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I-131-MIBG 標靶治療在神經母細胞瘤可行性之評估研究
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I-131-MIBG 標靶治療在神經母細胞瘤可行性之評估研究

The Safety and Efficacy of I-131 MIBG Therapy for Refractory Neuroblastoma

(計畫編號：NSC 96-NU-7-002-005)

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計畫中文摘要

神經母細胞瘤是源於脊索神經分枝的一種癌症。半數以上在腹部發現，偶而可在胸部、頸、骨盆或頭部發現。此種腫瘤為孩童第四種常見之腫瘤，全台灣每年佔兒童癌症的百分之 6~8 的發病率，約有 30 位新個案發生。通常是從腎上腺髓質或是由交感神經節以腹部腫瘤形式出現，但神經母細胞瘤生長快速並容易轉移。70%的病童，在症狀出現，被診斷前便已發生了轉移。治療方式多採合併療法，包括手術治療、放射線治療和化學藥物治療、自體骨髓移植治療，但仍然有七成的病童會在五年內陸續復發，五年存活率只有 10-20%。而復發後的腫瘤多產生抗藥性，對化學治療反應不佳。

I-/123,131 MIBG 能與腎上腺素受體結合，且具有高度特異性碘標記，在臨床上已被公認對於神經元源起之腫瘤，具十分有效之診斷定位功能，所以在神經母細胞瘤的診斷、轉移追蹤上已經是公認的標準檢查，而且顯影強度可做為腫瘤和骨髓內轉移治療效果評估。新的神經母細胞瘤治療方向就是，利用 MIBG 對神經母細胞瘤的專一性，加上具有細胞毒性的放射性元素，把神經母細胞瘤細胞殺死，但對正常細胞影響較少，提高療效、降低副作用，其治療反應有 4 成左右(10-80%)。主要的副作在於骨髓毒性，造成全乏血球症。

另外氟 18 左旋多巴（6-[18F]fluoro-levo-dopa，簡稱 18F-dopa）會由神經內分泌細胞所吸收和儲藏於細胞內，進而被 aromatic acid decarboxylase （簡稱 AADC）代謝成氟 18 多巴胺（18F-dopamine）和其他神經傳導物質，因此理論上 18F-dopa 可以用在神經母細胞瘤的特異性功能性造影，因此在 18F-dopa 正子造影可以比一般正子造影更具專一性和診斷價值。

本研究共有 14 位神經母細胞瘤病童參與，14 位皆接受 FDG, F-DOPA PET 檢查，10 位接受 I131 MIBG scan 檢查。在 I131 MIBG scan 檢查中，有 2 位病童的主腫瘤仍存在，同時有 I131 MIBG scan 顯影，其餘 8 位病童則無 I131 MIBG scan 顯影。在 DOPA PET 檢查中，6 位病童有顯影。其中 1 位病童的腫瘤分成兩部分，一部份有 FDOPA+顯影，病理報告較分化的 ganglioneuroma ，而另一部份無 FDOPA+顯影，病理報告較不分化的 neuroblastoma。目前全世界皆無 DOPA PET 在神經母細胞瘤造影檢查應用上的報告，臨床意義為何，需收集更多資料。

計畫英文摘要

Purpose:

Tumors of neuroblastic cell origin including neuroblastoma, ganglioneuroblastoma and ganglioneuroma are common tumors in children. Iodinated MIBG and In-111-DTPA-octreotide are first choice for imaging. However, the availability of these two agents is very limited in Taiwan. We try to apply and characterize the functional status of the neuroblastic tumors in limited number of cases of our institution.

Materials & Methods:

After 100 mg of carbidopa was given orally for 60 mins, the patients was injected with 200 MBq of F-18-DOPA and wait for 90 mins for imaging. Whole body imaging was performed using PET/CT. The patients were operated on and the pathology was compared.

Results:

Total 14 patients with Neuroblastoma were collected in this pilot study. Their ages ranged from 2 months -10 years old. Four patients were newly diagnosed and other ten patients were enrolled after treatment. Two patients were stage 3, two patients were stage 4s and ten patients were stage 4. Initial pathologic diagnosis were 13 neuroblastoma and 1 ganglioneuroblastoma. Seven patients were without mycN amplification, five patients were with mycN amplification and one patient was unknown. All patients had F-18-DOPA and FDG PET scan. Ten patients had ^{131}I-labeled MIBG scan.

In MIBG scan, 2 patients were revealed uptake of I131 in main tumor compatible with CT/MRI finding. Other 8 patients revealed no uptake of I131 and no mass lesions in CT/MRI. In DOPA PET, six patients with uptake of F-18-DOPA showed neuroblatoma or ganglioneuroblastoma of the tumor cell type. One of the FDOPA+ cases showed a large (6x5x4 cm) neuroblastoma (DOPA-) with a small (1.4x0.3x0.2 cm) ganglioneuroma (DOPA+) component in the right adrenal. Three others with no uptake of F-18-DOPA all showed a poorly differentiated neuroblastoma cells in the tumor. Four patients without main tumors showed no uptake of F-18-DOPA.

Conclusions:

No studies on the possible role of F-18-DOPA in neuroblastoma have been published yet. With the high spatial resolution of PET, F-18-DOPA positivity indicates the ability of tumor cells to accumulate and the ability to decarboxylate F-18-DOPA by AADC (aromatic amino acid decarboxylase) in a well differentiated tumor or tumor component. This may indicate better prognosis. The clinical significance needs further follow up. F-18-DOPA PET scan is useful when the supply of MIBG and octreoscan is unavailable or limited.

壹、計畫緣起與目的

神經母細胞瘤是源於脊索神經分枝的一種癌症。半數以上在腹部發現，偶而可在胸部、頸、骨盆或頭部發現。此種腫瘤為孩童第四種常見之腫瘤，全台灣每年佔兒童癌症的百分之 6~8 的發病率，約有 30 位新個案發生。50%在二歲以前發病，75%於五歲以前發病。

臨床症狀上約 65%源發自後腹腔，通常是從腎上腺髓質或是由交感神經節以腹部腫瘤形式出現，但神經母細胞瘤最初表徵通常來自轉移之病兆：如轉移之皮下結節而發現，因肝轉移而致肝腫大，骨侵犯產生疼痛或腫塊，眼睛是很特殊之轉移部位，會造成上眼瞼下垂及上下眼瞼附近之瘀斑（熊貓眼）；多於 50%之患可侵犯骨髓，而造成出血傾向、貧血、淋巴腺腫、發燒、躁動不安等症狀。神經母細胞瘤生長快速並容易轉移到骨髓、骨骼、肝、軟組織、遠處淋巴腺、腦、皮膚等處。70%的病童，在症狀出現，被診斷前便已發生了轉移。

治療方式多採合併療法，包括手術治療、放射線治療和化學藥物治療，近年來有報告以自體骨髓移植治療第三、四期之患者。根據臺灣兒童癌症基金會的統計顯示，高危險群的神經母細胞瘤病人經過高劑量化學治療、自體造血幹細胞移植、腫瘤摘除手術和局部放射線治療後，仍然有七成的病童會在五年內陸續復發，五年存活率只有 10-20%。而復發後的腫瘤多產生抗藥性，對化學治療反應不佳。

新的神經母細胞瘤治療方向就是使用標靶治療，利用單株抗體或 MIBG 對神經母細胞瘤的專一性加上具有細胞毒性的放射性元素、化學治療藥物，把神經母細胞瘤細胞殺死，但對正常細胞影響較少，提高療效、降低副作用。

I-131 MIBG 能與腎上腺素受體結合，且具有高度特異性碘標記，在臨床上已被公認對於神經元源起之腫瘤，具十分有效之診斷定位功能，所以在神經母細胞瘤的診斷、轉移追蹤上已經是公認的標準檢查。自 1981 年起，有人開始嘗試利用 I-131 MIBG 來對復發、高危險群的神經母細胞瘤病童進行治療，其治療反應有 4 成左右 (10-80%)。主要的副作在於骨髓毒性，造成全乏血球症。

目前國內醫療所用之碘標記 MIBG 皆需仰賴國外進口，不但浪費時間，更可能因此延誤病人的診斷與治療，而且費用昂貴(NT$ 10,000/mCi)，以致不能普遍推廣。目前行政院原子能委員會核能研究所已成功合成 I-131 MIBG，本人體試驗計畫的目的在測試 I-131 MIBG 人體運用的安全性和治療效果。

另外氟 18 左旋多巴（6-[18F]fluoro-levo-dopa，簡稱 18F-dopa）會由神經內分泌細胞所吸收和儲藏於細胞內，進而被 aromatic acid decarboxylase （簡稱 AADC）代謝成氟 18 多巴胺（18F-dopamine）和其他神經傳導物質，因此理論上 18F-dopa 可以用在神經母細胞瘤的特異性功能性造影，因此在 18F-dopa 正子造影可以比一般正子造影更具專一性和診斷價值，目前為止 18F-dopa 正子造影在神經母細胞瘤的應用報告仍很少數。

本實驗計畫第一年由核研所進行 I-/123,131 MIBG 之標幟研究與毒性試驗及品管分析方法建立，臺大醫院則開始對新發病和現有病人進行 I-123/131 MIBG、F18DG、F18DOPA 造影，做為第二年人體實驗選擇病人的準備。

貳、研究方法與過程

I-123/131 MIBG、F18DG、F18 DOPA 正子斷層造影

(一)受試者選擇標準：新發病和現有病人神經母細胞瘤病童。

受試者條件：1.已診斷神經母細胞瘤之現有病人或懷疑神經母細胞瘤之新病人

2.簽署受試者同意書

(二)試驗設計與流程：

1.本試驗為一開放性實驗，在神經母細胞瘤病患比較 I-123/131 MIBG、F18DG、F18 DOPA 正子斷層造影檢查的敏感度(sensitivity)和特異度(specificity)。

2.向受試者解釋本試驗之細節後，請受試者詳細閱讀「受試者說明及同意書」並簽名。

3.神經母細胞瘤病童將每三個月接受一次 I-123/131 MIBG scan 做為定期追蹤。F18DG、F18 DOPA 正子斷層造影檢查陽性者，則繼續追蹤；陰性者則停止該項檢查

(三)所需藥品或醫療器材名稱及數量

製劑：F-18 FDG 、6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine

(6-[^{18}F]fluoro-levo-dopa) 在本院所裝設之 cyclotron 及其附屬製藥設備，經由 fluorodestannylation reaction，進行自動化製造。

I-123/131 MIBG 由核研所/提供。

(四) 受試者將安排接受 ^{18}F-DOAP PET、FDG PET 與 $^{123/131}$I –MIBG scan 等檢查

進行 ^{18}F-DOPA PET 之程序:

1. 檢查前八小時禁食
2. 檢查前口服 Carbidopa，2 ㎎/kg 體重
3. 檢查前病患測量生命徵象
4. 由靜脈注射已溶於 10mL 生理食鹽水的 185mBq 6-[^{18}F]fluoro-levo-dopa，約 30 秒注射完畢。
5. 藥物注射完畢之後，馬上再次測量病患之生命徵象，並記錄任何的不良反應(adverse events)
6. 在接受 6-[^{18}F]fluoro-levo-dopa 注射後 1.5 小時接受 PET 掃描。
7. PET 儀器造影條件
   i. 收集模式：2D mode
   ii. 造影程式：1.2 FDOPA PET-CT brain 2D3.75 Th (PET/CT)
   iii. 先做 CT，再做 PET(whole body)，再做 PET(brain)。
   iv. 造影時間約 15-20 分鐘。
8. PET 影像處理步驟

i. 影像處理：在 Xeleris 工作站上同時點選 PET 影像。
ii. 點選 Oblique TOMO 程式。
iii. 對準中心線取得 TRANSAXIAL、CORONAL 及 SAGITTAL。
iv. 點選 TRANSAXIAL 打開檔案，Display 4x4，選 Inverse gray color 及 PET 10 color 各印一份。

9. 測試者離開之前再次確認無任何臨床上嚴重之不良反應，並於出院前抽血進行生化檢測（Na, K, Creatinine, ALP, AST/ALT）和血液學檢測（CBC）。

進行 ^{18}FDG PET 之程序:

1. 檢查前八小時禁食
2. 檢查前病患測量生命徵象
3. 由靜脈注射已溶於 10mL 生理食鹽水的 ^{18}FDG，約 30 秒注射完畢。
4. 藥物注射完畢之後，馬上再次測量病患之生命徵象，並記錄任何的不良反應
5. 在接受 FDG 注射後 1.5 小時接受 PET 掃描。
6. PET 儀器造影條件
   i. 收集模式：2D mode
   ii. 造影程式：1.2 FDOPA PET-CT brain 2D3.75 Th (PET/CT)
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   viii. 點選 TRANSAXIAL 打開檔案，Display 4x4，選 Inverse gray color 及 PET 10 color 各印一份。
8. 測試者離開之前再次確認無任何臨床上嚴重之不良反應，並於出院前抽血進行生化檢測（Na, K, Creatinine, ALP, AST/ALT）和血液學檢測（CBC）。

進行 $^{123/131}$I-MIBG 掃描之程序:

1. 為預防 I-123/131 聚積而傷害甲狀腺，打針前二天要服用 Lugol's solution，每天 4 滴，滴入開水中稀釋服用，一直持續到檢查結束三天為止
2. 檢查前病患測量生命徵象
3. 由靜脈注射已溶於 10mL 生理食鹽水的 $^{123/131}$I-labeled MIBG (3.7 MBq/kg of body weight)，約 30 秒注射完畢。
4. 藥物注射完畢之後，馬上再次測量病患之生命徵象，並記錄任何的不良反應 (adverse events)
5. 在接受 $^{123/131}$I-labeled MIBG 注射後 24、48、72 小時接受掃描。

6.再次抽血進行生化檢測（Na, K, Creatinine, ALP, AST/ALT）和血液學檢測（CBC），並於測試者離開之前在次確認無任何臨床上嚴重之不良反應。

參、主要發現與結論

Total 14 patients with Neuroblastoma were collected in this pilot study. Their ages ranged from 2 months -10 years old. Four patients were newly diagnosed and other ten patients were enrolled after treatment. Two patients were stage 3, two patients were stage 4s and ten patients were stage 4. Initial pathologic diagnosis were 13 neuroblastoma and 1 ganglioneuroblastoma. Seven patients were without mycN amplification, five patients were with mycN amplification and one patient was unknown. All patients had F-18-DOPA and FDG PET scan. Ten patients had ^{131}I-labeled MIBG scan.

In MIBG scan, 2 patients were revealed uptake of I131 in main tumor compatible with CT/MRI finding. Other 8 patients revealed no uptake of I131 and no mass lesions in CT/MRI. In DOPA PET, six patients with uptake of F-18-DOPA showed neuroblatoma or ganglioneuroblastoma of the tumor cell type. One of the FDOPA+ cases showed a large (6x5x4 cm) neuroblastoma (DOPA-) with a small (1.4x0.3x0.2 cm) ganglioneuroma (DOPA+) component in the right adrenal. Three others with no uptake of F-18-DOPA all showed a poorly differentiated neuroblastoma cells in the tumor. Four patients without main tumors showed no uptake of F-18-DOPA.

四、結論

Improvements in prognosis of Neuroblastoma are resulting from refinements in biologic characterization of neuroblastomas and from increased accuracy in establishing the extent of disease via expanding usage of sensitive imaging modalities ($^{123/131}$I- MIBG, FDG PET) and tests for detecting minimal residual disease (immunocytology, immunocytometry, RT-PCR). Assessment of the disease status requires a multitude of imaging studies to detect tumor location, extent and metastasis. Today, there are several morphologic and functional imaging methods available. CT and MRI are the morphologic imaging studies. Both provide excellent anatomic details and sensitivity, but both are lacking in specificity and only applied in local region. $^{123/131}$I- MIBG, FDG PET are the functional imaging studies. They are high specificity and the routinely performed whole-body scanning. Furthermore, in follow-up examinations, functional imaging is not affected by postoperative artifacts such as scar tissue or metallic clips. $^{123/131}$I- MIBG scan is the gold standard scan for Neuroblastoma. In our study,^{131}I- MIBG has excellent specificity. But the disadvantages are high radiation exposure, poor imaging quality and not available routinely. We hope the ,^{123}I- MIBG will be available as soon as possible.

FDG PET is another function imaging method in neuroblastomas. FDG PET scan findings correlate well with disease status as determined by MIBG scans, CT/MRI, bone marrow test and clinical history. Sequential PET scans accurately depict treatment effects and disease evolution. Because of higher spatial resolution of the PET scanner and the tomographic nature of PET images, PET may be better than routine $^{123/131}$I- MIBG scan for identifying small lesions and for delineating the extent or localizing anatomic sites of disease. In our study, we found a major drawback of PET is lack of visualization of lesions in the liver and cranium because of high physiologic activity. Another disadvantage of PET is the specificity. The “flip-flop” phenomenon was also found.

No studies on the possible role of F-18-DOPA in neuroblastoma have been published yet. In pheochromocytoma, F-18-DOPA scanning has shown high sensitivity and specificity for primary and metastatic disease. F-18-DOPA is a better substrate for the cell membrane norepinephrine transporter than MIBG and a more specific substrate for neuroblastoma cells than FDG. With the high spatial resolution of PET, F-18-DOPA

positivity indicates the ability of tumor cells to accumulate and the ability to decarboxylate F-18-DOPA by AADC (aromatic amino acid decarboxylase) in a well differentiated tumor or tumor component. This may indicate better prognosis. The clinical significance needs further follow up. F-18-DOPA PET scan is useful when the supply of MIBG and octreoscan is unavailable or limited.

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