How do we administrate Bortezomib ?

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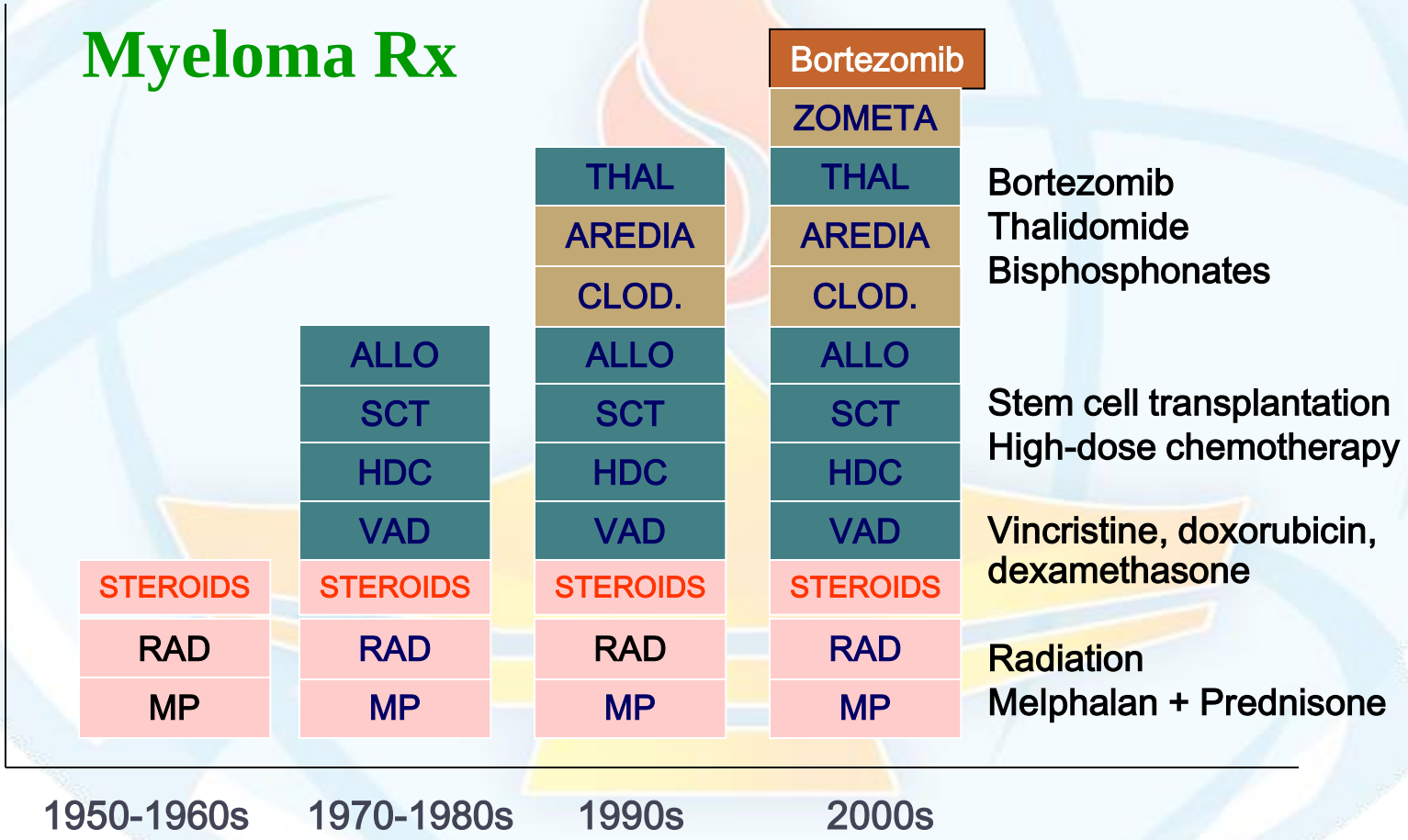
Increase in Treatment Options Over Time



National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Multiple Myeloma

Version 2.2015

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

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MYELOMA THERAPY[1-3]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

	Preferred Regimens	Other Regimens
Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide[4]/dexamethasone • Bortezomib/thalidomide/dexamethasone (category 1) • Lenalidomide[4]/dexamethasone (category 1)	• Carfilzomib[7]/lenalidomide[4]/dexamethasone • Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Thalidomide/dexamethasone (category 2B)
Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone • Lenalidomide/low-dose dexamethasone (category 1)[5] • Melphalan/prednisone/bortezomib (MPB) (category 1) • Melphalan/prednisone/lenalidomide (MPL) (category1) • Melphalan/prednisone/thalidomide (MPT) (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Melphalan/prednisone (MP) • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance Therapy	• Bortezomib • Lenalidomide[6] (category 1) • Thalidomide (category 1)	• Bortezomib + prednisone (category 2B) • Bortezomib + thalidomide (category 2B) • Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with bortezomib and carfilzomib. Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[3]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
[4]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[5]Continuously until progression. Facon T, Dimopoulos MA, Dispenzieri A, et al. Continuous lenalidomide and low-dose dexamethasone demonstrates a significant PFS and OS advantage in transplant ineligible NDMM patients. The FIRST: MM-020/IFM0701 [oral]. Oral presented at: 55th Annual Meeting of the American Society of Hematology (ASH) 2013; December 7-10; New Orleans, LA USA.
[6]There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.
[7]Optimal dosing in this regimen has not been defined.

Continued on next page

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Bortezomib Strength

Bortezomib 3.5 mg

- **3.5 mg of** bortezomib as a sterile lyophilized powder (white to off-white) Inactive ingredient: 35 mg mannitol, USD/EP (IV or SC use)

Bortezomib 1.0 mg

- **1.0 mg of** bortezomib as a sterile lyophilized powder. Inactive ingredient: 10 mg mannitol, USD/EP (IV use only)
- Each single-dose vial is intended for administration to one patient

Shelf storage

- Do not store unopened vials above 30°C (86°F). Retain in original package to protect from light.

Bortezomib
A Well-Defined Dosing Schedule

- Regimen
  - Bortezomib is dosed 1.3 mg/m^2/dose
    - IV (at a concentration of 1 mg/mL) as a 3 to 5 second bolus injection
    - SC (at a concentration of 2.5 mg/mL)

Bortezomib
A Well-Defined Dosing Schedule

Twice weekly for 2 weeks

days 1, 4, 8, 11

followed by a 10-day rest period

3 weeks cycle

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
1	2	3	4	5	6	7

Once weekly for 4 weeks

days 1, 8, 15, 22

followed by a 13-day rest period

5 weeks cycle

1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
1	2	3	4	5	6	7

At least 72 hours should elapse between Consecutive doses of Bortezomib

MAHARAJ NAKORN CHIANGMAI HOSPITAL

Division of Hematology Department of Medicine

Velcade – Cyclophosphamide – Dexamethasone for MM Cycle ……

PATIENT'S NAME……..…… HN……AGE……..……WARD……..

Date	Orders for one day	Date	Orders for continuation
	Investigation prior start Chemotherapy - CBC,Plt - BS, Bun, Cr, electrolyte, Ca, Mg, PO_4, LFT, LDH, uric acid - ☐ Serum protein electrophroresis (SPEP) - ☐ Urine protein electrophroresis (UPEP) - ☐ IgG ☐ IgA ☐ IgM		Medication - **Bortezomib** (1.3 mg/m^2) ……mg SC on **D1, D4, D8, D11** D1…… D4…… D8…… D11…….. - **Cyclophosphamide (300 mg/m^2)** (50 mg/tab) ……tab oral bid ac on Day ……..

MAHARAJ NAKORN CHIANGMAI HOSPITAL

Division of Hematology Department of Medicine

Velcade – Cyclophosphamide – Dexamethasone weekly for MM Cycle ……

PATIENT'S NAME……HN……AGE……WARD……..

Date	Orders for one day	Date	Orders for continuation
	Investigation prior start Chemotherapy - CBC,Plt - BS, Bun, Cr, electrolyte, Ca, Mg, PO_4, LFT, LDH, uric acid - ☐ Serum protein electrophroresis (SPEP) - ☐ Urine protein electrophroresis (UPEP) - ☐ IgG ☐ IgA ☐ IgM		Medication - **Bortezomib** (1.3 mg/m^2) ……mg SC on D1, D8, D15, D22 D1…… D8…… D15…… D22…… - **Cyclophosphamide (300 mg/m^2)** (50 mg/tab) ……tab oral bid ac on D1, D8, D15, D22

Bortezomib Reconstitution

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered

	IV		SC
	(1 mg bortezomib)	(3.5 mg bortezomib)	(3.5 mg bortezomib)
Volume of diluent (0.9% Sodium Chloride) added to reconstitute one vial	1.0 mL	3.5 mL	1.4 mL
Final Concentration after reconstitution (mg/mL)	1.0 mg/ML	1.0 mg/mL	2.5 mg/mL

Bortezomib Reconstitution for SC

concentration of 2.5 mg/mL		concentration of 2.5 mg/mL	
2.5 mg	1.0 CC	1.9 mg	0.76 CC
2.4 mg	0.96 CC	1.8 mg	0.72 CC
2.3 mg	0.92 CC	1.7 mg	0.68 CC
2.2 mg	0.88 CC	1.6 mg	0.64 CC
2.1 mg	0.84 CC	1.5 mg	0.60 CC
2.0 mg	0.8 CC	1.4 mg	0.56 CC

Stability after reconstitution

Reconstituted Bortezomib

- Bortezomib contains no antimicrobial preservative.
- When reconstituted as directed, Bortezomib may be stored at 25°C (77°F).
- Reconstituted Bortezomib should be administered within 8 hours of preparation.
- The total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting

Bortezomib Administration

IV

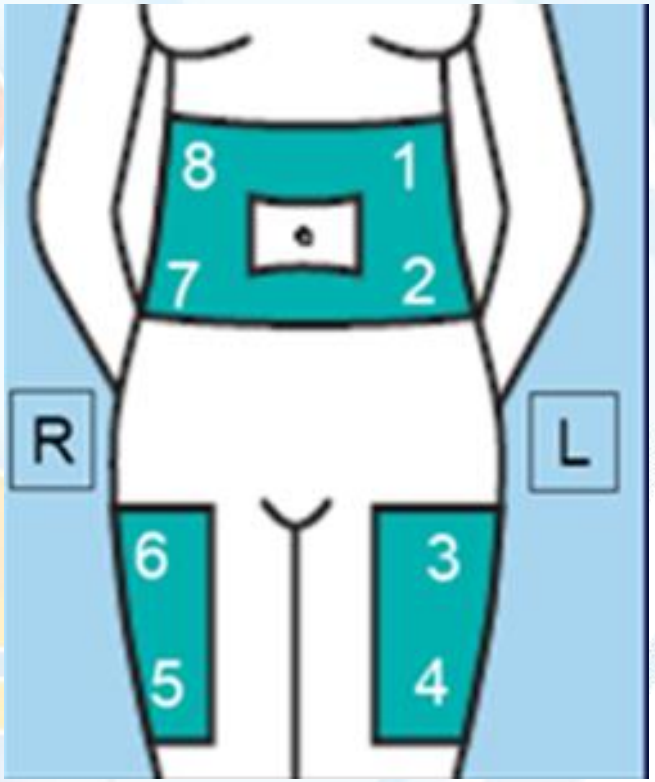
- Bortezomib is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter
- followed by a flush with 0.9% sodium
- In clinical trials, local skin irritation was reported in 5% of patients; no tissue damage associated with extravasation

Millennium Pharmaceuticals, Inc., 2004.

Bortezomib Administration

SC

- The reconstituted solution is injected into the thighs (right or left) or abdomen (right or left)
- Injection sites should be rotated for successive injections.



A Phase 3 Prospective, Randomized, International Study (MMY-3021) Comparing Subcutaneous and Intravenous Administration of Bortezomib in Patients with Relapsed Multiple Myeloma

Philippe Moreau,[1] Halyna Pylypenko,[2] Sebastian Grosicki,[3] Evgeniy Karamanesht,[4] Xavier Leleu,[5] Maria Grishunina,[6] Grigoriy Rekhtman,[7] Zvenyslava Masliak,[8] Tadeusz Robak,[9] Anna Shubina,[10] Jean-Paul Fermand,[11] Martin Kropff,[12] James Cavet,[13] Dixie-Lee Esseltine,[14] Huaibao Feng,[15] Donna Skee,[15] Helgi van de Velde,[16] William Deraedt,[16] Jean-Luc Harousseau[17]

[1]University Hospital, Nantes, France; [2]Cherkassy Regional Oncology Dispensary, Cherkassy, Ukraine; [3]Oddzial Hematologiczny ZSM, Chorzow, Poland; [4]Kiev BMT Center, Kiev, Ukraine; [5]Hopital Huriez, CHRU, Lille, France; [6]Nizhniy Novgorod Region Clinical Hospital, Nizhniy Novgorod, Russia; [7]Khmelnitskiy Regional Hospital, Khmelnitskiy, Ukraine; [8]SI Institute of Blood Pathology and Transfusion Medicine UAMS, Lviv, Ukraine; [9]Medical University of Lodz, Lodz, Poland; [10]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [11]Hopital Saint-Louis, Paris, France; [12]University of Münster, Münster, Germany; [13]The Christie NHS Foundation Trust, Manchester, UK; [14]Millennium Pharmaceuticals Inc., Cambridge, MA, USA; [15]Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ, USA; [16]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium; [17]Centre René Gauducheau, Nantes/St Herblain, France

Moreau et al. Blood 2010;116(21): Abstract 312, oral presentation

Primary Endpoint: Response After 4 Cycles (Single-Agent Bortezomib)

Response rate, %	Bortezomib IV (n=73)	Bortezomib SC (n=145)	Relative risk (95% CI)
ORR (CR + PR)	42	42	0.99 (0.71, 1.37)
CR	8	6	
CR + nCR	14	12	
PR	34	36	
nCR	5	6	
VGPR	3	4	
≥VGPR (CR + nCR + VGPR)	16	17	

Data shown for the response-evaluable population

Primary hypothesis of non-inferiority of ORR after 4 cycles clearly demonstrated

Moreau et al. Blood 2010;116(21): Abstract 312, oral presentation

Adverse Events (AEs)

	Bortezomib IV (n=74)	Bortezomib SC (n=147)
AEs, all grades, %	99	95
AEs, grade ≥3, %	**70**	**57**
Any serious AE, %	35	36
Bortezomib dose reductions due to AEs, %	43	31
Discontinuations due to AEs, %	27	22

Moreau et al. Blood 2010;116(21): Abstract 312, oral presentation

Hematology Laboratory Data

Grade 3/4, %	Bortezomib IV (n=74)	Bortezomib SC (n=147)
Hemoglobin	12	14
WBC	18	8
ANC	28	22
Platelets	23	18

Moreau et al. Blood 2010;116(21): Abstract 312, oral presentation

Peripheral Neuropathy (PN)

	Bortezomib IV (n=74)	Bortezomib SC (n=148)	*P*-value*
Any PN event, %	**53**	**38**	**0.04**
Grade ≥2, %	**41**	**24**	**0.01**
Grade ≥3, %	**16**	**6**	**0.03**
Risk factors for PN, %			
Grade 1 PN at baseline	28	23	
Diabetes at baseline	11	13	
Exposure to prior neurotoxic agents	85	86	

**P*-values based on 2-sided Fisher's exact test

Moreau et al. Blood 2010;116(21): Abstract 312, oral presentation

Local Injection Site Reactions

- 6% of patients had at least one SC injection site reaction reported as an AE
  - Changes to bortezomib treatment were rare (2%)
- Detailed local injection site questionnaire:
  - Most common reaction was redness: 57% of patients
  - Only 1% of patients had severe injection site reactions
  - Median time to resolution was 6 days (100% resolved)

Moreau et al. Blood 2010;116(21): Abstract 312, oral presentation

Conclusions

- The efficacy of bortezomib was similar by SC and IV administration in patients with relapsed MM
  - IV and SC administration also resulted in similar PK (systemic exposure) and PD (proteasome inhibition) profiles
- SC administration of bortezomib appeared to have an **improved safety profile** compared with IV administration
  - With SC administration there were **significantly fewer** all-grade, grade ≥2, and grade ≥3 **PN** events compared with IV administration
- SC administration had acceptable local tolerability

Moreau et al. Blood 2010;116(21): Abstract 312, oral presentation

How do we administrate Bortezomib-Subcutaneous ?

อุปกรณ์

- อุปกรณ์ฆ่าเชื้อ แอลกอฮอล์ 70% + สำลี
- Syringe ขนาด 3 CC สำหรับผสมยา
- Syringe สำหรับฉีดยา : Insulin or tuberculin syringe
- เข็มดูดยา ขนาด 20 – 21 guage
- เข็มฉีดยาขนาด 27 - 25 gauge ยาว 3/8 – 5/8 นิ้ว
- พลาสเตอร์

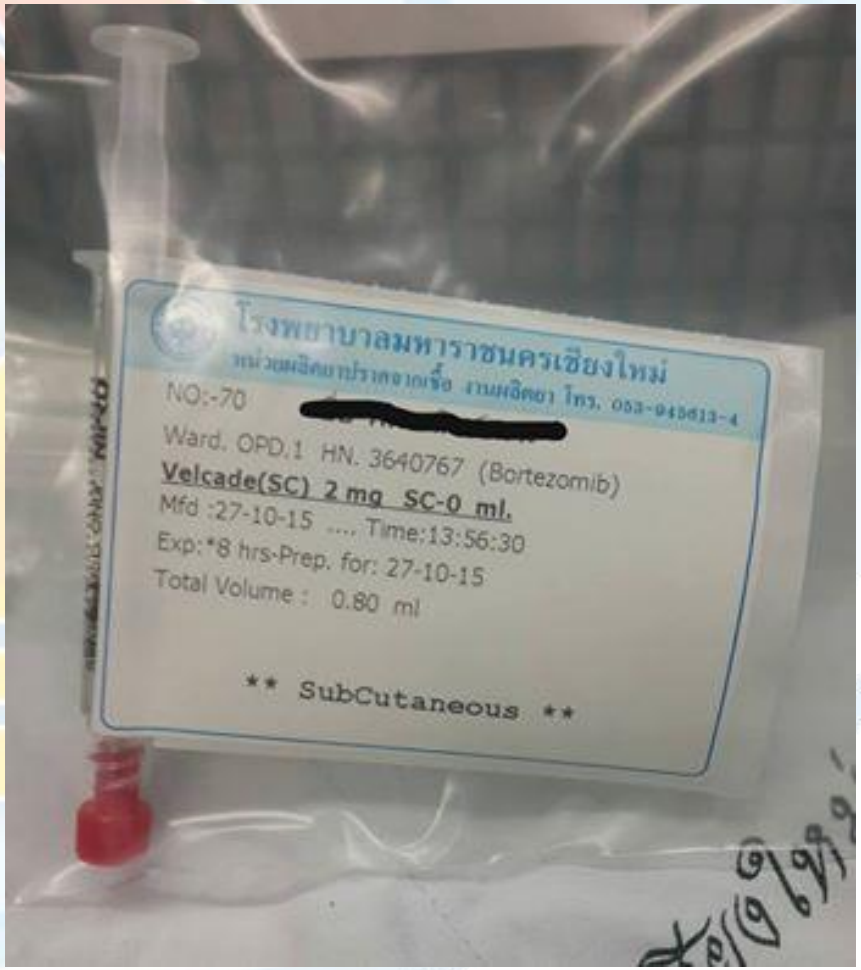
How do we administrate Bortezomib-Subcutaneous ?

วิธีปฏิบัติ

- ล้างมือให้สะอาด เช็ดให้แห้ง
- การปฏิบัติทุกขั้นตอนให้ยึดหลัก Aseptic technique และหลักการให้ยา
- ผสมยาให้ได้ความเข้มข้นตามแผนการรักษา จากนั้นจึงดูดยาเข้ากระบอกฉีดยา
- เตรียมยาที่จะฉีด โดยไล่ฟองอากาศออกให้เหลือประมาณ0.1-0.2 CC เพื่อให้ฟองอากาศช่วยดันน้ำยาออกจากเข็มไปหมด (air lock technique) ซึ่งฟองอากาศที่อยู่บริเวณที่ฉีดยาจะช่วยปกคลุมปริมาณยาที่ฉีดไม่ให้รั่วไหลผ่านรูที่แทง และฟองอากาศจำนวนนี้จะไม่ก่อให้เกิดการอุดกั้นในเลือด

How do we administrate Bortezomib-Subcutaneous ?

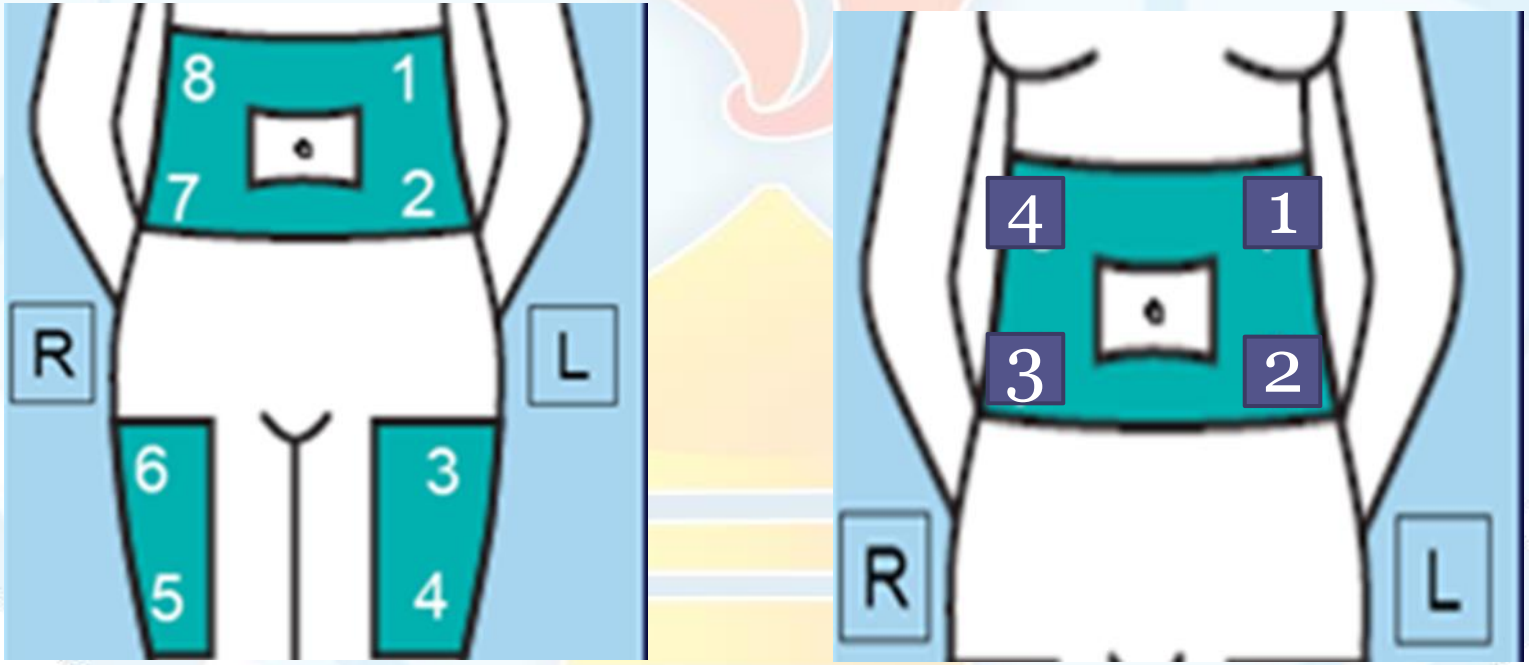
- ในกรณีที่ยาถูกเตรียมจากฝ่ายเภสัชกรรม ให้ตรวจสอบความถูกต้องอีกครั้ง ก่อนนำไปให้ผู้ป่วย



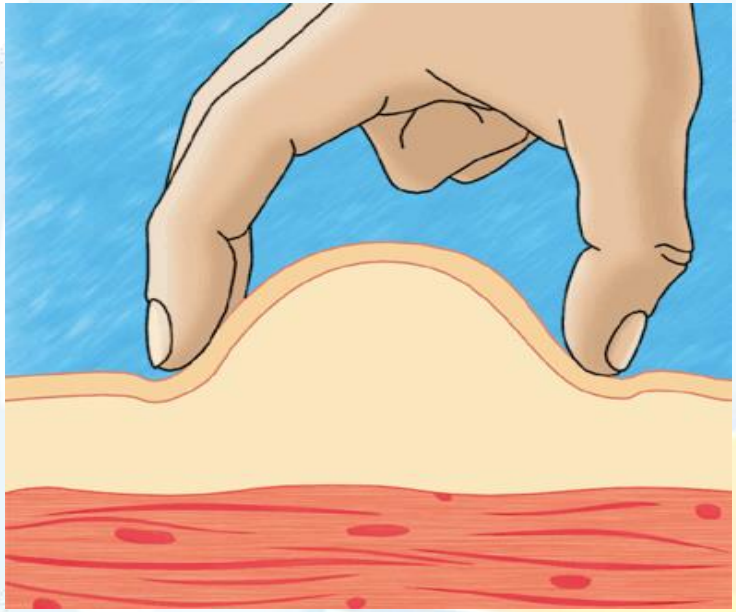
How do we administrate Bortezomib-Subcutaneous ?

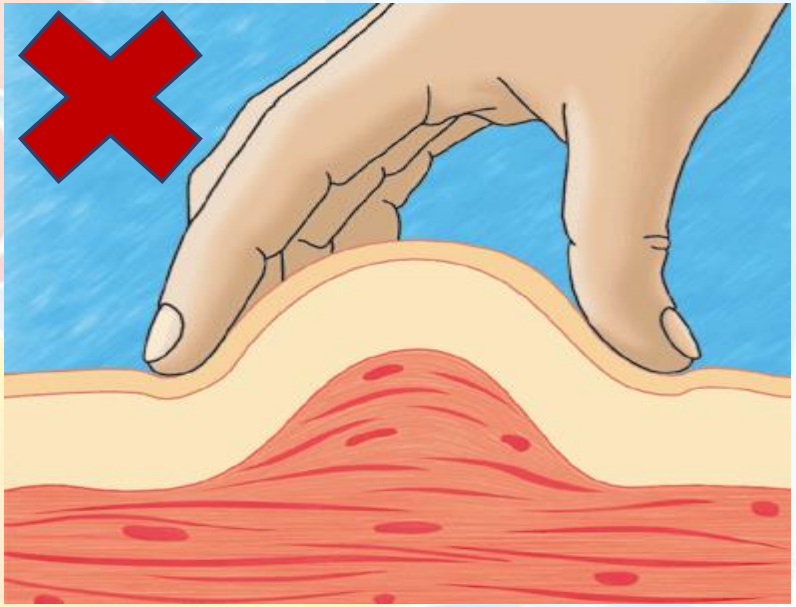
- เปลี่ยนเข็มฉีดยา ให้เป็นขนาด 27 - 25 gauge
- เลือกบริเวณที่จะฉีดยา ได้แก่ ต้นขาด้านหน้า หรือ หน้าท้อง เลือกบริเวณที่ไม่มีผื่นแผลอักเสบ บวม แดง คัน มีแผลเป็นไตแข็ง หรือลักษณะเนื้อเยื่อถูกทำลาย เนื่องจากฉีดยาซ้ำที่บ่อย
- ทำความสะอาดผิวหนังด้วยยาฆ่าเชื้อ แล้วรอให้แห้ง

Injection site



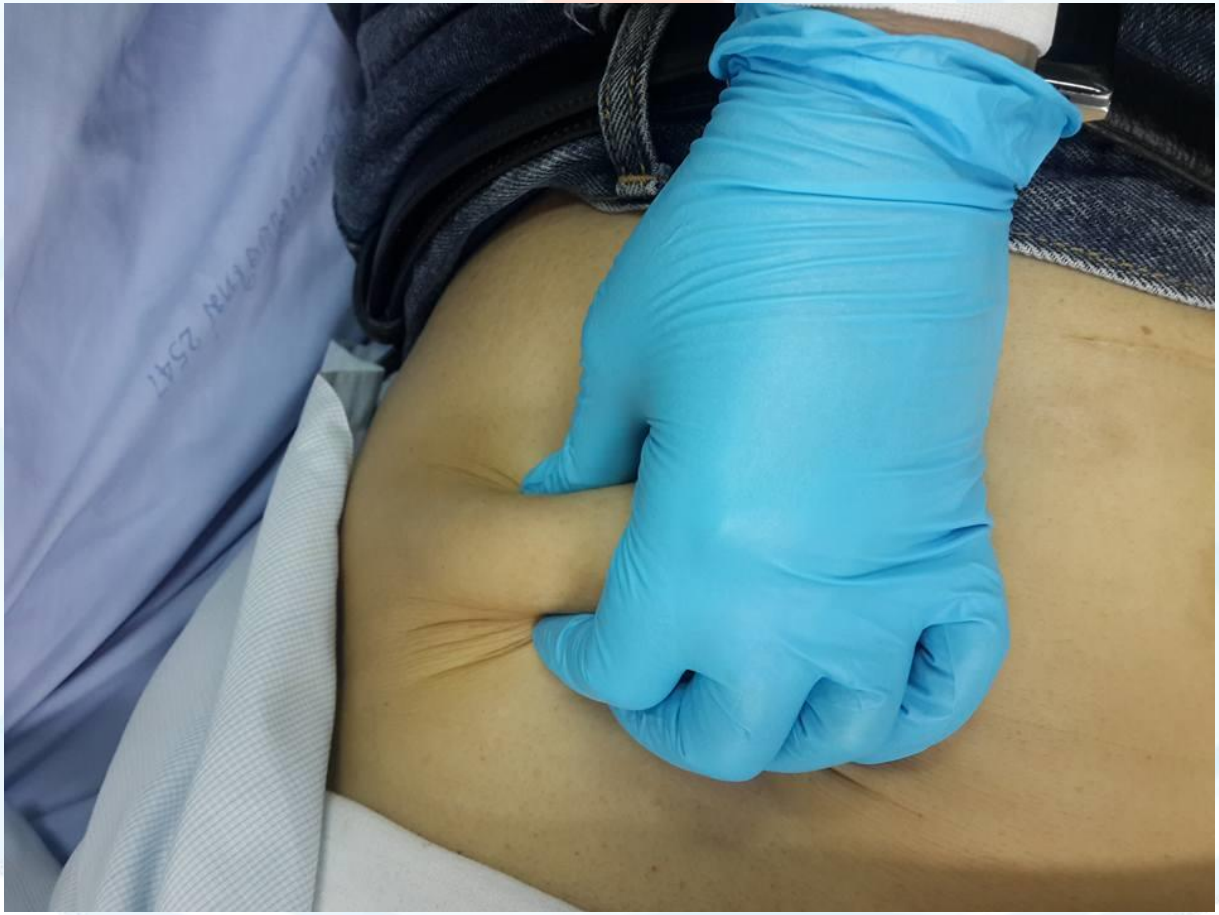
Injection site



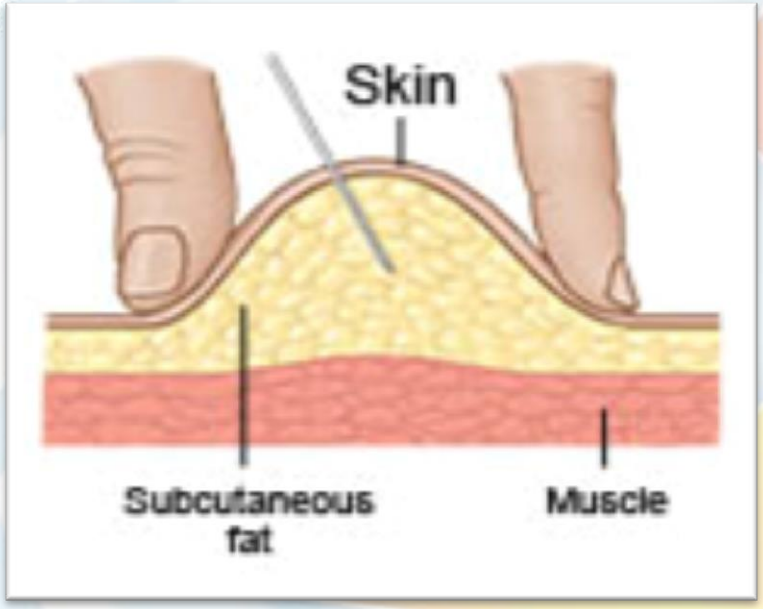


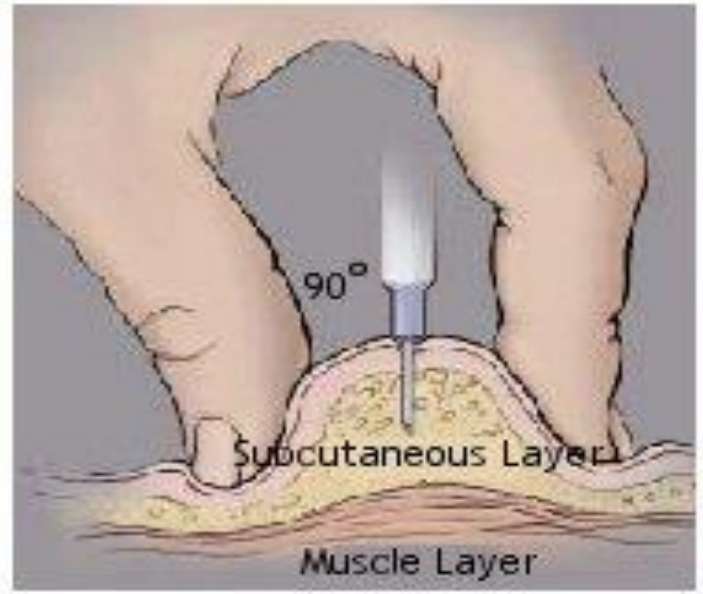
จับผิวหนังให้ตึง โดยยกขึ้นหรือดึงลง

Injection site



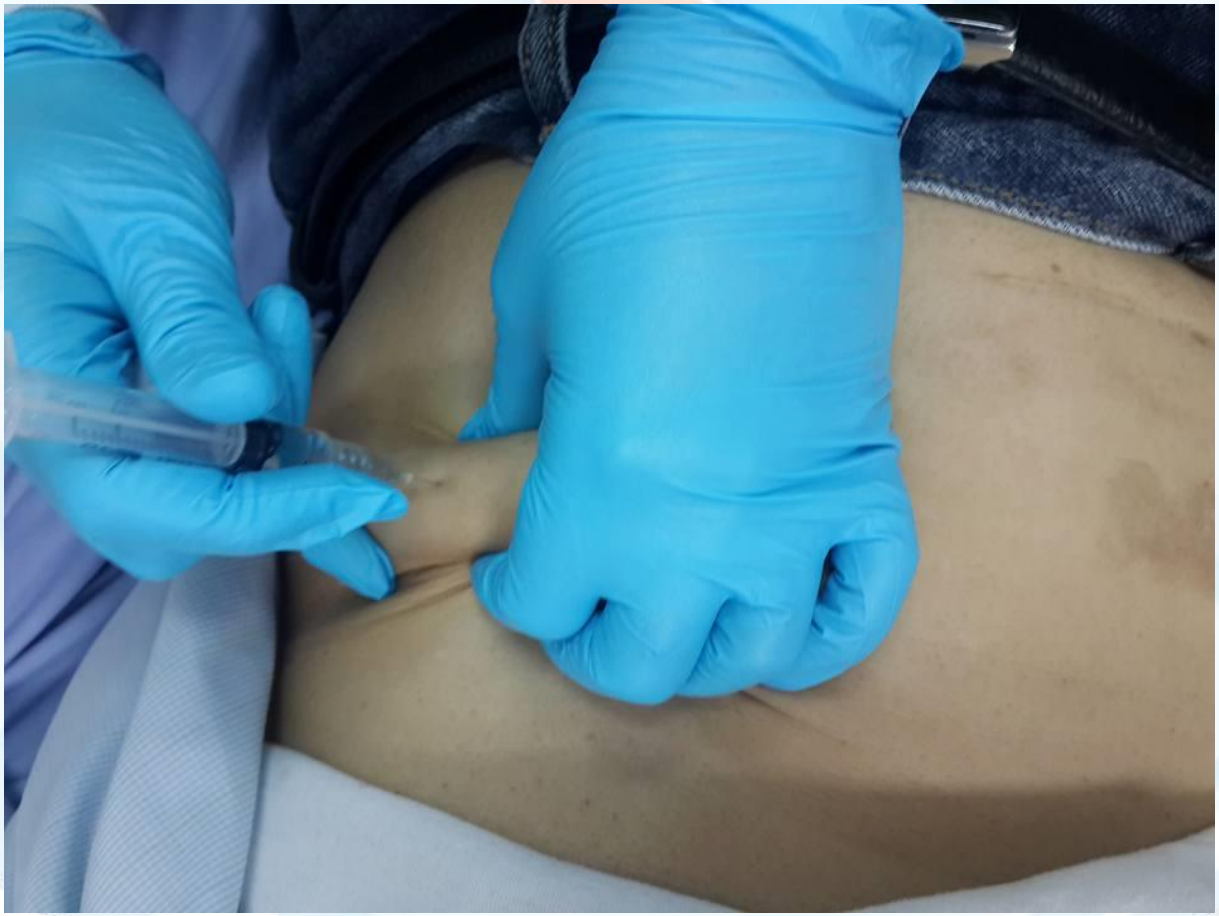
Injection technique



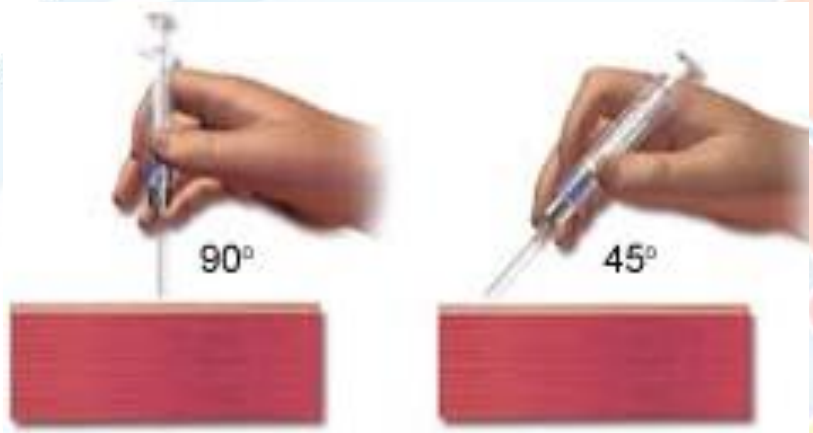


จับกระบอกฉีดยาให้ปลายตัดของเข็มหงายขึ้น แทงเข็มฉีดยาทำมุม 45 องศากับผิวหนังให้เข็มลึก 5/8 นิ้ว ในคนอ้วนอาจแทงเข็มลึกถึง 1 นิ้ว ถ้าใช้เข็มขนาด 1/2 นิ้ว แทงเข็มทำมุม 90 องศา

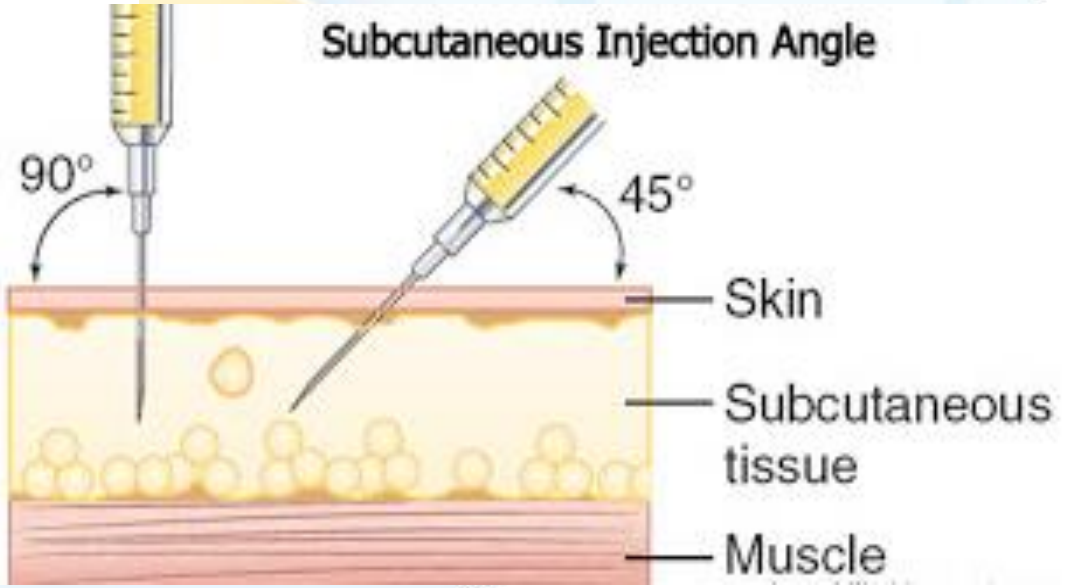
Injection technique



Injection technique



The Correct Angle and Way to Hold the Syringe



How do we administrate Bortezomib-Subcutaneous ?

- เมื่อแทงเข็มแล้ว ดึงลูกสูบออกเล็กน้อย เพื่อทดสอบว่าปลายเข็มแทงถูกหลอดเลือดหรือไม่ ถ้าไม่พบเลือดในกระบอกฉีดยา ให้ดันยาเข้าไปช้า ๆ จนหมด
- หากดึงลูกสูบแล้วได้เลือดให้ดึงเข็มออก แล้วเริ่มต้นใหม่
- ใช้สำลีแห้งวางเหนือจุดแทงเข็ม ดึงเข็มออกโดยเร็วตามทิศทางเดียวกับที่แทงเข็ม เลื่อนสำลีกดรอยเข็ม
- คลึงบริเวณที่ฉีดยาเบา ๆ ถ้ามีเลือดออกให้ใช้สำลีแห้งหรือก็อซ กดไว้สักระยะจนกว่าเลือดจะหยุด
- เก็บเครื่องใช้และทำความสะอาดให้ถูกวิธี
- ลงบันทึกการให้ยา และบันทึกการพยาบาลเกี่ยวกับยา ขนาด วิถีทางและตำแหน่งที่ฉีดยารวมทั้งอาการผิดปกติภายหลังฉีดยาแล้ว

NATURE AND MANAGEMENT OF COMMON BORTEZOMIB SIDE EFFECTS

- Peripheral Neuropathy
- Varicella Zoster Reactivation

Antiviral prophylaxis

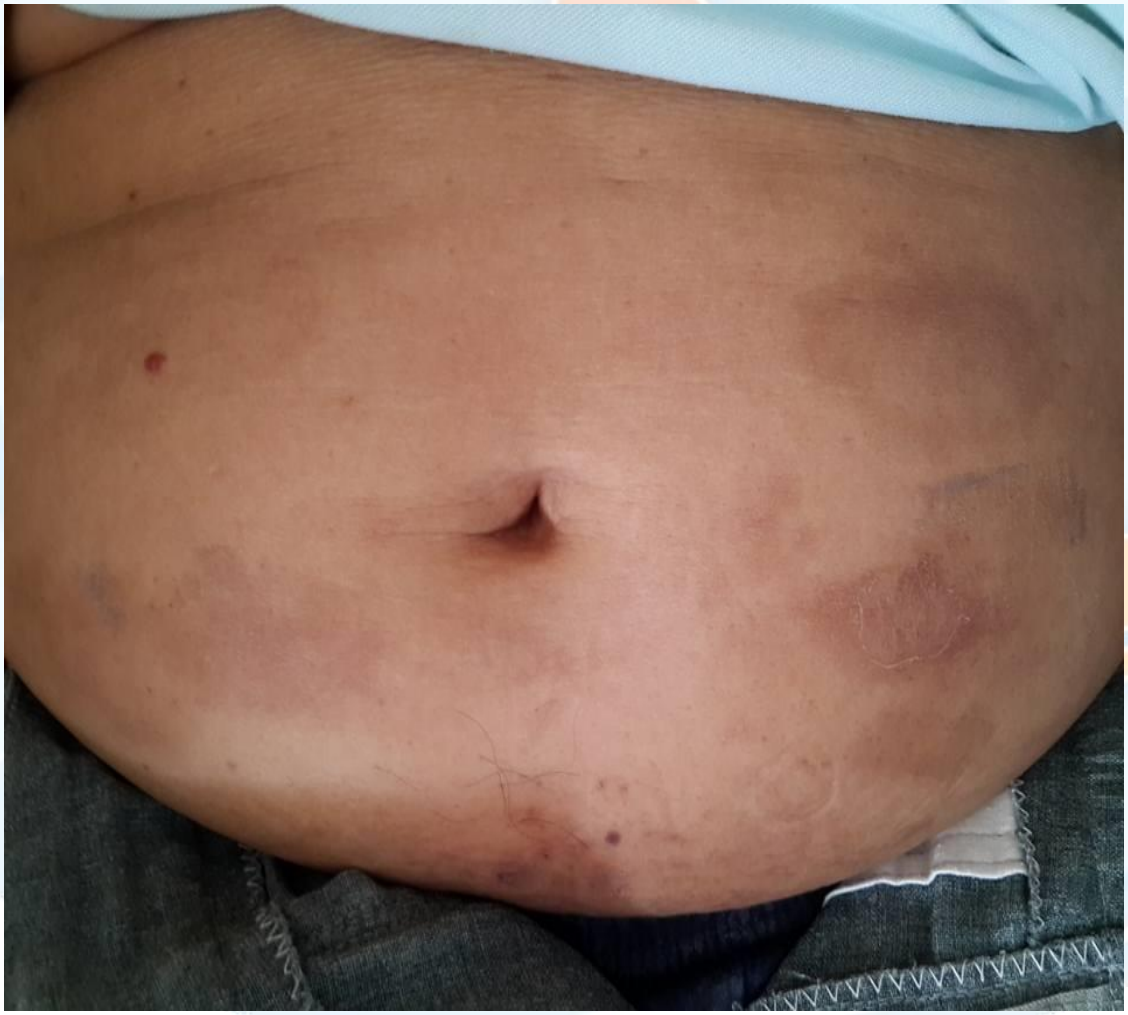
NATURE AND MANAGEMENT OF COMMON BORTEZOMIB SIDE EFFECTS

Severity of Peripheral Neuropathy Signs/Symptoms	Modification of Dose and Regimen
Grade 1 without pain or loss of function (asymptomatic; loss of deep tendon reflexes or paresthesia)	**No action**
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental activities of daily living (ADL))	**Reduce bortezomib to 1.0 mg/m2 or Change bortezomib treatment schedule to 1.3 mg/m2 once per week**
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)	**Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of bortezomib at 0.7 mg/m²once per week.**
Grade 4 (life-threatening consequences; urgent intervention indicated)	**Discontinue bortezomib**

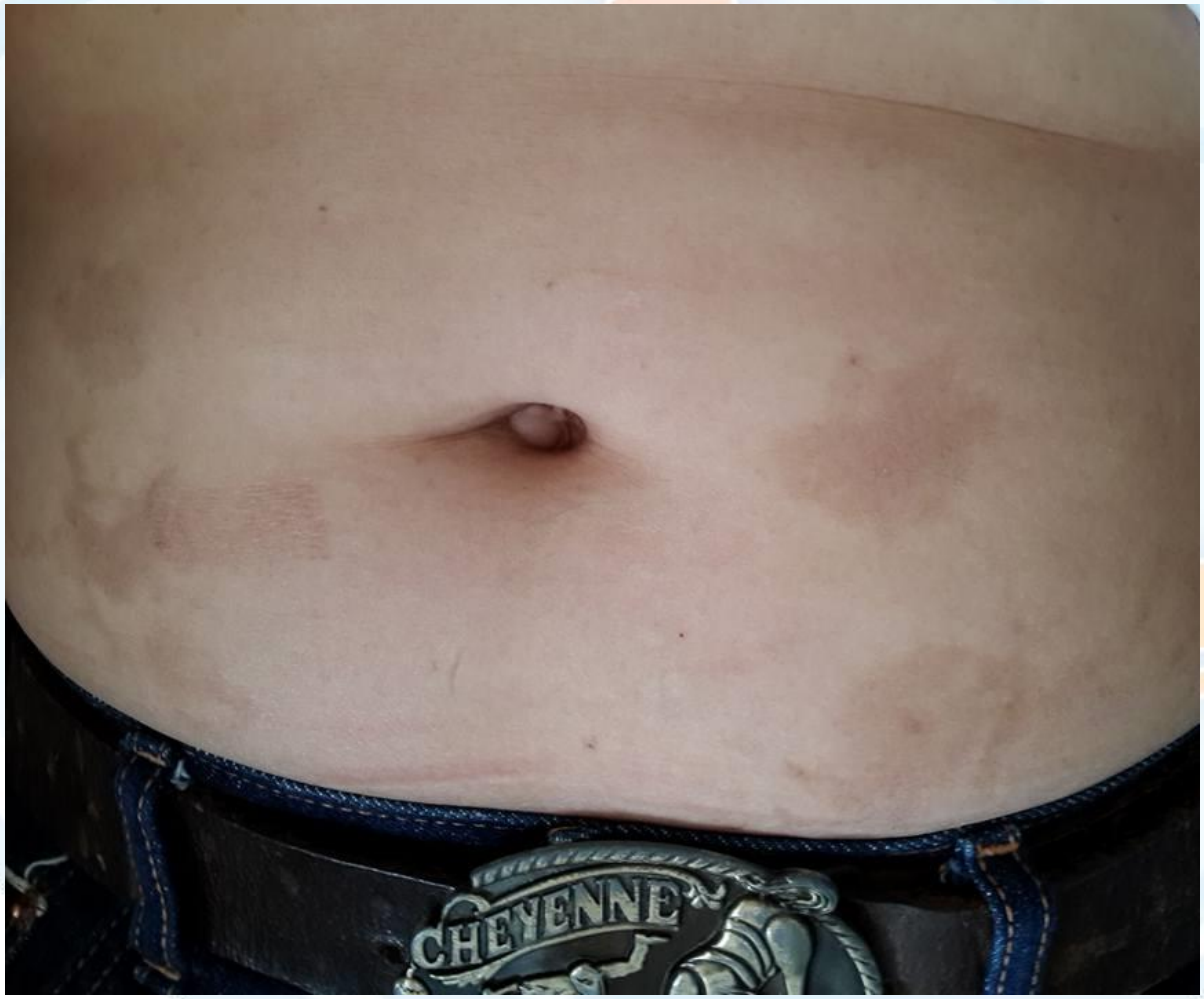
Other toxicities

- Nausea – antiemetics (e.g. ondansetron)
- Diarrhoea – Anti-diarrhoeal (loperamide)
- Constipation – laxatives
- Dehydration – normal saline ; 500cc – 1litre
- Rash – steroids, antihistamines
- Fatigue – role of steroids, hydration
- Skin and subcutaneous tissue disorders

Skin and subcutaneous tissue disorders



Skin and subcutaneous tissue disorders



การดูแลและการป้องกัน

- ใช้เข็มฉีดยาที่มีขนาดเล็ก
- เลือกตำแหน่งที่เหมาะสม
- หลังฉีดยา คลึงเบาๆ แล้วกดไว้ 1-2 นาที
- ให้ข้อมูลผู้ป่วย อาการจะค่อยๆ หายไปเอง

Thank you for your attention!

Any questions?