶原者HBsAg(+)，接受癌症化學療法中發作B型肝炎者，經照會消化系專科醫師同意後，得使用。其實，等到B肝病毒活化，並產生肝炎發作，其死亡率爲4-60%。

(二)慢性B型肝炎帶原者HBsAg(+)，接受器官移植後發作B型肝炎者，得使用。若爲接受肝臟移植者，則可預防性使用。其實，花了極

大的心力、經費去做配對、移植，不管任何器官（除眼角膜外）之移植均應給預防性干安能，不能等到B肝病毒活化才給予干安能。將來宜爭取納入預防性用藥。

五、對於長期或高劑量使用類固醇、免疫抑制劑之患者，（如SLE或腎絲球病變之脈衝療法，Pulse therapy），也會導致B肝病毒活化。惟文獻記載不多，是否需要預防性、先給予干安能，仍有待進一步觀察。

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Prevention and Management of Hepatitis B Virus Reactivation in Cancer Patients Undergoing Chemotherapy

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For cancer patients receiving cytotoxic chemotherapy, hepatitis B virus reactivation is well-described complication resulting in varying degree of liver damage. Therefore, we discuss how to prevent and manage the HBV reactivation in cancer patients undergoing chemotherapy; analyze the risk factors of HBV reactivation. According to the evidence-base medicine: The prophylactic, preemptive lamivudine significantly decreases the incidence of HBV reactivation, morbidity and disruption of chemotherapy. So the HBsAg or HBV-DNA positive patients are recommended the preemptive lamivudine before initiation of chemotherapy. The treatment was then continued throughout the course of chemotherapy for at least 3 months after discontinuation of chemotherapy and when the total white cell counts had become normalized. If the physician and patient do regular follow up carefully, it is not difficult to deal with the YMDD mutation and withdrawal hepatitis after cessation of preemptive lamivudine. (J Intern Med Taiwan 2007; 18: 236- 243)