順鉑造成急性腎損傷之最新進展

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摘　要

近年來癌症化學治療藥物日新月異，但是順鉑(cisplatin)與其相關鉑金類藥在化學治療物中卻依然爲不可替代藥物之一。順鉑於臨床使用上最爲顯著的副作用：急性腎損傷，一直是臨床醫師想要克服之處。不論是投予藥物前給予大量點滴或是藥物，在臨床上依然無法完全避免腎臟功能受到影響。因此急性腎損傷生物標記的最新發現似乎提供給臨床醫師一個早期診斷、更早介入治療，可爭取更長的有效治療時間。本文回顧近年文獻關於順鉑造成急性腎損傷的機轉、治療與最新沿革，盼能提供臨床醫師對於順鉑造成急性腎損傷有更進一步了解。

關鍵辭：順鉑(Cisplatin)
急性腎損傷(Acute kidney injury)

前言

順鉑(cisplatin)在1960年代被意外發現可以抑制細胞分裂後已經成爲世界上治療腫瘤的化學治療用藥中最不可或缺的一項藥物[1-3]。在當今的化學治療藥物中，cisplatin和其相關的鉑金類藥物主要被應用在治療包括頭頸部癌症、食道癌、生殖器癌症(包含睪丸癌、卵巢癌)、子宮頸癌、非小細胞肺癌等其他類型癌症[4-5]。Cisplatin之所以可以抑制癌細胞的機轉尚未被完全了解，不過從目前實驗證實的機轉包括了cisplatin與去氧核糖核酸(deoxyribonucleic acid; DNA)交叉結合使得DNA在複製與合成時遭到阻礙而無法進行[6-9]。也因此在快速分裂的細胞，例如癌症細胞，cisplatin可以造成DNA的損傷。輕微損傷的DNA尚可得到修復，但若是大範圍的DNA損傷會導致細胞的破壞乃至於死亡。

雖然cisplatin在臨床的應用上極爲廣泛，但是它本身的副作用卻也讓臨床醫師在治療病人上，面對了不少的挑戰。已知cisplatin造成的副作用包括了：神經毒性、耳毒性、腎毒性以及噁心嘔吐等。數年來臨床研究上一直在尋找方法來避免cisplatin的副作用，其中一個方式就是合成或是尋找新的cisplatin類異構物但是副作用卻比cisplatin來的小，最有名的例子便是卡鉑(carboplatin)，它的腎毒性比cisplatin來得小[10]。另外預防cisplatin造成腎毒性的方法包括

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了在cisplatin治療時，給予大量的點滴注射，或是使用包括了甘露醇(mannitol)等藥物來加以預防[11-12]。不過，有越來越多的證據顯示，雖然在用cisplatin治療時，使用了這些方式加以預防，部分的病人依然會發生腎損傷[3,13]。也因此，cisplatin造成的腎損傷依然是目前臨床治療上最大的挑戰。

Cisplatin造成的急性腎損傷在使用時就被報導過[14]。目前估計cisplatin造成的腎損傷盛行率依舊偏高，約三分之一的病人在接受cisplatin治療時會發生急性腎損傷[3,15]。在臨床上，cisplatin造成的急性腎損傷通常於開始接受cisplatin治療後十天出現，其臨床表徵包含了腎絲球過濾率下降、血清肌酸酐上升、血清中電解質包括鎂離子與鉀離子下降。至於cisplatin是否會造成慢性腎臟影響卻尚未完全得到證實。Cisplatin造成的腎毒性機轉一直是這三十年來科學上探索的主要目標之一，目前的研究發現，當腎小管細胞暴露到cisplatin時會開啓一連串的反應最後導致了腎小管細胞受損乃至於死亡。而cisplatin造成的發炎反應(inflammatory response)也會加重腎小管細胞的傷害。而腎臟血管循環系統也會受到cisplatin傷害並且造成腎臟的血流減少產生缺血性損傷。綜合上述各種腎臟實質的傷害，cisplatin的腎毒性導致了最後急性腎損傷的結果[16]。

順鉑在人體的代謝

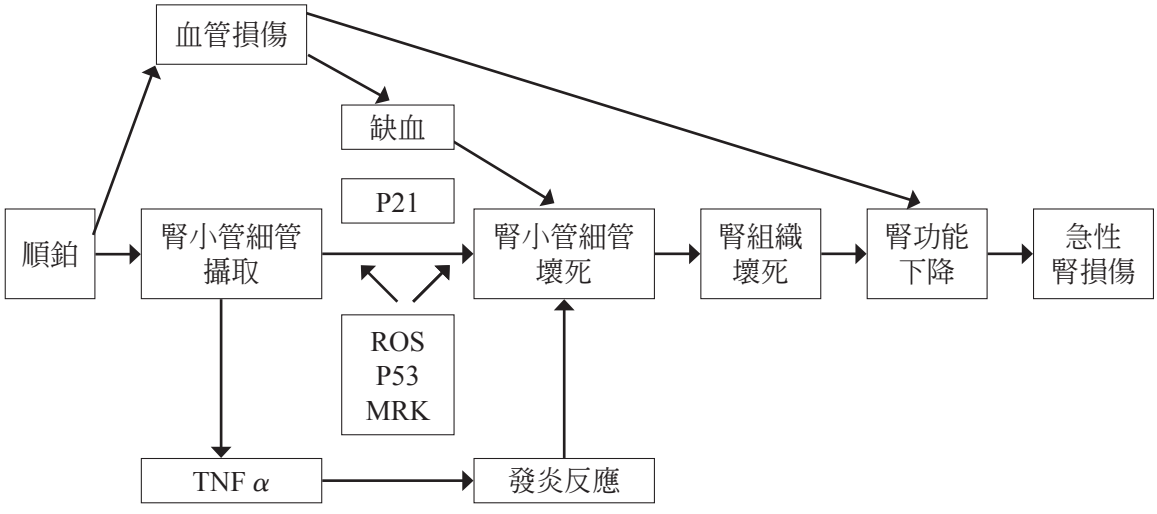
Cisplatin在腎臟泌尿系統主要是經由有機陽離子轉運體(organic cation transporters, OCTs)來攝取(uptake)[17-18]。OCTs主要是在腎小管細胞負責基底側(basolateral)至頂側(apical)的陽離子複合物運送。已發表的實驗證明了cisplatin會造成小獵犬腎臟(Madin-Darby canine kidney, MDCK)細胞基底側比頂側更嚴重的傷害[17]，因此cisplatin的腎毒性跟基底側OCTS應該有密切的關係。實驗也證明，西咪替丁(cimetidine)是一種OCTs的抑制劑，可以藉由減低經上皮電　阻(transepithelial electrical resistence)來　預防cisplatin的腎毒性[17]。目前在近端腎小管的OCTS已知共有三種同型體(isorforms)[19]，而且大部分都存在於基底側。經過實驗證明，OCT2是OCTS中主要負責在腎臟攝取cisplatin，而cimetidine被證明可以抑制近端腎小管細胞攝取cisplatin[20]。糖尿病腎臟病人的近端腎小管細胞因爲受糖尿病影響而OCT2的表現減低，也使得cisplatin的攝取跟著減低[16]。OCT1則因爲主要分布在肝臟，並沒有負責腎臟內cisplatin之攝取。較低腎毒性的鉑金類藥物包括carboplatin或是奧沙粒鉑(oxaliplatin)並沒有被OCT2攝取[20]。當cisplatin被攝取進入腎臟會引發一連串的路徑，包括了丙穀氨轉酶(γ-glutamyl transpeptidase)和半胱氨酸S結合β裂合酶(cysteine-S-conjugate β-lyase)[21]。在老鼠的實驗中也證實了當抑制了這兩個酶之一可以減輕cisplatin造成的腎毒性[22-23]。

順鉑造成的急性腎損傷

Cisplatin造成的腎損傷最主要的病理組織學變化就是腎小管細胞的損壞。實驗已經證實了腎小管細胞的損壞主因是壞死(necrosis)和凋亡(apoptosis)[24]。較早期的實驗可以發現，cisplatin的濃度可以決定腎小管細胞是壞死或是凋亡[25]。腎小管細胞是否壞死或是凋亡是不是有一定的關係呢？目前已知，cisplatin的毒性可以直接造成腎小管細胞的壞死，而腎小管細胞的壞死可以視爲凋亡後的結果。當我們使用保護腎臟的方法來預防cisplatin造成的腎損傷也的確可以減低順鉑來造成腎小管細胞的壞死或是凋亡[26-28]。腎小管細胞是cisplatin造成腎毒性的最主要影響細胞，早期多半認爲是遠端腎小管細胞受到主要損傷[29]，近來有越來越多證據顯示近端腎小管細胞也有因爲順鉑的影響而出現凋亡[28,30]。2007年Wei等人用染色解答了順鉑造成的腎毒性究竟是造成哪個部分腎小管細胞損傷[31]。在實驗中發現了凋亡細胞主要被染色的是植物血細胞凝集素(phytohemagglutinin)；一種近端腎小管細胞結合的凝集素(lectin)。只有少量的花生凝集素(peanut lectin agglutinin)在遠端腎小管的凝集素被染色。所以cisplatin可同時造成兩個部分的腎小管細胞凋亡，不過主要是在近端。另外也有研究發現順鉑也會造成

內皮細胞的凋亡[32]。而cisplatin是如何造成腎小管細胞凋亡呢？目前已知主要分爲兩種路徑：包括了外在路徑和外在路徑。在外在路徑中，順鉑會活化半胱氨酸蛋白酶8 (caspase-8)而引起凋亡[33]。而會引發這一系列凋亡路徑的受器包括了兔抗人(Fas)，腫瘤壞死因子α受器第一型(tumor-necrosis factor-α receptor 1, TNF-αR 1) 和 TNF-αR 2[33]。實驗證明如果用藥物或是基因的方式抑制了TNF-α並使其減少產生相關化學激素(chemokines)，可以減輕順鉑造成的腎損傷[34]。而且當老鼠缺乏TNF-αR 2而不是TNF-αR 1時，是可以抵抗cisplatin造成的腎損傷[35]。而內在路徑是cisplatin造成凋亡最主要路徑。其主要發生在粒線體裡面，也就是當粒腺體接收到順鉑造成的細胞壓力(cell stress)，會釋放細胞凋亡性因子(apoptogenic factors)，包括了細胞色素C (cytochrome C)、凋亡誘導因子(apoptosis-inducing factor, AIF)、第二線粒體來源胱氨酸酶啓動劑/等電點IAP直接結合蛋　白(Second Mitochondria-derived Activator of Caspases/Direct IAP Binding Protein with Low PI, Smac/DIABLO)、核酸內切酶 G(endonuclease G)等[33,36-37]。Cytochrome C在被釋放出來後又會產生一連串的訊息路徑，最後導致半胱氨酸蛋白酶9 (caspase-9)被活化而使細胞走向凋亡；相反的，AIF被釋放出來則是走非caspase的路徑，最後也是導致細胞凋亡。目前有越來越多的藥物實驗進行，主要是希望能夠降低cytochrome C 的釋放，以達到減少caspase被活化乃至於凋亡[38-43]。此外除了內在路徑和外在路徑，內質網壓迫路徑(Endoplasmic reticulum stress pathway)也被證實在cisplatin造成的腎小管細胞凋亡扮演一部分角色。目前已知，cisplatin會造成ER stress，接著活化了半胱氨酸蛋白酶12(caspase-12)，最後導致腎小管細胞凋亡[44]。

而在基因部分，目前已知cisplatin可以活化抑癌基因蛋白p53[45]，不過確切活化原因上有待釐清。 目前一般相信是因爲cisplatin如前文所提本身會造成DNA的損傷，而導致其下游的p53被活化，接著引起一系列的路徑，最後使腎小管細胞凋亡[16]。另外，有絲分裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK) 路徑[46-47]和氧化壓力(oxidative stress)[42,48]也被發現在cisplatin造成腎損傷扮演了一部分的角色。在發炎方面，有抗發炎效果的細胞介白素第十因子(IL-10)可以減低cisplatin對腎小管細胞的傷害[49]，而發炎造成的機轉主要還是由前文所提的TNFα爲主，導致一連串chemokine的產生，



圖一：順鉑造成急性腎損傷機轉。
順鉑在進入腎細胞後，遭到暴露的腎小管細胞會活化訊息傳導入徑，包括了MAPK, p53, ROS等導致細胞死亡；而p21路徑則會出現細胞保護效果。同時順鉑也會造成腎小管細胞產生TNF-α，使得發炎反應更為劇烈，加速了腎小管細胞壞死。另外順鉑也會使得腎臟血管構造產生缺血性壞死，而使得腎功能進一步惡化，因為這些原因最後在臨床上出現了急性腎損傷。

最後使腎小管細胞受到損傷。綜合上述證據，cisplatin造成急性腎損傷的機轉可簡單如附圖所示(圖一)。

許多人嘗試用各種不同方法來防止cisplatin造成的腎毒性，不過不管是從基因方面、分子生物學方面、抗氧化方面、甚至是發炎方面，大部分都僅止於動物實驗上之證據。目前之所以臨床應用上受限，主要是cisplatin造成腎毒性是多方面的，當我們採取了其中一種方式來加以防止，也只能部分緩解cisplatin造成的腎損傷，因此使得在臨床上要達到顯著預防效果變得有限。那麼如果可以提早預測病人是否會遭遇急性腎損傷，並加以介入治療，是否可以改變目前的侷限呢？

急性腎損傷生物指標於順鉑腎損傷扮演的角色

目前用來評估診斷和分級急性腎損傷的指標是血清肌酸酐(creatinine)[50]。近年來，有越來越多的證據顯示，血清肌酸酐或是經由肌酸酐所換算而成的估計腎臟過濾率(estimated glomerular filatration rate, eGFR)並無法準確的早期預測出急性腎損傷[51]。臨床上若無法及時反應出急性腎損傷，會造成臨床醫師的延遲診斷與治療[52]。目前經經報告證明有用的生物指標包括了尿液的腎損傷因子-1(kidney injury molecule-1, KIM-1)[53]、中性球凝原蛋白酶(neutrophil gelatinaseassociated lipocalin, NGAL)[54]、細胞介白素第十八因子(interleukin-18, IL-18)[55]、胱蛋白酶抑制劑C (cystatin C)[56]、肝型脂肪酸結合蛋白(fatty acid binding protein-liver type, L-FABP)[57]、N-乙酰-β-D-葡萄糖苷酶(N-acetyl-b-D-glucosaminidase, NAG)[58]、基質金屬蛋白酶9 (matrix metalloproteinase-9, MMP-9)以及鈉氫交換蛋白3(sodium hydrogen exchanger 3, NHE 3)[58]等。

中性球凝原蛋白酶(neutrophil gelatinase associated lipocalin,NGAL)，是一種在中性球蛋白中與基質金屬蛋白酶9 (MMP-9)結合的25,000道爾頓(KD)的蛋白質[59]。雖然NGAL在人體大部分組織的數值非常低，可是當人體器官包含腎臟、肝臟、結腸以及肺臟的表皮細胞遭到破壞，它的數值就會急遽升高[60]。NGAL在動物實驗中被發現當腎臟遭受缺血性或是腎毒性藥物影響造成損傷時，是會急遽升高的蛋白質之一[61-63]。在數個前瞻性研究發現，在接受心臟開刀的兒童有部份人在一至三天不等時會發生急性腎損傷(血清肌酸酐比原本上升大於百分之五十)[64-66]，而這些人的血清或尿液中的NGAL經由酵素免疫分析法(Enzyme-linked immunosorbent assay, ELISA)測定發現在開刀後二至六小時會有比原本數值大於十倍以上增加。而這些血清或尿液NGAL的ROC曲線下之區域(area under the receiver-operating characteristic curve, AUC-ROC) 在二至六小時幾乎都可以大於0.9。因爲NGAL比血清肌酸酐對於急性腎損傷的提早發現與靈敏性，有越來越多的臨床研究評估用NGAL來預測其他原因造成的急性腎損傷，包括了腎移植[67]、顯影劑造成的急性腎損傷[68]、以及肝移植等[69]，都可以發現NGAL在預測急性腎損傷有其一定角色。

Cisplatin造成的急性腎損傷在臨床上雖然嘗試用各種方法加以防止，也只能部分緩解順鉑造成的腎損傷，因此一個比血清中肌酸酐更能提早診斷出急性腎損傷的生物指標可以提供臨床醫師更充裕的時間針對病人做有效的治療。在動物實驗方面，在cisplatin造成的急性腎損傷實驗組中，利用西方墨點法檢測尿液中NGAL可以發現在cisplatin注射後3小時就會出現升高，而血清中則要到96小時後才會出現升高[70]。而在人體方面，尿液中的NGAL在cisplatin造成的急性腎損傷實驗組中可以發現在cisplatin注射後第1、2、3天可出現統計學上有意義的升高；而血清中肌酸酐要到第3天才會出現升高[71]。其他的新一代急性腎損傷生物指標cystatin C[72]也被證實可以比傳統肌酸酐提早預測cisplatin造成急性腎損傷。因此應用這些指標似乎可以提供臨床醫師一個早期診斷、早期介入的契機。

總結

預防醫學已經是目前醫學治療的主流，過去的醫療多半著重於提升治療的效果，不過越

來越多的證據證明提早預防更勝過對於已發疾病的治療。順鉑造成的急性腎損傷是目前醫師在臨床使用時的一大挑戰，相信隨著急性腎損傷診斷與治療領域的蓬勃發展，對於鉑金類藥物的腎損傷預防與治療，吾人定能有長足發現與改善。

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Recent Update on Cisplatin induced Acute Kidney Injury

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Cisplatin and platinum related medication are mainly use in treating head and neck cancer, esophageal cancer, genital cancer(including testis and ovarian cancer), cervical cancer and non small cell lung cancer. Cisplatin induced acute kidney injury is the major concern for clinicians prescribing cisplatin based chemotherapy regimen. Many years, researchers and clinicians did lots of efforts to get rid of cisplatin side effects. The ways preventing cisplatin induced kidney injury include large intravenous fluid and mannitol. But there are more and more studies revealing that even with these managements, around one third of patients receiving cisplatin based chemotherapy suffered with acute kidney injury. Early diagnosis of AKI(acute kidney injury) may help primary clinicians prevent its further deterioration and related complications, and augment the chance of renal recovery. (J Intern Med Taiwan 2011; 22: 416-422)