高雄榮民總醫院癌症診療指引

婦癌化療藥物停藥準則

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婦癌醫療團隊制定
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注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如妳是一個癌症病人，直接引用這個診療指引並不恰當，只有妳的醫師與妳才能共同決定給屬於妳最恰當的治療。

修訂指引

- 本共識依下列參考資料修改版本
  - 前次會議時間： 無.

與上一版的差異

無.

目標與成效評估

1. 減少因化療副作用造成患者直接死亡的事件。
2. 減少與化療相關的重大醫療事件。
3. 患者滿意度提升 (如:副作用程度平均值下降等) 。
4. 維持病患接受化學治療的RDI。
5. 提升病患PFS及OS。
6. 減少無效醫療之醫療費用。

Relative dose intensity (RDI)

= RDI was calculated as the delivered dose intensity (total dosedelivered/total time of therapy) divided by standard dose intensity calculated for each regimen and compared to progression-free survival (PFS).

=>RDI is a significant predictor of survival in patients with EOC. Effort should be made to achieve an RDI of at least 70%.

Progression free survival (PFS)

Overall survival (OS)

婦癌病人入院化療基本評估項目

1. 症狀及病史詢問。
2. 生命徵象。
3. 理學檢查及身體評估。
4. 婦產科腹部超音波。
5. 胸部X光。
6. 抽血檢查: CBC/DC, BUN/Crea, Na/K, GOT/GPT, T. Bil., Glu, Urine routine
7. 紀錄目前使用中藥物。
8. 檢查目前可能有的潛在感染並先予以處理(含B型肝炎，C型肝炎，HZV，蛀牙，身體傷口 等等)
9. 告知病人此次化學治療使用藥物，及可能帶來之療效與副作用。

婦癌病人化療出院衛教

1. 注意臨床症狀及生命徵象，例如有無發燒、心悸、血壓不穩定、喘等等。
2. 注意有無局部感染跡象(紅腫熱痛)。
3. 注意進食量及尿量。
4. 目前使用藥物注意事項。 若病人化療期間有疲倦、噁心、嘔吐、便秘、黏膜發炎、身體傷口等等情況，應該幫病人處理並帶藥返家使用。
5. 鼓勵多補充營養食物。
6. 減少出入人群眾多處，戴口罩並勤洗手以自我保護。
7. 化療後7~14天回診抽血檢查: CBC/DC。 如有不適，應立刻向醫師反映。
8. 衛教師定期追蹤病人情況並回報主治醫師(機制?)。

婦癌化療藥物停藥準則 – 身體狀態評估

Performance status	Grade 1	Grade 2	Grade 3	Grade 4
身體狀況評估[1.] (ECOG PS)	無法進行出力的工作，但可做些輕鬆的家事或工作。	可以自行移動或自我照顧，旦無法工作。	需人協助自我照顧，一天有一半以上的時間臥床或坐輪椅。	完全需人照顧，完全臥床或坐輪椅。
建議事項	按照標準化療評估及療程。	按照標準化療評估及療程。	可視情況考慮停止化學治療。	建議停止化學治療 。

Grade 5: 死亡

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 – 治療效果

治療效果	Complete remission	Partial response	Stable disease	Progressive disease
Response evaluation[2.] **(RECIST guideline)**	**CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.**	**PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.**	**SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sumdiameters while on study.**	**PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). 註1註2**
建議事項	按照標準化療評估與流程。	按照標準化療評估與流程。	可視情況考慮停止化學治療，或考慮換藥。	可視情況考慮停止化學治療，或考慮換藥。

註1: In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
註2: the appearance of one or more new lesions is also considered progression.

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 – 血液副作用

Adverse event-1	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia k/cumm	**<4000-3000**	**<3000-2000**	**<2000-1000**	**<1000**
	建議藥物處理;恢復後再行化療。	建議藥物處理;恢復後再行化療。	可考慮停藥。建議藥物處理;恢復後再行化療。	建議停藥。建議下次化療前調整劑量; 藥物處理;恢復後再行化療。

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 – 血液副作用

Adverse event-2	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia k/cumm	**<150k-75k**	**<75k-50k**	**<50k-25k**	**<25k**
	建議輸血處理;恢復後再行化療。	建議輸血處理;恢復後再行化療。	可考慮停藥。建議輸血處理;恢復後再行化療。	建議停藥。建議下次化療前調整劑量;輸血處理;恢復後再行化療。

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 – 血液副作用

Adverse event-3	Grade 1	Grade 2	Grade 3	Grade 4
Anemia HB 女性LLN=12g%	**<LLN-10.0**	**<10.0-8.0**	**<8.0**	**危及生命**
	建議補充鐵劑;按照標準化療評估與流程。	建議輸血處理;恢復後再行化療。	可考慮停藥。建議輸血處理;恢復後再行化療。	建議停藥。建議下次化療前調整劑量;輸血處理;恢復後再行化療。

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 – 肝臟副作用

Adverse event-4	Grade 1	Grade 2	Grade 3	Grade 4
GOT 增加 ULN=35U/L	**>35-105**	**>105-175**	**>175-700**	**>700**
	調整用藥劑量 (見附錄二 肝毒性藥物劑量調整)	建議停藥。	建議停藥。	建議停藥。

Drug with caution: 見附錄一 具肝毒性之藥物

1. **Methotrexate**
2. **Oxaliplatin**
3. **Paclitaxel**
4. **Irinotecan**
5. **Topotecan**
6. **Fluorouracil**
7. **Gemcitabine**
8. **Cisplatin**
9. **Cyclophosphamide**
10. **Dacarbazine**
11. **Doxorubicin**
12. **Etoposide**

婦癌化療藥物停藥準則 – 肝臟副作用

Adverse event-5	Grade 1	Grade 2	Grade 3	Grade 4
GPT 增加 ULN=40U/L	**>40-120**	**>120-200**	**>200-800**	**>800**
	調整用藥劑量 (見附錄二 肝毒性藥物劑量調整)	建議停藥。	建議停藥。	建議停藥。

Drug with caution: (見附錄一 具肝毒性之藥物)

1. **Methotrexate**
2. **Oxaliplatin**
3. **Paclitaxel**
4. **Irinotecan**
5. **Topotecan**
6. **Fluorouracil**
7. **Gemcitabine**
8. **Cisplatin**
9. **Cyclophosphamide**
10. **Dacarbazine**
11. **Doxorubicin**
12. **Etoposide**

婦癌化療藥物停藥準則 – 肝臟副作用

Adverse event-5	Grade 1	Grade 2	Grade 3	Grade 4
T. Bil 增加 (ULN = 1.6mg/dL)	**>ULN - 1.5 x ULN**	**>1.5 - 3.0 x ULN**	**>3.0 - 10.0 x ULN**	**>10.0 x ULN**
	按照標準化療評估與流程。	調整用藥劑量 (見附錄二 肝毒性藥物劑量調整)	建議停藥。	建議停藥。

Drug with caution: (見附錄一 具肝毒性之藥物)

1. **Methotrexate**
2. **Oxaliplatin**
3. **Paclitaxel**
4. **Irinotecan**
5. **Topotecan**
6. **Fluorouracil**
7. **Gemcitabine**
8. **Cisplatin**
9. **Cyclophosphamide**
10. **Dacarbazine**
11. **Doxorubicin**
12. **Etoposide**

婦癌化療藥物停藥準則 – 肝臟副作用

Adverse event-5	Grade 1	Grade 2	Grade 3	Grade 4
肝衰竭	-	-	蹼翼樣震顫;輕度肝腦性病變	中~重度肝性腦病變;昏迷;危及生命
			建議停藥。	建議停藥。

Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, LDH, and alk-p.

Drug with caution: (見附錄一 具肝毒性之藥物)

1. **Methotrexate**
2. **Oxaliplatin**
3. **Paclitaxel**
4. **Irinotecan**
5. **Topotecan**
6. **Fluorouracil**
7. **Gemcitabine**
8. **Cisplatin**
9. **Cyclophosphamide**
10. **Dacarbazine**
11. **Doxorubicin**
12. **Etoposide**

婦癌化療藥物停藥準則 – 腎臟副作用

Adverse event-6	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine 增加 女性 **ULN=1.2 mg/dl**	**>1.5**	**>1.8-3.6**	**>3.6-7.2**	**>7.2**
	矯正其他可處理因素；調整用藥劑量。(見附錄三)	矯正其他可處理因素；調整用藥劑量，或更換藥物。(見附錄三)	矯正其他可處理因素；調整用藥劑量，或更換藥物或停藥。(見附錄三)	矯正其他可處理因素；調整用藥劑量，或更換藥物或停藥。(見附錄三)

Take special caution with Patients who had comedication of **diuretics** and **ACE-inhibitor**.

Drug with caution:
CYTOTOXIC DRUGS:
1. Cisplatin.
2. Carboplatin.
3. Alkylating agents: Cyclophosphamide, Ifosfamide.
4. Antitumor antibiotics: Bleomycin.
5. Antimetabolites: Methotrexate, Gemcitabine.
6. Vinca alkaloids.
7. Topotecan
8. Etoposide
9. Taxanes
10. Irinotecan,

婦癌化療藥物停藥準則 – 腎臟副作用

Adverse event-8	Grade 1	Grade 2	Grade 3	Grade 4
Hematuria	顯微性血尿;輕度頻尿，排尿困難，無尿或夜尿	中度血尿;中度頻尿，排尿困難，無尿或夜尿	肉眼可見的血尿;輸血，靜脈治療	危及生命
	考慮調整劑量; 藥物預防及補充水分。 (見附錄四)	考慮調整劑量; 藥物預防及補充水分。 (見附錄四)	建議停藥;藥物治療及補充水分;輸血;考慮高壓氧治療。 (見附錄四)	建議停藥;藥物治療及補充水分;輸血;高壓氧治療。 (見附錄四)

Drug with caution:
CYTOTOXIC DRUGS:
1. Alkylating agents: Cyclophosphamide, Ifosfamide. **(Hemorrhagic cystitis)**

婦癌化療藥物停藥準則 – 腎臟副作用

Adverse event-7	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	**1+** **<1.0g/24h**	**2+** **1.0~3.4g/24h**	**≧ 3.5g/24h**	**-**
	按照標準化療評估與流程 (見附錄五)	評估並控制血壓;評估血尿;考慮會診腎臟科做腎臟切片。 (見附錄五)	建議停藥;評估並控制血壓;評估血尿;考慮會診腎臟科做腎臟切片。 (見附錄五)	

Drug with caution:
TARGET THERAPY:
1. Avastin (**Bevacizumab)**

婦癌化療藥物停藥準則 –腎臟副作用

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
續發性高血壓	Prehypertension (SBP 120 - 139 mm Hg or DBP 80 - 89 mm Hg)	SBP 140 - 159 mm Hg or DBP 90 - 99 mm Hg	SBP ≧160 mm Hg or DBP ≧100 mm Hg)	危及生命
	必要時口服降血壓藥物治療;按照標準化療評估與流程。	口服降血壓藥物治療;評估蛋白尿;若無蛋白尿則按照標準化療評估與流程(見附錄五)	口服降血壓藥物治療，可多重藥物盡速降壓;評估蛋白尿。(見附錄五)	建議停藥。

Drug with caution:
TARGET THERAPY:
1. Avastin (**Bevacizumab)**

婦癌化療藥物停藥準則 – 免疫系統及全身性症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
過敏反應	暫時性皮疹，藥物熱<38℃	症狀治療立即有反應;預防性用藥≦24h	反覆症狀或需住院治療	危及生命
	抗過敏藥物使用。按照標準化療評估與流程。	抗過敏藥物使用。按照標準化療評估與流程。	建議停藥。	建議停藥。

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 –免疫系統及全身性症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
發燒 ℃	38.0-39.0	>39.0-40.0	>40.0 持續小於24小時	>40.0 持續大於24小時
	建議停藥，直到確認發燒原因並已處理緩解。	建議停藥，直到確認發燒原因並已處理緩解。	建議停藥，直到確認發燒原因並已處理緩解。	建議停藥，直到確認發燒原因並已處理緩解。

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 –免疫系統及全身性症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
疲倦	休息可緩和	休息無法緩和	休息無法緩和並影響日常生活	危及生命
	按照標準化療評估與流程。	建議停藥;積極確認原因並協助病人緩解。	建議停藥。	建議停藥。

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 –免疫系統及全身性症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
體重增加或減輕 評估的Interval每三個月到六個月	增加或減少 **5~10%**	增加或減少 **10~20%**	增加或減少 **>20%**	-
	按照標準化療評估與流程;積極確認原因並協助病人緩解。	建議停藥;積極確認原因並協助病人緩解。會診營養師。	建議停藥。會診營養師。	

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 – 腸胃道症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
噁心	無食慾，但不改變飲食習慣	進食量減少，但無體重減輕或脫水。	進食量減少，需管灌餵食或靜脈營養補充	-
chemotherapy-induced nausea and vomiting (CINV)	按照標準化療評估與流程。	按照標準化療評估與流程; 積極確認原因並協助病人緩解。	建議停藥;積極確認原因並協助病人緩解。	

Drug with caution: 參考 全民健康保險藥品給付規定 第7章 腸胃藥物

高致吐性藥品：

cisplatin (>50mg/m2/day)、carmustine(≧250mg/m2 /day)、cyclophosphamide (>1500mg/m2/day)、methotrexate (≧1.2gm/m2/day)。

中致吐性藥品：

cisplatin (≧30mg/m2/day, ≦50mg/m2/day)、carmustine (<250mg/m2/day)、Cyclophosphamide (≦1500mg/m2 /day)、doxorubicin (≧45mg/m2/day)、epirubicin (≧70mg/m2/day)、CPT-11、idarubicin (≧10mg/m2/day)、daunorubicin (≧60mg/m2/day)、dactinomycin (actinomycin-D)、arsenic trioxide、melphalan (≧50mg/m2/day)、cytarabine、 carboplatin、oxaliplatin、 ifosfamide、mitoxantrone、dacarbazine 且其使用劑量為一般公認治療劑量或上述規定劑量時。

婦癌化療藥物停藥準則 – 腸胃道症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
嘔吐	1~2次/24h	3~5次/24h	>6次/24h，需管灌餵食或靜脈營養補充	危及生命
chemotherapy-induced nausea and vomiting (CINV)	止吐藥物使用; 按照標準化療評估與流程。	止吐藥物使用; 按照標準化療評估與流程。	建議停藥。 營養支持。 會診營養師。	建議停藥。 營養支持。 會診營養師。

Drug with caution: 參考 全民健康保險藥品給付規定 第7章 腸胃藥物

1高致吐性藥品：

cisplatin (>50mg/m2/day)、carmustine(≧250mg/m2 /day)、cyclophosphamide (>1500mg/m2/day)、methotrexate (≧1.2gm/m2/day)。

中致吐性藥品：

cisplatin (≧30mg/m2/day, ≦50mg/m2/day)、carmustine (<250mg/m2/day)、Cyclophosphamide (≦1500mg/m2 /day)、doxorubicin (≧45mg/m2/day)、epirubicin (≧70mg/m2/day)、CPT-11、idarubicin (≧10mg/m2/day)、daunorubicin (≧60mg/m2/day)、dactinomycin (actinomycin-D)、arsenic trioxide、melphalan (≧50mg/m2/day)、cytarabine、 carboplatin、oxaliplatin、 ifosfamide、mitoxantrone、dacarbazine 且其使用劑量為一般公認治療劑量或上述規定劑量時。

婦癌化療藥物停藥準則 – 腸胃道症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
腹瀉	每天比正常多**1~3**次/**24h**	每天比正常多**4~6**次/**24h**	每天比正常多**7**次以上或肛失禁或其他症狀。	危及生命
	查找其他症狀;藥物治療;營養支持;協助病人緩解症狀。(見附錄六)	查找其他症狀;藥物治療;營養支持;協助病人緩解症狀。(見附錄六)	評估體重及尿量; 營養支持;建議停藥。(見附錄六)	評估體重及尿量; 營養支持;建議停藥。(見附錄六)

All patients with severe (grade 3 or 4) diarrhea are considered complicated. Patients with mild to moderate diarrhea (grade 1 or 2) with one or more complicating factors also are considered complicated (Cherny, 2008; Richardson & Dobish, 2007).

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 – 腸胃道症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
口腔黏膜炎	不痛或輕微疼痛	中度疼痛但不影響進食	嚴重疼痛而影響進食	危及生命
	傷口處理；按照標準化療評估與流程。 (見附錄七)	傷口處理及止痛； **考慮調整劑量或更換藥物**。 (見附錄七)	傷口處理及止痛；營養支持; 建議停藥。 (見附錄七)	傷口處理及止痛；營養支持; 建議停藥。 (見附錄七)

Treatment: Morphine is the treatment of choice for pain control; cryotherapy or low level laser therapy was suggested for ulceration.

Drug with caution:
1.見附錄七: 黏膜炎 **Mucositis** 相關化療藥物

婦癌化療藥物停藥準則 – 神經系統症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
周邊神經病變	輕微的感覺異常；深部肌腱反射損失	中度症狀致日常；深部肌腱反射消失;生活有困難	嚴重症狀影響自我照顧	呼吸抑制及癱瘓
ECOG	緩解病人症狀。 (見附錄八)	緩解病人症狀。 (見附錄八)	建議停藥或更換藥物。	建議停藥。

Drug with caution: 見附錄八

1. Pure sensory and painful neuropathy: **cisplatin, oxaliplatin, carboplatin**
2. A mixed sensorimotor neuropathy with or without involvement of the autonomic nervous system (with **vincristine, taxol, suramin**)

婦癌化療藥物停藥準則 – 感染

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
甲溝炎	甲床紅腫	甲床紅腫伴隨疼痛，產生分泌物或指板分離	需外科治療或注射抗生素	-
	建議停藥。 感染控制。	建議停藥。 感染控制。	建議停藥。 感染控制。	建議停藥。 感染控制。

Drug with caution:
1. All cytotoxic agents and target therapy.

婦癌化療藥物停藥準則 –皮膚或皮下組織症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
脫髮	<50%掉髮	≧50%掉髮		-
	心理支持;衛教外觀修飾。按照標準化療評估與流程。	心理支持;衛教外觀修飾。按照標準化療評估與流程。或更換藥物。		

Drug with caution:
1. Paclitaxel.
2. Docetaxel

婦癌化療藥物停藥準則 –皮膚或皮下組織症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
手足症候群	輕微皮膚變化	皮膚病變(如皮膚剝落，水泡，出血，水腫或角質增生)，並伴隨疼痛	嚴重皮膚病變(如皮膚剝落，水泡，出血，水腫或角質增生)，並伴隨疼痛	-
Palmar Plantar Erythrodysesthesia (**Hand-Foot**) syndrome	緩解症狀。(見*)	傷口處理及止痛;調整施打化療藥物間隔。(見**)	傷口處理及止痛; 調降劑量。(見**)	

* Apply cold compression for patient under liposomal doxorubicin.
** Patients received intravenous (I.V.) liposomal doxorubicin 50 mg/m2 every 3 weeks with a dose reduction to 40 mg/m2 in the event of grade 3 or 4 toxicities, or a lengthening of the interval to 4 weeks (and occasionally to 5 weeks) with persistence of grade 1 or 2 toxicities beyond 3 weeks.

Drug with caution:
1. Liposomal doxorubicin

婦癌化療藥物停藥準則 –皮膚或皮下組織症狀

Adverse event-	Grade 1	Grade 2	Grade 3	Grade 4
痤瘡狀疹	丘疹範圍涵蓋 **<10% BSA**	丘疹範圍涵蓋 **10 - 30% BSA**	丘疹範圍涵蓋 **>30% BSA**；合併局部感染需口服抗生素	丘疹範圍涵蓋任何**% BSA**並合併嚴重感染需注射抗生素治療或危及生命
	藥物治療; 建議暫時停藥。	藥物治療; 建議暫時停藥。	建議停藥。	建議停藥。

Drug with caution:
1.

附錄一：具肝毒性之藥物

	Liver toxic effects	Frequency	Severity	References
Asparaginase	Inhibition of protein synthesis (decreased albumin and increased aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin)	Common	Mostly reversible	33
	Steatosis	Very common (up to 87% of patients)	Mostly reversible	
Azathioprine and mercaptopurine	Cholestatic jaundice or intrahepatic cholestasis Increased aminotransferases	Common (more so with mercaptopurine than with azathioprine)	Mostly reversible	34
Busulfan	Veno-occlusive disease in high doses or in transplantation	Common in bone-marrow transplantation (10–25% of patients)	Severe and life-threatening	30,35
	Cholestatic hepatitis	Rare case reports	Reversible	35
Capecitabine	Hyperbilirubinaemia, usually without increased alkaline phosphatase and gamma-glutamyltransferase; might be related to haemolysis	Common (23–25% of patients)	Grade 3–4 in up to 23% of patients	36–38
Carmustine	Increased aminotransferases and alkaline phosphatase, with or without increased bilirubin	Common, up to 26% of patients	Usually mild and reversible; rare fatalities	39
Chlorambucil	Fibrosis and cirrhosis	Rare, anecdotal	Case reports of severe damage (but viral infection not excluded)	40
Cisplatin	Increased aminotransferases	Common (more so with high doses)	Usually transient	41
	Steatosis and cholestasis	Rare	Usually transient	41
Cyclophosphamide	Veno-occlusive disease in high doses or in transplantation	Common in bone-marrow transplantation (10–25% of patients)	Severe and life-threatening	30,42
	Isolated case reports of idiosyncratic reactions	Uncommon	Usually transient	42
Cytarabine	Increased aspartate aminotransferase and alanine aminotransferase; cholestatic jaundice and intrahepatic cholestasis	Common	Usually reversible	43
Dacarbazine	Case reports of fulminant liver failure (thrombotic occlusions)	Rare	Can be life-threatening	44
Dactinomycin	Increased aminotransferases in children	Up to 17% of patients	Can be life-threatening	45
Doxorubicin	Idiosyncratic reactions, including increased aminotransferases and bilirubin	Rare	Usually transient	46
Etoposide	Veno-occlusive disease in high doses or in transplantation	Common in bone-marrow transplantation (10–25% of patients)	Severe and life-threatening	30,47
	Case reports of severe hepatocellular damage at standard doses	Rare	Severe	47
Fluorouracil	Steatosis	Common	Usually subclinical	48,49
	Hepatotoxicity	Rare	Usually subclinical	48,49
Floxuridine (into hepatic artery)	Increased aminotransferases, alkaline phosphatase, and bilirubin	Common, transaminitis in up to 50% of patients	Hepatitis improves after cessation	50,51
	Biliary stricture or sclerosis	Up to 16% of patients	Secondary sclerosing cholangitis irreversible	51

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附錄一：具肝毒性之藥物

Gefitinib	Increased aminotransferases	Uncommon	Usually subclinical	52
Gemcitabine	Increased aminotransferases	Very common, up to 60% of patients	Generally transient and reversible	53,54
	Case reports of fatal cholestatic hepatotoxicity	Rare	Can be fatal	53,54
Imatinib	Increased aminotransferases or bilirubin	Up to 10% of patients	2–6% grade 4	55,56
	Liver necrosis or failure	Rare	Case reports of fatalities	55,56
Interferon	Increased aminotransferases	Common	Usually mild and improve after cessation	57
Interleukin 2	Increased bilirubin (ie, intrahepatic cholestasis)	Common	Usually reversible	58
	Increased aminotransferases and alkaline phosphatase	Common	Usually reversible	58
Irinotecan	Steatosis and steatohepatitis	Common (25–50% of patients)	Steatohepatitis can increase morbidity if used before liver resection	48,59–61
	Increased aminotransferases and bilirubin	Up to 25% of patients	Usually reversible	48,59–61
Melphalan	Hepatotoxicity, thrombus, and veno-occlusive disease with isolated liver perfusion	Rare, but veno-occlusive disease common in bone-marrow transplantation (10–25% of patients)	Veno-occlusive disease severe and life-threatening	30,62
	Transient enzyme increase	Common at high doses	Usually transient	62
Methotrexate	Increased aspartate aminotransferase and alanine aminotransferase at high doses	Common with high dose	Transient and reversible	63–66
	Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis at chronic low dose	More common with chronic use (eg, in rheumatoid arthritis) and cumulative dose >2 g	Potentially irreversible	63–66

(Continues on next page)

	Liver toxic effects	Frequency	Severity	References
(Continued from previous page)				
Oxaliplatin	Vascular changes; sinusoidal obstruction or dilatation syndrome	Common (20–80% of patients)	Might increase morbidity, but not mortality, after liver resection	59,60,67,68
Paclitaxel	Increased bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase	For high doses, up to 37% of patients	Generally reversible	69
Topotecan	Increased aminotransferases and alkaline phosphatase	Up to 5–8% of patients	Low-grade and reversible	70

Table 2: **Anticancer agents associated with toxic liver effects**

Lancet Oncol 2008; 9: 1092–101

附錄二：肝毒性藥物劑量調整

	Effect of liver impairment	Dose modification	Ref
Capecitabine	Increased aspartate aminotransferase or bilirubin: no relation to pharmacokinetics or toxic effects	No dose adjustment needed	2
Cisplatin and carboplatin	No published studies	Unlikely to need dose adjustments; mainly renal excretion	3
Cyclophosphamide	No changes in clearance	No dose adjustments needed	4
Docetaxel	Increased risk of neutropenia, mucositis, and death Increased bilirubin, with or without raised transaminases: 12–27% decreased drug clearance	Use not recommended if bilirubin is more than upper limit of normal, or if ratio of aspartate aminotransferase to alanine aminotransferase is >1·5-times upper limit of normal and alanine phosphatase is >2·5-times upper limit of normal	5,6
Doxorubicin	Myelosuppression; mucositis	Bilirubin <51 µmol/L: normal dose Bilirubin 34–51 µmol/L: decrease dose by 50% Bilirubin 51–85 µmol/L: decrease dose by 75% Bilirubin >85 µmol/L: withhold treatment	4 7 7 7
Epirubicin	Aspartate aminotransferase more sensitive marker of clearance than bilirubin	Consult dose guidelines based on levels of aspartate aminotransferase	8
Erlotinib	Increased aspartate aminotransferase or bilirubin	Aspartate aminotransferase ≥3-times upper limit of normal or bilirubin 17–120 µmol/L: 50% dose reduction	9
Etoposide	Mild to moderate impairment: no pharmacokinetic effect Severe impairment: myelosuppression; mucositis Decreased albumin increases unbound drug concentration and increases haematological toxic effects	Unclear (increased renal clearance might compensate)	10
Fluorouracil	Increased bilirubin: no relation to toxic effects	No dose adjustment needed	11
Gemcitabine	Increased aspartate aminotransferase alone: no increase in toxic effects Increased bilirubin: deterioration in liver function	Usual dose: 1000 mg/m² Increased aspartate aminotransferase: no dose change needed Increased bilirubin: reduce dose by 20% (ie, to 800mg/m²) and increase if tolerated	12
Imatinib	No notable pharmacokinetic differences or increased toxic effects	Stop treatment if hepatotoxicity develops; should probably not rechallenge	13

附錄二：肝毒性藥物劑量調整

Irinotecan	Increased aspartate aminotransferase alone: no increase in toxic effects Increased bilirubin: neutropenia and diarrhoea	Increased aspartate aminotransferase: no dose change Increased bilirubin: reduce dose: 3-weekly irinotecan (usual dose 350 mg/m² every 3 weeks) • Bilirubin <1·5-times upper limit of normal: 350 mg/m² • Bilirubin >1·5–3-times upper limit of normal: 200 mg/m² • Bilirubin >3-times upper limit of normal: irinotecan not recommended Weekly irinotecan (usual dose 125 mg/m² for 4 of 6 weeks) • Bilirubin 1·5–3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase <5-times upper limit of normal: 60 mg/m² • Bilirubin 3·1–5-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase <5-times upper limit of normal: 50 mg/m² • Bilirubin <1·5-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase 5·1–20-times upper limit of normal: 60 mg/m² • Bilirubin 1·5–3-times upper limit of normal and ratio of aspartate aminotransferase to alanine aminotransferase 5·1–20-times upper limit of normal: 40 mg/m²	14–16
Oxaliplatin	Increased bilirubin, aspartate aminotransferase, or alkaline phosphatase: no effect on drug clearance or neurotoxicity	No dose adjustment	17
Paclitaxel	Increased aspartate aminotransferase or bilirubin increases myelosuppression	Reduce dose if increased aspartate aminotransferase or increased bilirubin	18
Sorafenib	Clearance does not differ between patient cohorts	Bilirubin ≤1·5-times upper limit of normal: 400 mg twice a day Bilirubin 1·5–3-times upper limit of normal: 200 mg twice a day Bilirubin 3–10-times upper limit of normal: sorafenib not recommended Albumin <25 g/L: 200 mg daily	19
Topotecan	No obvious effects	No dose adjustment needed if bilirubin 29–84 μmol/L	20
Vinorelbine	Increased bilirubin decreases drug clearance Volume of liver affected correlates with clearance	Suggested dose: Bilirubin 2·1–3-times upper limit of normal: reduce dose by 50% Bilirubin >3-times upper limit of normal: reduce dose by 75% Diffuse liver metastases: decrease dose by 50% (irrespective of bilirubin concentration)	21

Table 1: **Anticancer agents specifically studied in setting of liver dysfunction**

附錄三: 腎毒性藥物劑量調整

Table 1 – Summary of dosage adjustment recommendations for renally cleared anticancer drugs

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Alkylating agents						
Carmustine	60–70	No recommendations, due to lack of pharmacokinetic and/or safety data in patients with renal insufficiency. However, care is warranted since a major part is renally excreted. Kintzel and Dorr[25] have generated guidelines on the basis of renal excretion, but not pharmacokinetic data: 80% normal dose for patients with CLcr ⩽60 mL/min, 75% normal dose for patients with CLcr ⩽45 mL/min, and 70% normal dose in patients with CLcr ⩽30 mL/min.				De Vita et al.[92] Levin et al.[93] Oliverio[94] Russo et al.[95]
Ifosfamide	45	Intermittent dose/day: 1.5 to 3 g/m^2; dose/cycle: 5 to 10 g/m^2			Intermittent dose/day: 1.13 to 2.25 g/m^2 dose/cycle: 3.75 to 7.5 g/m^2	Allen & Creaven[96] Bennett et al.[97] Carlson et al.[98] Cerny et al.[99] Creaven et al.[100] Fleming[101] Kerbusch et al.[102] Kurowski et al.[103] Kurowski et al.[104] Nelson et al.[105] Norpoth et al.[106] Wagner[107]
		Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 5 to 8 g/m^2	Continuous dose/day: 3.75 to 6 g/m^2	

Eur J Cancer. 2007 Jan;43(1):14-34.

附錄三: 腎毒性藥物劑量調整

Table 1 – (continued)

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Platinum agents						
Carboplatin	95	Adjust according to patient using a formula such as the Calvert formula.				Calvert et al.[15] Chatelut et al.[126] Curt et al.[127] Dooley et al.[17] Egorin et al.[16] Elferink et al.[128] English et al.[129] Gaver et al.[130] Harland et al.[131] Himmelstein et al.[132] Koeller et al.[133] Oguri et al.[134] Suzuki et al.[135] Van Warmerdam et al.[44] Yanagawa et al.[136]
Cisplatin	90	50 to 120 mg/m^2 every 3 to 6 weeks	Not recommended, however if unavoidable an appropriate dose should be used: 25 to 60 mg/m^2 every 3 to 6 weeks		Not recommended, however if unavoidable an appropriate dose should be used: 25 mg/m^2 (evidence in haemodialysis patients).	Bennett et al.[97] Bonnem et al.[137] Buice et al.[138] Gorodetsky et al.[139] Hirai et al.[140] Prestayko et al.[141] Ribrag et al.[142] Tomita et al.[143]
Oxaliplatin	54	85 or 100 mg/m^2 every 2 weeks, or 130 mg/m^2 every 3 weeks			Contraindicated	Graham et al.[144] Massari et al.[48] McKeage[145] Pendyala & Creaven[146] Takimoto et al.[50]

Eur J Cancer. 2007 Jan;43(1):14-34.

附錄三: 腎毒性藥物劑量調整

Table 1 – (continued)

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Methotrexate	55–88	Oral 15 to 30 mg/m^2 IM, IV, SC Solid tumours: 30 to 50 mg/m^2 IA 25 to 50 mg/24 h IR 10 to 15 mg/m^2	Oral 12 to 24 mg/m^2 IM, IV, SC Solid tumours: 24 to 40 mg/m^2 IA 20 to 40 mg/24 h IR 10 to 15 mg/m^2	Oral 7.5 to 24 mg/m^2 IM, IV, SC Solid tumours: 15 to 25 mg/m^2 IA 12 to 25 mg/24 h IR 10 to 15 mg/m^2	Contraindicated Contraindicated Contraindicated Contraindicated	Bennett et al.[97] Bleyer[151] Bostrom et al.[152] Calvert et al.[153] Creinin & Krohn[154] Djerassi et al.[155] Freeman-Narrod et al.[156] Huffman et al.[157] Liegler et al.[158] Shapiro et al.[159] Shen & Azarnoff[160] Teresi et al.[161] Wall et al.[162]
Miscellaneous						
Bleomycin	50–70	10 to 20 mg/m^2	7.5 to 15 mg/m^2	7.5 to 15 mg/m^2	5 to 10 mg/m^2	Alberts et al.[201] Bennett et al.[97] Crooke et al.[202] Crooke et al.[203] Hall et al.[204] Harvey et al.[205] McLeod et al.[206] Oken et al.[207] Simpson et al.[208]

Eur J Cancer. 2007 Jan;43(1):14-34.

附錄三: 腎毒性藥物劑量調整

Table 1 – (continued)

Agent	% dose excreted in urine	Dose based on patient's CLcr				References
		90–60 mL/min	60–30 mL/min	30–15 mL/min	<15 mL/min and/or haemodialysis[a]	
Topoisomerase inhibitors						
Etoposide	40–60	Oral 80 to 300 mg/m²/day for 3 to 5 days, followed by 50 to 100 mg/m²/day IV 50 to 150 mg/m²/day for 1 to 3 days Intensive dosing: 40 to 50 mg/kg	Oral 60 to 225 mg/m²/day for 3 to 5 days, followed by 37.5 to 75 mg/m²/day IV 37.5 to 112.5 mg/m²/day for 1 to 3 days Intensive dosing: 30 to 45 mg/kg		Oral 40 to 150 mg/m²/day for 3 to 5 days, followed by 25 to 50 mg/m²/day IV 25 to 75 mg/m²/day for 1 to 3 days Intensive dosing: 20 to 30 mg/kg	Bennett et al.[97] Chabot et al.[182] de Jong et al.[183] Hande et al.[167] Higa et al.[184] Inoue et al.[185] Kamizuru et al.[186] Pfluger et al.[187] Pfluger et al.[188] Slevin et al.[189] Watanabe et al.[190]
Topotecan	20–60	1.5 mg/m²/day	60–40 mL/min: 1.5 mg/m²/day; 39–20 mL/min: 0.75 mg/m²/day; <20 mL/min and haemodialysis: not available			Anastasia[191] Grochow et al.[192] Haas et al.[193] Herben et al.[194] Herrington et al.[195] Iacono et al.[196] O'Dwyer et al.[197] O'Reilly et al.[73] Seiter[198] Van Warmerdam et al.[199] Van Warmerdam et al.[200]

Eur J Cancer. 2007 Jan;43(1):14-34.

附錄四: **Hemorrhagic cystitis** 病理機轉

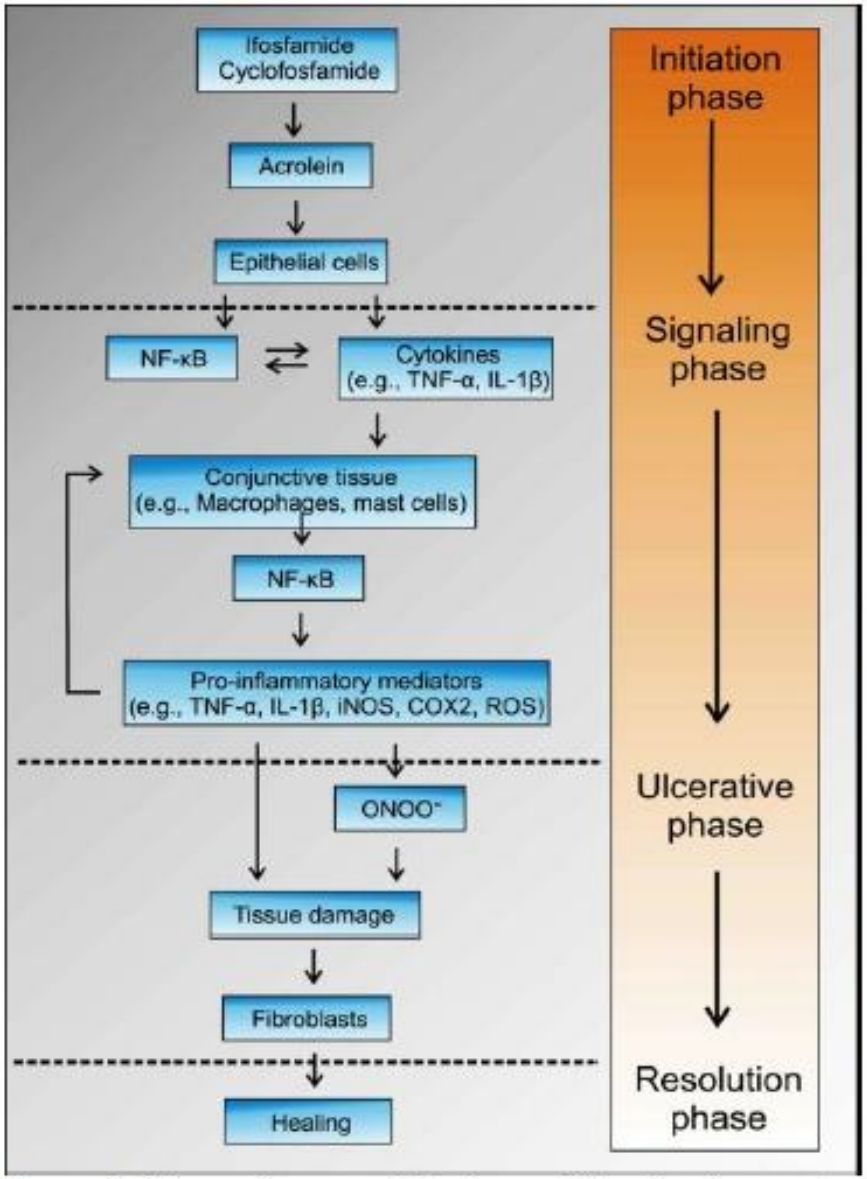

Figure 2. Proposed sequential phases of the development of hemorrhagic cystitis.

Journal of Experimental and Integrative Medicine 2.2 (2012): 95-112.

附錄四: **Hemorrhagic cystitis**病理機轉

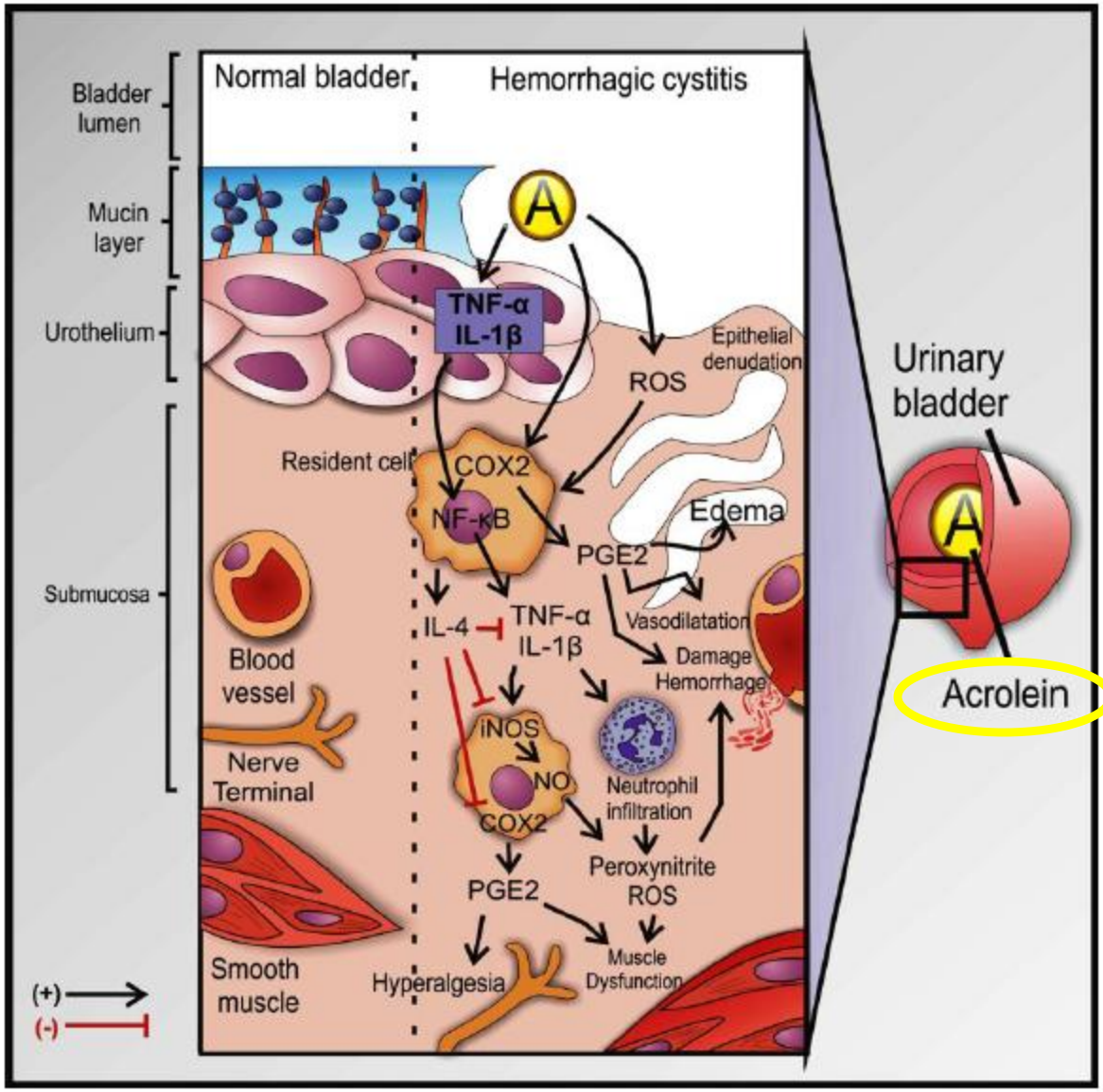

Figure 3.
Proposed pathways for the pathogenesis of hemorrhagic cystitis.

Journal of Experimental and Integrative Medicine 2.2 (2012): 95-112.

附錄四: Hemorrhagic cystitis預防與治療

Table 1. Acrolein-initiated pathophysiological mechanisms and preventive/treatment modalities of hemorrhagic cystitis (step by step).

Pathophysiological Mechanisms	Preventive/Treatment modalities
Acrolein and others rapidly bind to and deplete cellular nucleophiles such as glutathione; proteins (enzymatic and structural) those reach of sulfur containing amino acids	Mesna Hyperhydration
Acrolein causes increased ROS production in the bladder epithelium	Antioxidants Melatonin
Acrolein causes both directly and/or indirectly (through transcription factors) iNOS induction leading to NO overproduction	iNOS inhibitors Melatonin
Acrolein induces several intracellular transcription factors such as NF-κB and AP-1	Steroids Non-Steroid anti-inflammatory drugs Melatonin
Activated NF-κB and AP-1 cause cytokine (e.g., TNF-α, IL-1β, IL-4, IL-6) gene expression, iNOS induction, and again ROS production	Antioxidants iNOS inhibitors Steroids Cytokine inhibitors Melatonin
The production of inflammatory molecules and enzymes (e.g., cytokines, ROS, RNS, COX-2 and iNOS) increases dramatically	Antioxidants iNOS inhibitors Steroids Cytokine inhibitors Melatonin
Cytokines leave the uroepithelium and spread to other uroepithelial cells, detrussor smooth muscle and into bloodstream	Cytokine inhibitors
Reactive nitrogen species, in particular $ONOO^-$, attacks cellular macromolecules (lipids, proteins, DNA) and causes further damage	Peroxynitrite scavengers Melatonin
ROS and RNS cause damage in both uroepithelium and detrussor smooth muscle	Peroxynitrite scavengers Melatonin
DNA damage induces PARP activation leading either recovery or cell necrosis via energy crisis	PARP inhibitors
Broken cellular and tissue integrity appear cystitis symptoms such as edema, hemorrhage, inflammation and ulceration	HBO

Journal of Molecular Pathophysiology 1.1 (2012): 53-62.

附錄五: anti-VEGF 蛋白尿處理流程

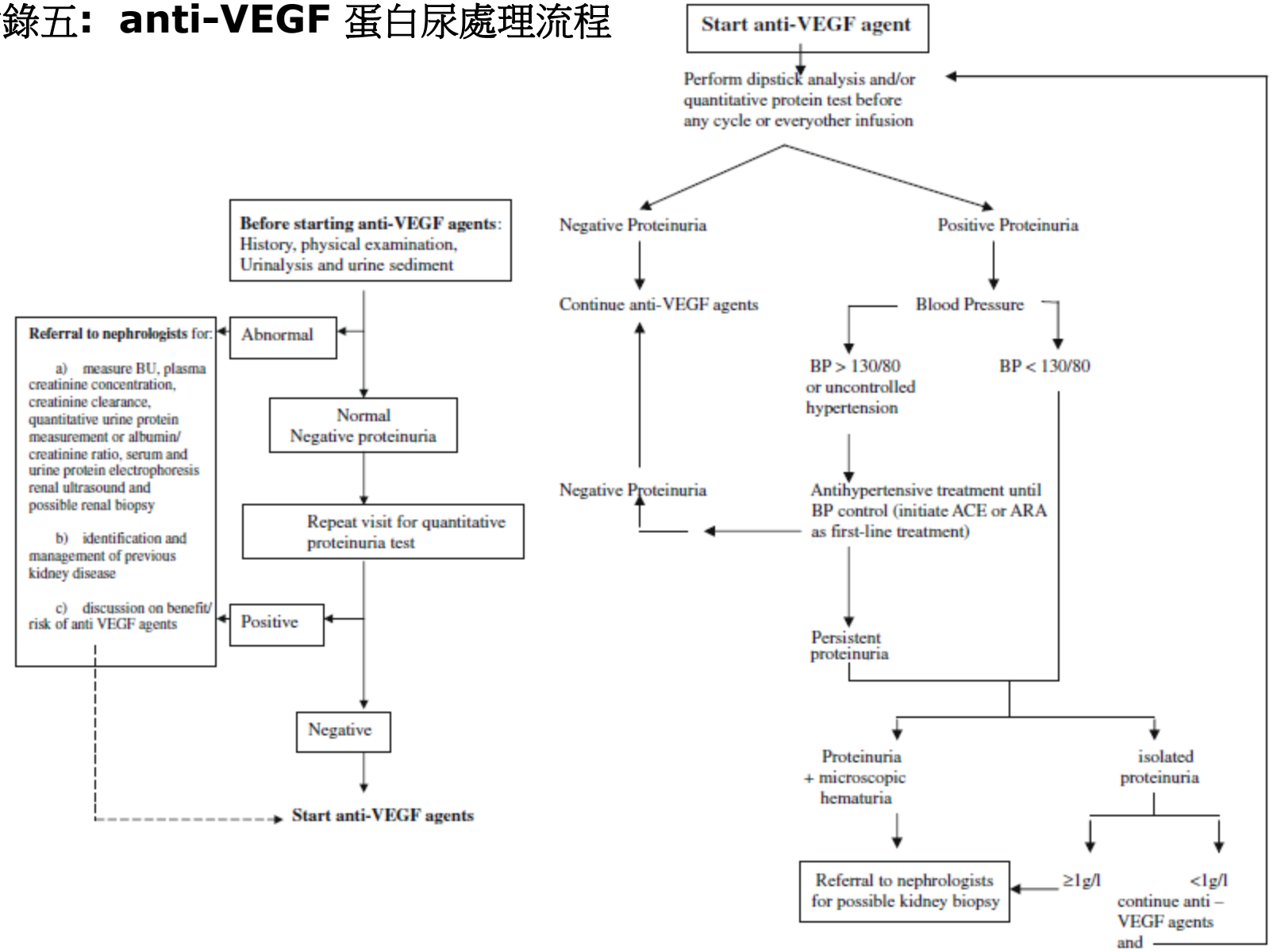

Fig. 1 – Management of proteinuria induced by angiogenic inhibitor.

European Journal of Cancer 46.2 (2010): 439-448.

附錄六：化療病人腹瀉處理

Table 2. Specific Recommendations of the Independent Panel for Management of Chemotherapy-Induced Diarrhea in Patients Receiving the IFL Regimen[7]

Clinical Presentation	Intervention
Diarrhea, any grade	Oral loperamide (2 mg every 2 hours): continue until diarrhea-free for ≥ 12 hours
Diarrhea persists on loperamide for > 24 hours	Oral fluoroquinolone × 7 days
Diarrhea persists on loperamide for > 48 hours	Stop loperamide; hospitalize patient; administer IV fluids
ANC < 500 cells/μL, regardless of fever or diarrhea	Oral fluoroquinolone (continue until resolution of neutropenia)
Fever with persistent diarrhea, even in the absence of neutropenia	Oral fluoroquinolone (continue until resolution of fever and diarrhea)

Abbreviations: IFL, irinotecan plus bolus fluorouracil/leucovorin; IV, intravenous; ANC, absolute neutrophil count.

Journal of Clinical Oncology 22.14 (2004): 2918-2926.

附錄六: 化療病人腹瀉處理

TABLE 2. Comparison of ASCO and ONS Evidence-Based Guidelines

Topic	American Society of Clinical Oncology (ASCO)	Oncology Nursing Society
First-line treatment	Dietary modifications Loperamide 4 mg followed by 2 mg every four hours	Dietary modifications Loperamide 4 mg followed by 2 mg every four hours
Diarrhea refractory to loperamide: mild to moderate diarrhea (ASCO) or grade 2 or 3 (ONS)	**CID:** Octreotide 100–500 mcg with dose escalation as needed or tincture of opium or budesonide **RID:** Continue loperamide 2 mg every two hours; replace fluid and electrolytes	**Likely to be effective for CRID:** 150 mcg octreotide SC TID for five days **Likely to be effective for RID:** Octreotide 100 mcg SC TID **Note:** According to the Oncology Nursing Society, budesonide's effectiveness is not established; however, the American Society of Clinical Oncology recommends it.
Complicated (ASCO) or severe (ONS) diarrhea	**Complicated CID:** IV octreotide 100–150 mcg SC or IV TID with dose escalation until controlled, and an antibiotic (fluoroquinolone); hospitalization may be necessary; stool workup; laboratory tests **Complicated RID:** Hospitalization may not be necessary; continue loperamide; may not need octreotide, and antibiotics may worsen	**Recommended for severe CID:** Octreotide 100 mcg SC TID for three days, then 50 mcg SC TID for three days **Likely to be effective for severe CID:** 30 mg long-acting repeatable octreotide intramuscularly 7–14 days prior to day 1 of chemotherapy, then every 28 days up to six doses **Likely to be effective for RID grade 2 or 3:** Octreotide 100 mcg SC TID **Note:** ONS did not offer recommendations for RID higher than grade 3.
Prevention	The American Society of Clinical Oncology states that no definitive data exist, but the future is promising.	**Effectiveness not established:** Budesonide, oral alkalization, charcoal, and levofloxacin for irinotecan-induced diarrhea; probiotics and glutamine for CID prevention
Important facts	**Assessment recommendations:** Increase monitoring (weekly assessment of gastrointestinal toxicity); blood tests no more than 48 hours prior to chemotherapy; increased management such as antibiotic treatment if diarrhea lasts more than 24 hours; discontinue chemotherapy if severe CID, may lead to death	**Benefits balanced with risks:** Amifostine infusion; neomycin for irinotecan-induced diarrhea **Effectiveness not established:** Antioxidants (vitamins E and C) for treatment for RID **Effectiveness unlikely:** Sulfasalazine and selenium supplementation for prevention of RID; pentosan polysulfate for treatment of RID **Not recommended for practice:** Sucralfate for prevention of RID

CID—chemotherapy-induced diarrhea; CRID—chemotherapy- and radiation-induced diarrhea; RID—radiation-induced diarrhea; SC—subcutaneously

Note. Based on information from Benson et al., 2004; ONS, 2008.

Clinical journal of oncology nursing 16.4 (2012): 413.

附錄七: 黏膜炎 **Mucositis** 相關化療藥物

TABLE 3
Risk of Grade 3 or 4 Oral Mucositis and Diarrhea by Chemotherapy Regimen*

Regimen	No. Studies	No. Patients	Risk of grade 3 or 4 oral mucositis %	Risk of grade 3 or 4 oral mucositis 95% CI	Risk of grade 3 or 4 diarrhea %	Risk of grade 3 or 4 diarrhea 95% CI
All NHL	19	1444	6.55	5.54–8	1.23	1.15–2.12
NHL-15: NHL regimen 15	1	100	3.00	0.50–7	0.50	0.50–2.00
CHOP-14: Cyclophosphamide, doxorubicin, vincristine, and prednisone	9	623	4.82	3.53–6.78	1.04	0.95–2.15
CHOP-DI-14: Cyclophosphamide, doxorubicin, vincristine, and prednisone (dose-intensified)	4	231	7.85	5.28–11.32	2.36	1.32–4.65
CHOEP-14: Cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone	2	346	10.40	7.23–13.44	0.29	0.29–1.01
CEOP/IMVP-Dexa: cyclophosphamide, etoposide, vincristine, prednisone/ifosfamide, and methotrexate-dexamethasone	3	144	4.17	1.74–7.99	2.78	1.39–5.90
All Breast	21	2766	4.08	3.44–4.85	3.41	2.86–4.224
A→T→C: Doxorubicin, taxane, and cyclophosphamide (administered sequentially)†	4	594	2.29	1.30–3.46	2.53	1.36–3.92
AC→T Doxorubicin, cyclophosphamide, and taxane (administered sequentially)	2	515	2.80	1.40–4.20	1.07	0.27–2.07
A→CT: Doxorubicin, cyclophosphamide, and taxane (administered sequentially)	1	19	5.26	2.63–15.79	5.26	2.63–15.79
A→T: Doxorubicin and taxane (administered sequentially)	2	60	4.17	1.67–10	9.17	4.17–15.83
AT: Doxorubicin and taxane	1	36	8.33	1.39–19.44	1.39	1.39–5.56
FAC (weekly): 5-FU, doxorubicin, and cyclophosphamide	1	30	3.33	1.67–10.00	1.67	1.67–6.67
AC (weekly): Doxorubicin and cyclophosphamide	1	22	13.64	2.27–27.27	2.27	2.27–9.09
Taxol (paclitaxel) (weekly)	2	87	2.87	1.15–6.90	1.15	1.15–4.02
TAC: docetaxel, doxorubicin, and cyclophosphamide	7	1403	4.92	3.83–6.07	4.38	3.27–5.54
All Lung (no XRT)	49	4750	0.79	0.88–1.33	1.38	1.30–1.99
Platinum and paclitaxel	16	2009	0.49	0.52–1.06	1.59	1.08, 2.44
Platinum and paclitaxel (low dose)	1	49	1.02	1.02–4.08	1.02	1.02, 4.08
Platinum and docetaxel	1	38	1.32	1.32–5.26	1.32	1.32, 5.26
Platinum, paditaxel, and other	7	451	1.47	1.20–3.07	2.80	2.17, 4.54
Platinum, docetaxel, and other	1	83	0.60	0.60–2.41	0.60	0.60–2.41
Gemcitabine and platinum	18	1476	1.08	0.09–1.91	1.08	0.99–1.89
Gemcitabine and paclitaxel	2	109	1.84	1.02–5.33	3.69	2.05–6.97
Gemcitabine and vinorelbine	1	67	0.75	0.75–2.99	2.99	0.75–7.46
Vinorelbine and paclitaxel	1	175	0.29	0.29–1.14	0.29	0.29–1.14
Vinorelbine and platinum	1	203	0.25	0.25–0.99	0.25	0.25–0.99
All Colon	10	898	1.67	1.17–2.67	15.42	13.14–17.82
FOLFOX: 5-FU, leucovorin, and oxaliplatin	5	482	1.35	0.73–2.59	10.06	7.52–12.97
FOLFIRI: 5-FU, leucovorin and irinotecan	2	79	4.43	1.90–9.49	10.13	4.43–16.46
IROX: Irinotecan and oxaliplatin	3	337	1.48	0.59–2.97	24.33	19.59–29.08

95% CI indicates 95% confidence interval; NHL, non-Hodgkin lymphoma; 5-FU, 5-fluorouracil; XRT, radiotherapy.

* Adapted from Jones JA, Avritscher EBC, Cooksley CD, Michelet M, Bekele BN, Elting LS. Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. Support Care Cancer. 2006;14:505–515.[8]

† Taxane is paclitaxel or docetaxel.

Cancer 109.5 (2007): 820-831.

附錄七: 黏膜炎
Mucositis 處理原則

TABLE 4
Summary of Evidence-based Clinical Practice Guidelines for Care of Patients With Oral and Gastrointestinal Mucositis (2005 Update)

I. Oral mucositis

Basic oral care and good clinical practices

1. The panel suggests multidisciplinary development and evaluation of oral care protocols, and patient and staff education in the use of such protocols to reduce the severity of oral mucositis from chemotherapy and/or radiation therapy. As part of the protocols, the panel suggests the use of a soft toothbrush that is replaced on a regular basis. Elements of good clinical practice should include the use of validated tools to regularly assess oral pain and oral cavity health. The inclusion of dental professionals is vital throughout the treatment and follow-up phases.
2. The panel recommends patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing HSCT. Regular oral pain assessment using validated instruments for self-reporting is essential.

Radiotherapy: Prevention

3. The panel recommends the use of midline radiation blocks and 3-dimensional radiation treatment to reduce mucosal injury.
4. The panel recommends benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy.
5. The panel recommends that chlorhexidine not be used to prevent oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy.
6. The panel recommends that antimicrobial lozenges not be used for the prevention of radiation-induced oral mucositis.

Radiotherapy: Treatment

7. The panel recommends that sucralfate not be used for the treatment of radiation-induced oral mucositis.

Standard-dose chemotherapy prevention

8. The panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30 minutes of oral cryotherapy to prevent oral mucositis.
9. The panel suggests the use of 20 to 30 min of oral cryotherapy to decrease mucositis in patients treated with bolus doses of edatrexate.
10. The panel recommends that acyclovir and its analogues not be used routinely to prevent mucositis.

Standard-dose chemotherapy: Treatment

11. The panel recommends that chlorhexidine not be used to treat established oral mucositis.

High-dose chemotherapy with or without total body irradiation plus HCST: Prevention

12. In patients with hematologic malignancies who are receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation, the panel recommends the use of keratinocyte growth factor-1 (palifermin) in a dose of 60 μg/kg per d for 3 d prior to conditioning treatment and for 3 d posttransplantation for the prevention of oral mucositis.
13. The panel suggests the use of cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan.
14. The panel does not recommend the use of pentoxifylline to prevent mucositis in patients undergoing HSCT.
15. The panel suggests that GM-CSF mouthwashes not be used for the prevention of oral mucositis in patients undergoing HSCT.
16. The panel suggests the use of LLLT to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT if the treatment center is able to support the necessary technology and training, because LLLT requires expensive equipment and specialized training. Because of interoperator variability, clinical trials are difficult to conduct, and their results are difficult to compare; nevertheless, the panel is encouraged by the accumulating evidence in support of LLLT.

II. GI mucositis

Basic bowel care and good clinical practices

17. The panel suggests that basic bowel care should include the maintenance of adequate hydration, and that consideration should be given to the potential for transient lactose intolerance and the presence of bacterial pathogens.

Radiotherapy: Prevention

18. The panel suggests the use of 500 mg sulfasalazine orally twice daily to help reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis.
19. The panel suggests that amifostine in a dose $\geq$340 mg/m^2 may prevent radiation proctitis in patients who are receiving standard-dose radiotherapy for rectal cancer.
20. The panel recommends that oral sucralfate not be used to reduce related side effects of radiotherapy; it does not prevent acute diarrhea in patients with pelvic malignancies undergoing external beam radiotherapy; and, compared with placebo, it is associated with more GI side effects, including rectal bleeding.
21. The panel recommends that 5-amino salicylic acid and its related compounds mesalazine and olsalazine not be used to prevent GI mucositis.

Radiotherapy: Treatment

22. The panel suggests the use of sucralfate enemas to help manage chronic radiation-induced proctitis in patients who have rectal bleeding.

Standard-dose and high-dose chemotherapy: Prevention

23. The panel recommends either ranitidine or omeprazole for the prevention of epigastric pain after treatment with cyclophosphamide, methotrexate, and 5-FU or treatment with 5-FU with or without folinic acid chemotherapy.
24. The panel recommends that systemic glutamine not be used for the prevention of GI mucositis.

Standard-dose and high-dose chemotherapy: Treatment

25. When loperamide fails to control diarrhea induced by standard-dose or high-dose chemotherapy associated with HSCT, the panel recommends octreotide at a dose $\geq$100 μg subcutaneously, twice daily.

Combined chemotherapy and radiotherapy: Prevention

26. The panel suggests the use of amifostine to reduce esophagitis induced by concomitant chemotherapy and radiotherapy in patients with nonsmall cell lung cancer.

HSCT indicates hematopoietic stem cell transplantation; 5-FU: 5-fluorouracil; GM-CSF, granulocyte-macrophage-colony stimulating factor; LLLT: low-level laser therapy; GI, gastrointestinal.

Cancer 109.5 (2007): 820-831.

附錄八：周邊神經炎

Table 1 Common Antineoplastic Agents Known to Induce Neuropathy

Drug	Incidence	Onset Dose	Clinical Manifestation	Recovery
Platinum compounds				
Cisplatin[1,8–11]	28%–100% (overall) + paclitaxel: 7%–8% (severe*)	300 mg/m²	Symmetrical painful paresthesia or numbness in a stocking-glove distribution, sensory ataxia with gait dysfunction	Partial, symptoms may progress for months after discontinuation
Carboplatin[1,9–14]	6%–42% (overall) + paclitaxel: 4%–9% (severe)	800–1600 mg/m²	Similar to cisplatin but milder	Similar to cisplatin
Oxaliplatin (acute)[1,15,16]	85%–95% (overall)	any	Cold-induced painful dysesthesia	Resolution within a week
Oxaliplatin (persistent/ chronic)[17–20]	FOLFOX: 10%–18% (severe)	750–850 mg/m²	Similar to cisplatin	Resolution in 3 months, may persist long-term
Vinca alkaloids				
Vincristine, vinblastine, vinorelbine, vindesine[21–24]	30%–47% (overall)	4–10 mg	Symmetrical tingling paresthesia, loss of ankle stretch reflexes, constipation, occasionally weakness, and gait dysfunction	Resolution usually within 3 months, may persist for vincristine
Taxanes				
Paclitaxel[10–12,25–34]	57%–83% (overall), 2%–33% (severe) + Cisplatin: 7%–8% (severe) + Carboplatin: 4%–16% (severe)	100–300 mg/m²	Symmetrical painful paresthesia or numbness in stocking-glove distribution, decreased vibration or proprioception, occasionally weakness, sensory ataxia, and gait dysfunction	Resolution usually within 3 months, may persist
Abraxane (albumin-bound paclitaxel)[31,35]	73% (overall) 10%–15% (severe)	undear	Similar to paclitaxel	Resolution usually within 3 weeks
Docetaxel[1,25,34,36–38]	11%–64% (overall) 3%–14% (severe)	75–100 mg/m²	Similar to paclitaxel	Resolution usually within 3 months, may persist
Others				
Bortezomib[39–44]	31%–55% (overall) 9%–22% (severe)	1.3 mg/m²	Painful paresthesia, burning sensation, occasionally weakness, sensory ataxia, and gait dysfunction. Rare autonomic dysfunction including orthostatic hypotension	Resolution usually within 3 months, may persist
Ixabepilone[45,46]	63% (overall), 14% (severe) + capecitabine: 67% (overall), 21% (severe)	40–120 mg/m²	Painful paresthesia, burning sensation	Resolution in 4–6 weeks
Thalidomide[47–53]	25%–83% (overall), 15%–28% (severe)	20 g	Symmetrical tingling or numbness, pain. Occasionally weakness, sensory ataxia, and gait dysfunction	May persist for over 1 year
Lenalidomide (thalidomide analog)[54,55]	10%–23% (overall), 1%–3% (severe)	unclear	Similar to thalidomide	Unclear

* Dose-limiting or grade 3 or 4 neuropathy according to the grading scale used by the study authors.

NCCN task force report: management_of_neuropathy_in_cancer 2009.

附錄八：周邊神經炎

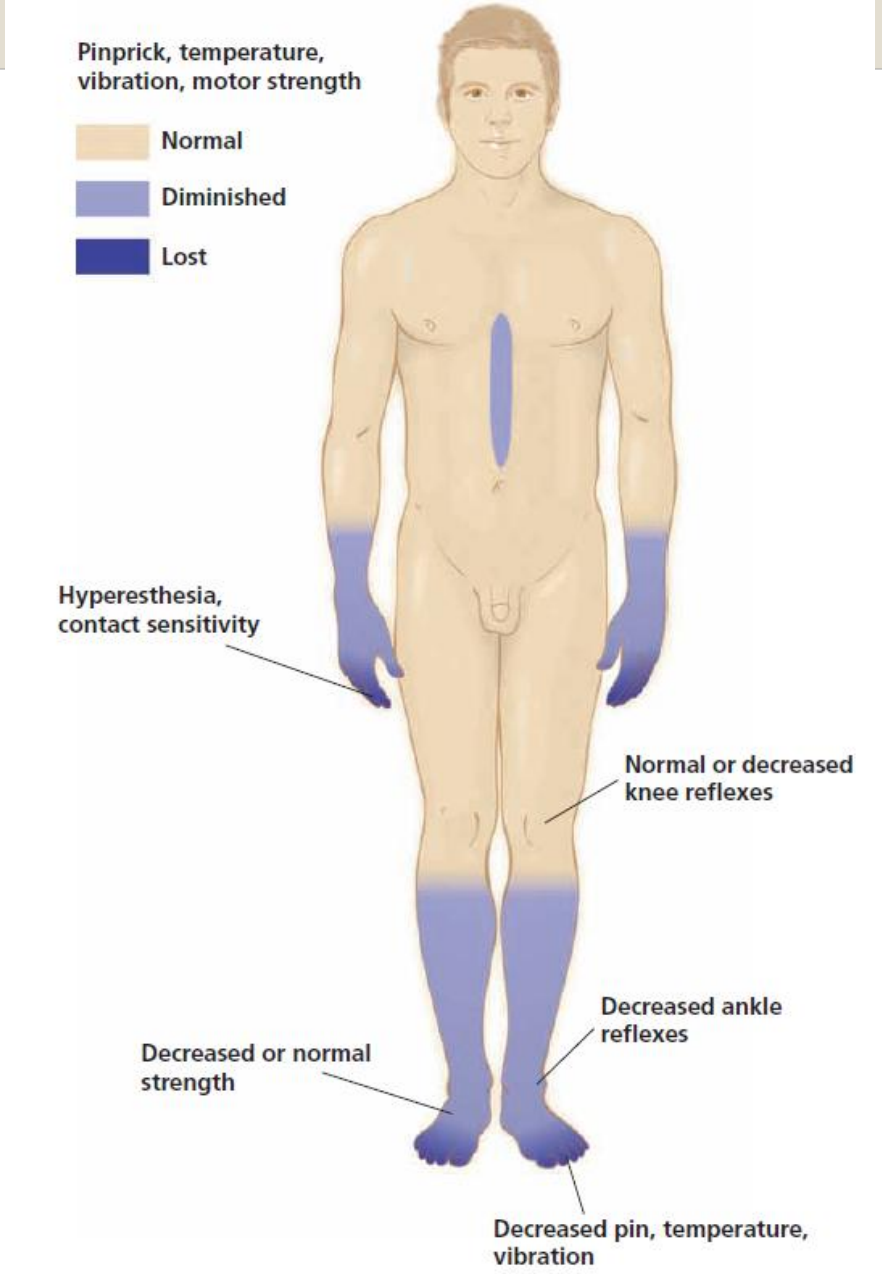

Figure 1 Symptoms of chemotherapy-induced peripheral neuropathy. Adapted from: Simpson DA, Tagliati M, Gonzales-Duarte A, [illegible] manifestations. In: Mildvan D, ed. International Atlas of AIDS. 4th edition. Hoboken, NJ: Current Medicine Group LLC; 2007; with permission.

NCCN task force report: management_of_neuropathy_in_cancer 2009.

Table 4 Proposed Agents for Preventing CIPN

Drug	Mechanism of Action	Findings From Randomized Controlled Trials (N)
Agents with Positive Findings in Randomized Controlled Trials		
Vitamin E	Antioxidant/minimizes neuronal damage	CIPN incidence and severity reduced (30-47)[102–104] CIPN severity reduced (81)[105] Ongoing trial: NCT00363129*
Ca^{++}/Mg^{++}	Facilitates Na channel function; binds oxalate (metabolite of oxaliplatin)	CIPN incidence reduced (104)[106]
Glutamine	Upregulation of nerve growth factor	CIPN incidence reduced (86)[107]
Glutathione	Hampers accumulation of platinum adducts in DRG	CIPN incidence reduced/trend towards reduction (50-151)[108–110]
N-acetylcysteine	Antioxidant; increases blood concentrations of glutathione	Incidence of grade 2-4 neuropathy reduced (14)[111]
Oxcarbazepine	Inhibits high-frequency firing of nerves; modulates ion channels	Neuropathy incidence reduced (32)[112]
Xaliproden	Non-peptide neurotrophic agent	Shift of CIPN from grade 3 to grade 2 (649)[113] Ongoing trial: NCT00603577*
Agents With Negative Findings in Randomized Controlled Trials		
Amifostine	Detoxifies chemotherapy; facilitates DNA repair	Not effective (66)[114] Improvement on NCI-CTC scale but not on patient questionnaire (72)[115]
Nimodipine	Calcium channel antagonist	Not effective; randomized trial closed early (51)[116]
Org 2766	Nerve growth factor family, adrenocorticotrophic hormone analog	Vibration perception maintained (55)[117] Not effective (150-196)[118,119]
rhuLIF	Neuroprotective cytokine	Not effective (117)[120]
Additional Agents Being Tested in Ongoing Phase III Randomized Controlled Trials		
Vitamin B12/B6	Essential for nerve function	Ongoing trial: NCT00659269*
Acetyl-L-carnitine	Oxidation of free fatty acids/nerve regeneration	New trial: NCT00775645*
Alpha lipoic acid	Antioxidant	Ongoing trial: NCT00705029*

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; DRG, dorsal root ganglion; NCI- CTC, National Cancer Institute Common Toxicity Criteria.
*ClinicalTrials.gov identification number

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附錄八：周邊神經炎治療藥物

Table 5 Common Agents for Pain Management in Neuropathy

Drug	Starting Dose	Titration	Maximum Dose	Duration of Adequate Trial	Potential Side Effects
Duloxetine	20–30 mg/d	No evidence that higher dose is more effective	120 mg/d	2 wk	Nausea, xerostomia, constipation, diarrhea
Gabapentin*	100–300 mg nightly or 100–300 mg 3 times/d	increase by 100–300 mg 3 times/day, every 1–7 days	3600 mg (depending on absorption)	1–2 wk at max tolerated dose	Somnolence, dizziness, GI symptoms, mild edema, cognitive impairment (elderly), exacerbation of gait problems
5% Lidocaine patch	Maximum of 3 patches daily	Non-applicable	3 patches	2 wk	Rash/erythema
Opioids (oxycodone, morphine, methadone)	5–15 mg every 4 h	Convert to long-acting after 1 wk, titrate based on breakthrough use	No ceiling effect	4–6 wk	Constipation, nausea, vomiting (self-limited), sedation, confusion, respiratory depression
Pregabalin	25–50 mg 3 times/d	Increase by 50 mg/dose after 1 wk	200 mg 3 times/d	Unclear (likely 2–4 wk)	Dizziness, somnolence, xerostomia, edema, blurred vision, decreased concentration
Tramadol	50 mg 1–2/d	Increase by 50-100 mg/d, individual doses every 3-7 days	400 mg/d (100 mg 4 times/d); elderly 300 mg/d	4 wk	Dizziness, constipation, nausea, somnolence, orthostatic hypotension, increased risk of seizure, serotonin syndrome
Tricyclic antidepressants (amitriptyline,* nortriptyline,* desipramine)	Starting dose: 10-25 mg nightly	Increase by 10-25 mg every 3-7 days	75–150 mg; may increase if blood level of drug plus metabolite <100 ng/mL	6-8 wk; 1-2 wk at max dose	Cardiovascular disease (needs screening), anticholinergic effects, interact with drugs metabolized by cytochrome P450 2D6 (e.g., cimetidine, phenothiazine)

*Negative results in randomized controlled clinical trials on chemotherapy-induced peripheral neuropathy

NCCN task force report: management_of_neuropathy_in_cancer 2009.

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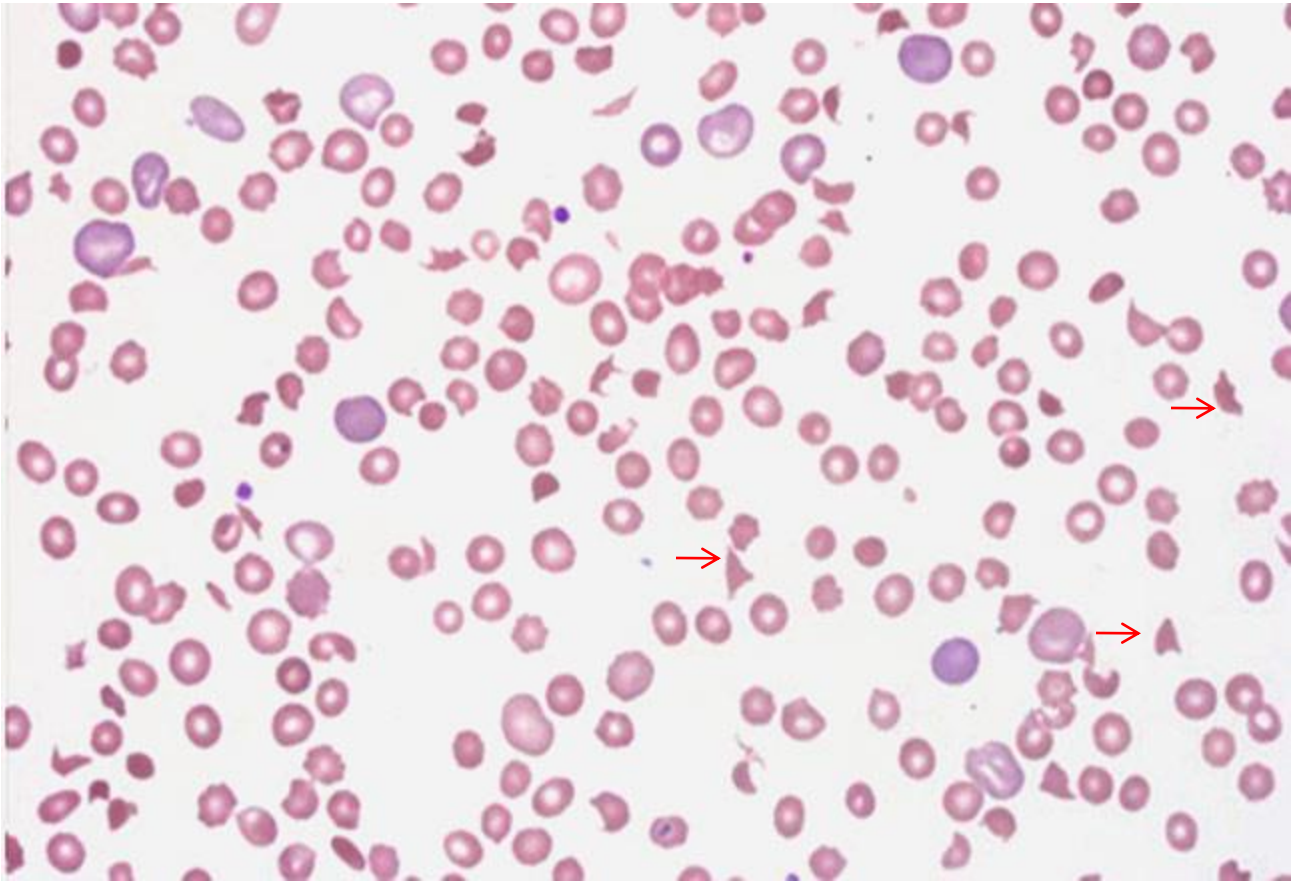
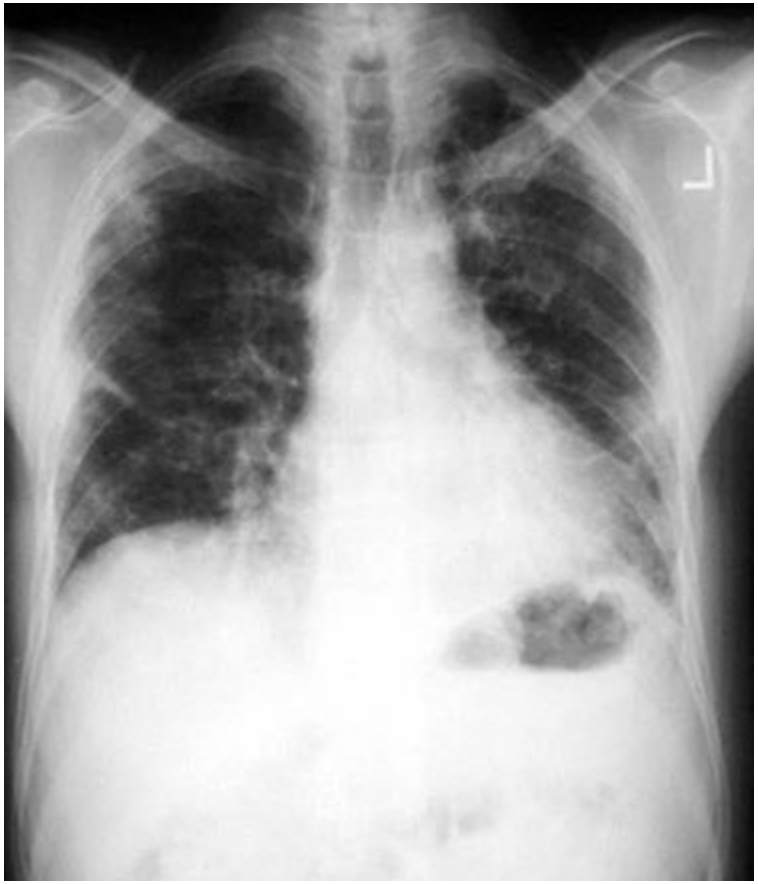
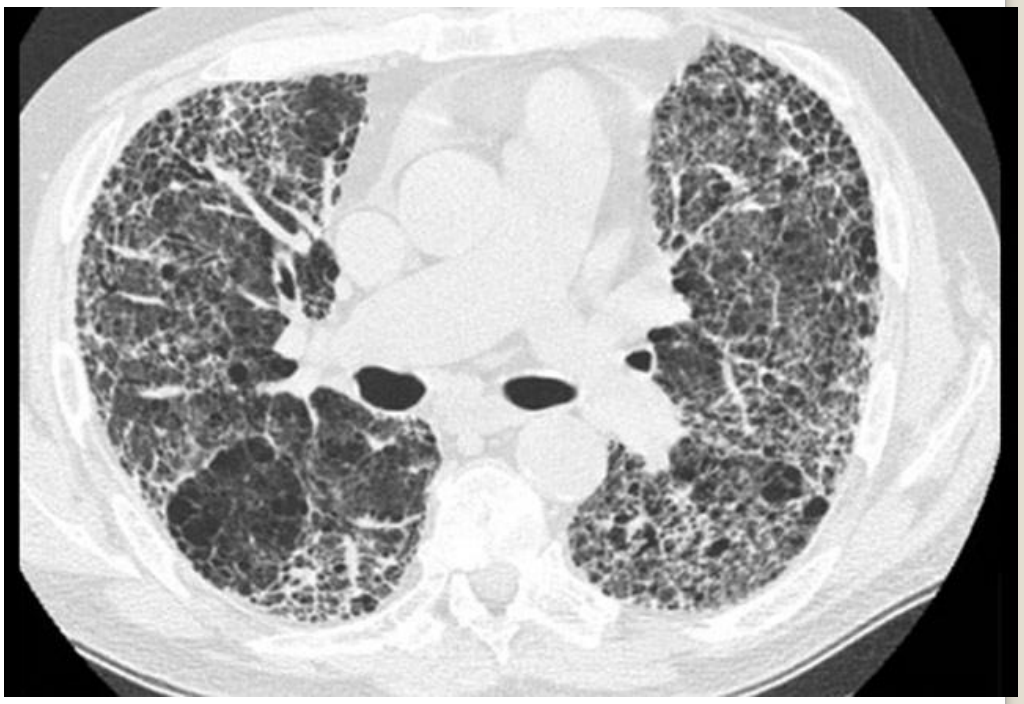
Gemcitabine + Carboplatin



Thrombotic thrombocytopenic purpura

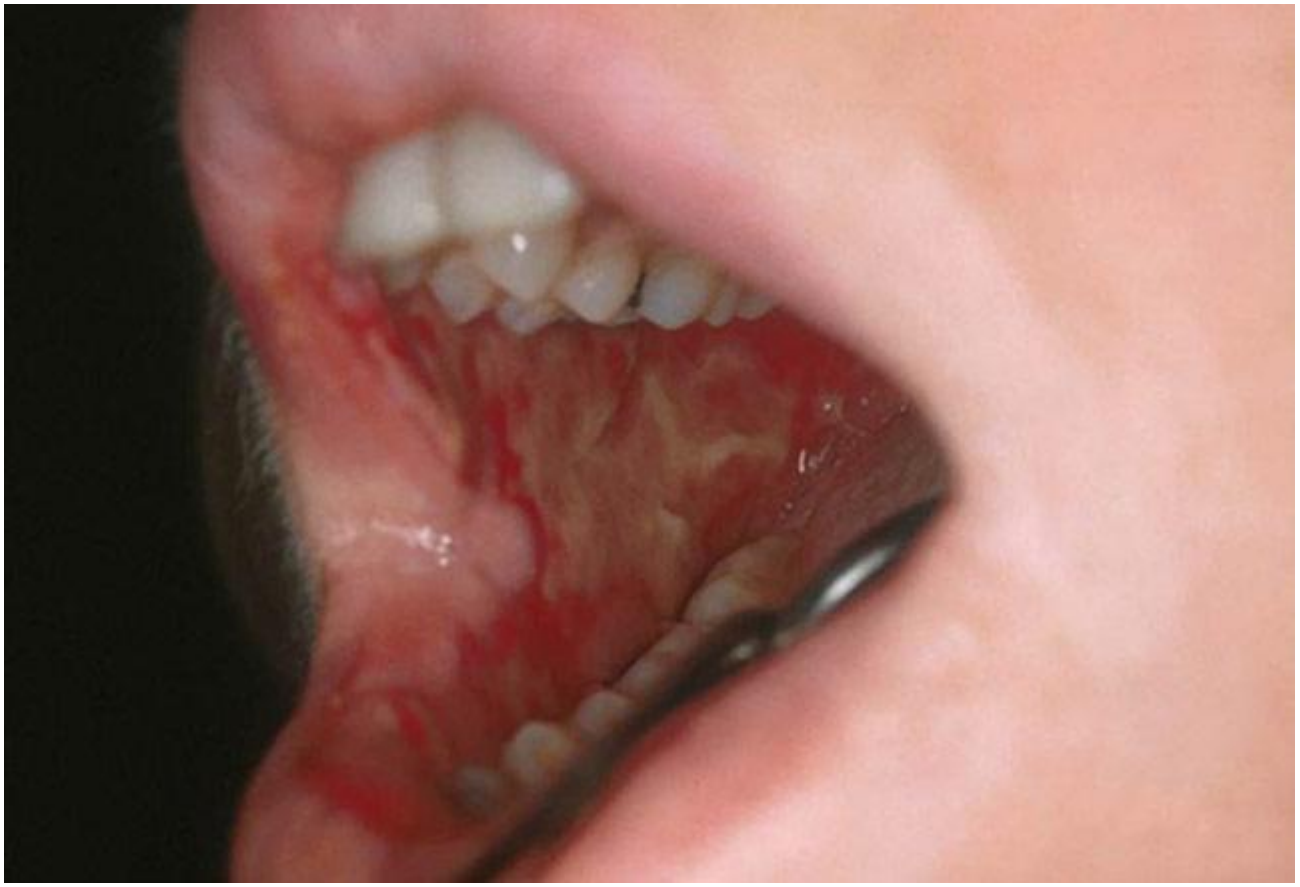
bleomycin, etoposide, and cisplatin





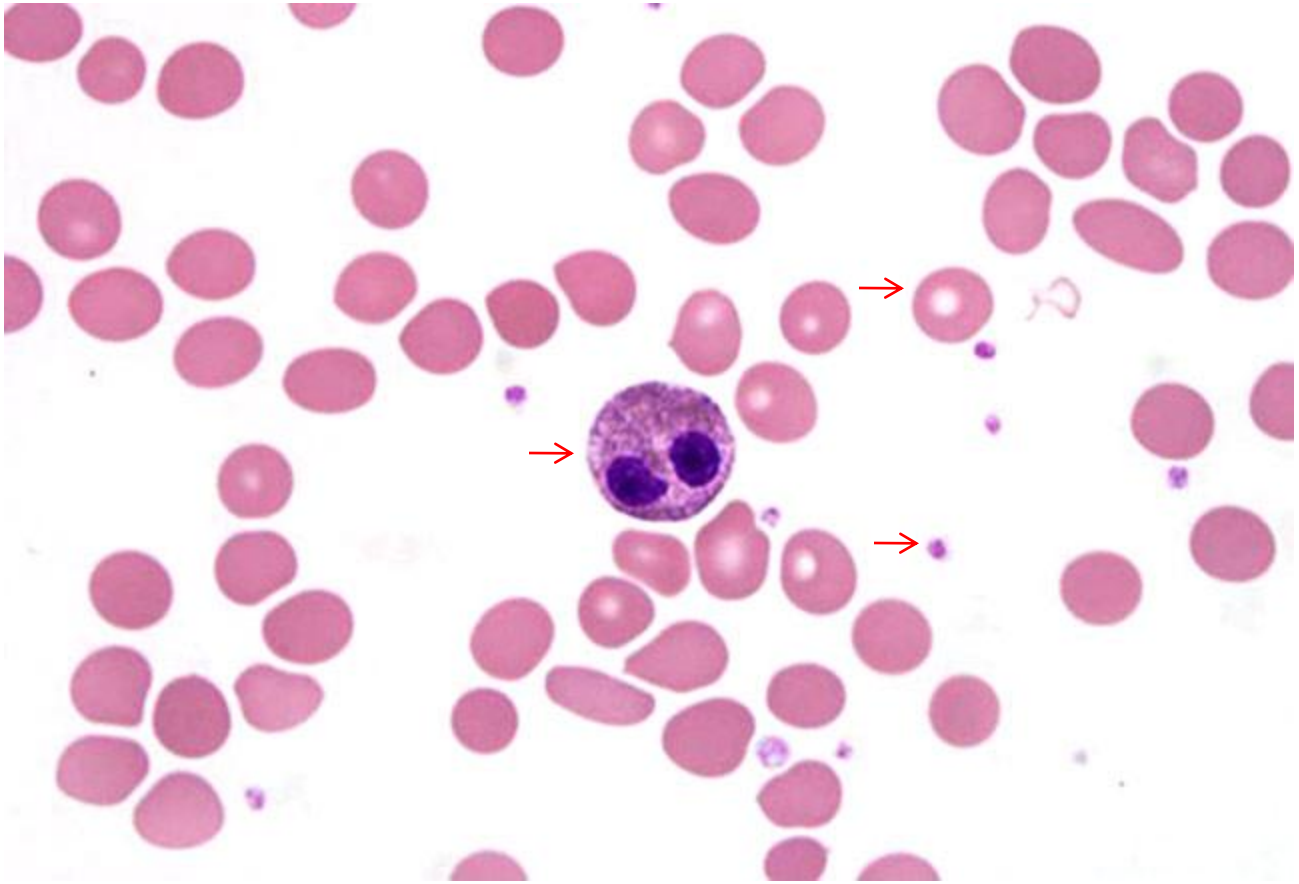
Pulmonary fibrosis

irinotecan, oxaliplatin, and 5-FU



Mucositis

Alkylating agent



Myelodysplastic syndrome (MDS)

The peripheral blood smear reveals

1. a hypolobulated neutrophil (known as a pseudo Pelger-Huët cell or Pelger-Huët anomaly)
2. oval macrocytic red blood cells (RBCs)
3. giant platelets

MDS can occur after treatment for another malignancy, particularly if an **alkylating agent** (eg, cyclophosphamide, busulfan, melphalan) was part of the chemotherapy regimen. **The latency period for MDS arising after alkylating agent therapy is typically 3–7 years.**