The Role of the Nurse in Managing Solid Tumour Patients on Oral Targeted Therapies

Dr. Rachel Goodwin

The Ottawa Hospital Cancer Centre

October 2012

Disclosures

- Participated in an advisory consultative meeting for Bayer.

Objectives

- Understand the rationale and use of current oral targeted agents in treating solid tumours in Canada
- Identify common side effect from oral targeted agents
  - Target class effect
  - Specific drug side effect
- Discuss nursing interventions that will assist in the management of these side effects for optimal patient outcomes

Role of the Nurse

"Oncology nurses play a key role within the multidisciplinary team, acting as a liaison between the patient and the oncology team."

"Nurses are in the ideal position to educate patients regarding the potential toxicities that may be encountered during treatment and also to identify and manage toxicities before they become problematic."

Grenon and Chan 2009 Clinical Journal of Oncology Nursing.

Persistence and adherence of oral cancer drugs

- Persistence
  - Continuing treatment for the prescribed duration
- Adherence
  - Taking medication as prescribed
- Is this a problem?

Hohneker et al, 2011J Oncol Practice; Partridge et al 2002 J National Cancer Institute.

Persistence and adherence of oral cancer drugs

	Persistence of anti-estrogen oral medications	
	ON Clinical Trial	OFF Clinical Trial
Tamoxifen	72%	65%
Letrozole	84%	77%

Hohneker et al, 2011J Oncol Practice; Partridge et al 2002 J National Cancer Institute.

Persistence and adherence of oral cancer drugs

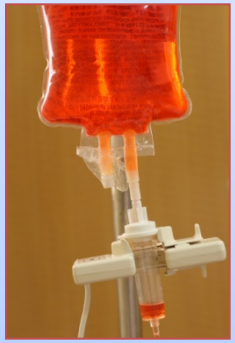
- Poor adherence potentially leads to serious clinical and economic consequences
- Strategies
  - Emphasize value of prescribed therapy
  - Simplify the regime
  - Encourage medication-taking systems
  - Obtain caregiver assistance
  - *Prevent and manage toxicities*

Hohneker et al, 2011J Oncol Practice; Partridge et al 2002 J National Cancer Institute.

Oral therapy in Solid Tumours

How are solid tumours systemically treated?

- Traditionally, solid tumours have been treated with chemotherapy and radiotherapy

Why are they used?	What are the problems?
Chemotherapy and radiotherapy kill cancer cells	Healthy cells are also damaged
 	There can be lots of side effects
Can cure cancer completely in some patients	They are not effective for treating some cancers (e.g. kidney cancer; GIST)

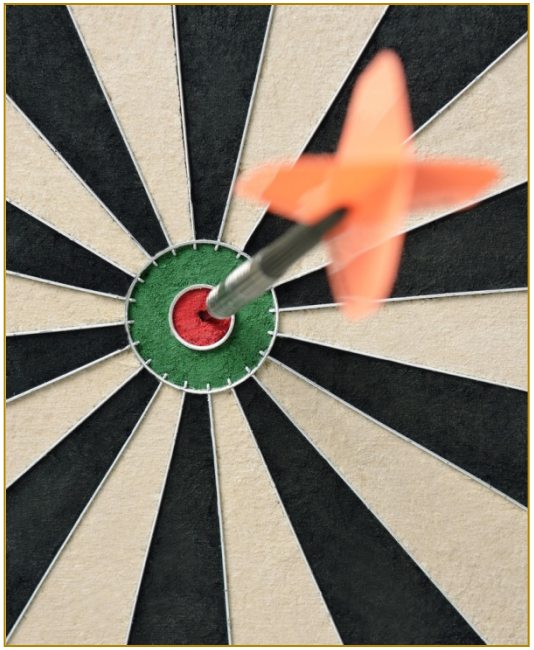
National Cancer Institute. http://www.cancer.gov/cancertopics/coping/chemotherapy-and-you.pdf and http://www.cancer.gov/cancertopics/coping/radiation-therapy-and-you/radiationttherapy.pdf. Accessed 18 July 2012.

Development of targeted agents for solid tumours

- Improved understanding of cancer biology has resulted in the development of novel ‘targeted’ agents
- These agents target key cancer cell processes, such as **proliferation**, **apoptosis** and **angiogenesis**

Good drug targets are those that play a key role in cancer cell proliferation and survival

The aim of targeted therapy is to improve effectiveness and reduce side effects

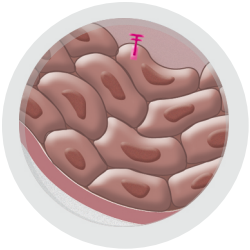


National Cancer Institute. http://www.cancer.gov/cancertopics/factsheet/Therapy/Fs7_49.pdf. Accessed 28 June 2012.

Proliferation and apoptosis

Proliferation = cell growth and division

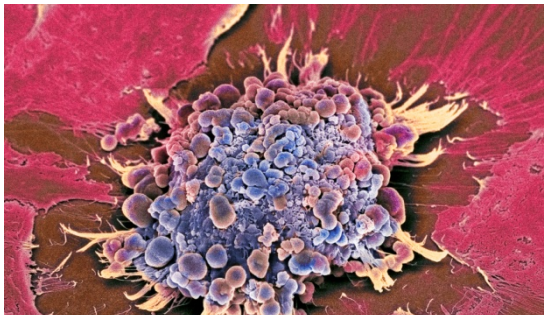
- Proliferation is controlled by molecular signals
- Blocking these signals can block cancer cell growth



Cancer cell proliferation

Apoptosis = programmed cell death (a process that makes cells die when they are no longer needed by the body)

- Apoptosis process is deranged in tumour cells
- Targeted cancer therapies can induce apoptosis



Cancer cell undergoing cell death (apoptosis)

National Cancer Institute. http://www.cancer.gov/cancertopics/factsheet/Therapy/Fs7_49.pdf. Accessed 28 June 2012

Apoptosis image courtesy of Steve Gschmeissner/Science Photo Library.

Angiogenesis

Angiogenesis = the formation of new blood

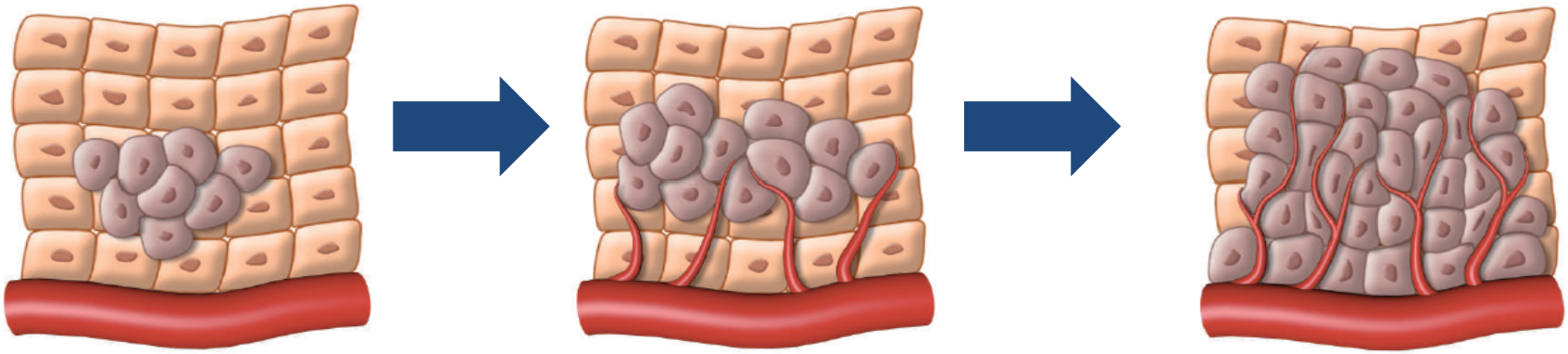
The new blood vessels are needed to carry nutrients and oxygen to the growing tumour

Blocking angiogenesis with targeted therapies blocks tumour growth

Tumour without its own blood supply

Angiogenesis is switched on – new blood vessels form

New blood vessels carry oxygen and nutrients to the tumour, allowing the tumour to grow

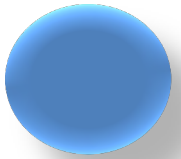


Poon ,RTP et al: J Clin Oncol Vol. 19 (Issue 4), 2001:1207–1225; National Cancer Institute. http://www.cancer.gov/cancertopics/factsheet/Therapy/Fs7_49.pdf. Accessed 28 June 2012.

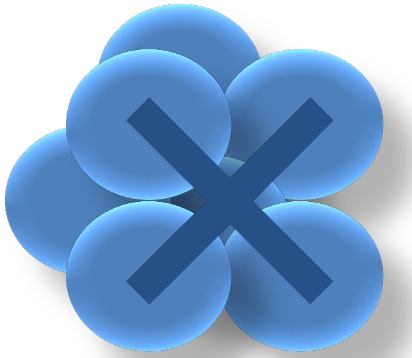
Development of targeted agents for solid tumours

Factors involved in cell proliferation and angiogenesis have been targeted in anti-cancer drug development

Tumour cells



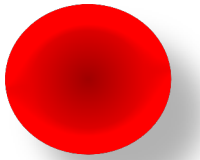
Cancer cell proliferation

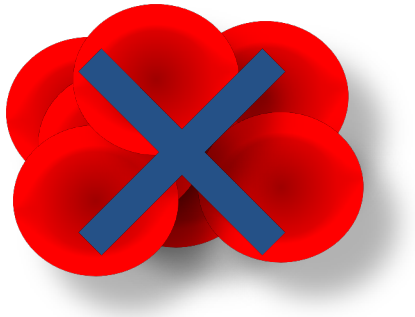


Cancer cell with limited blood supply

Growing tumour with increasing blood supply

Angiogenesis

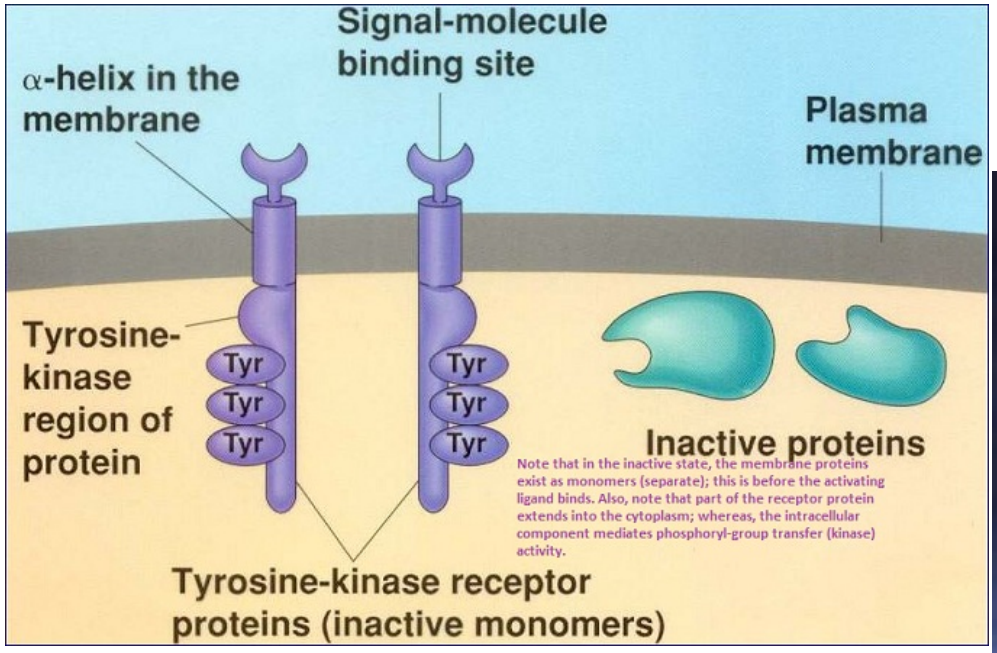


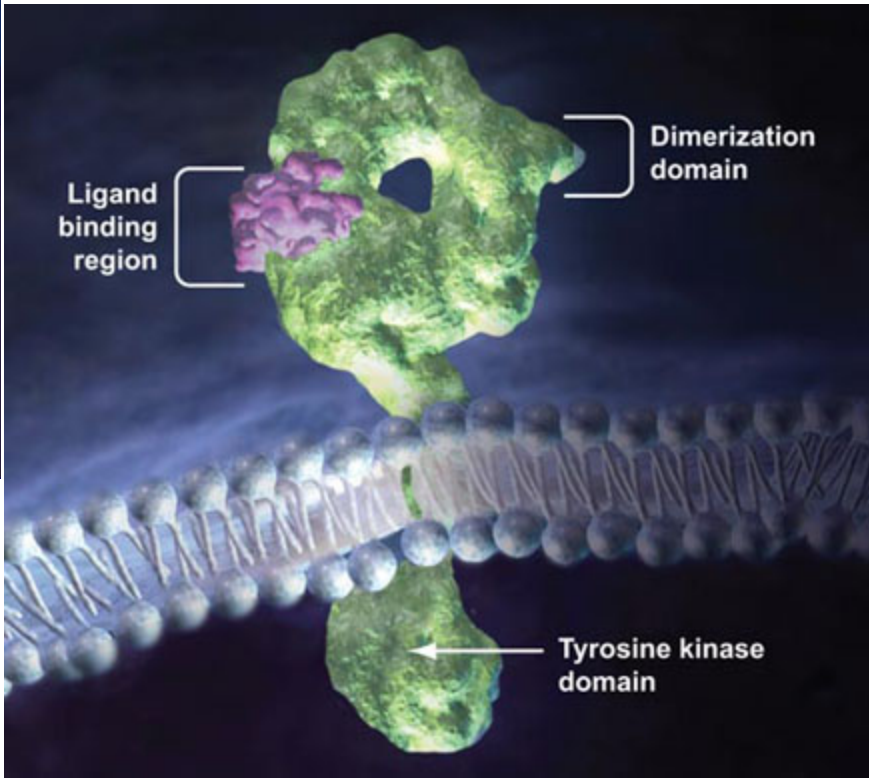


Endothelial cells

Cattley RC, et al. Toxicol Pathol 2004;32 (Suppl 1):116–21.

Potential drug targets



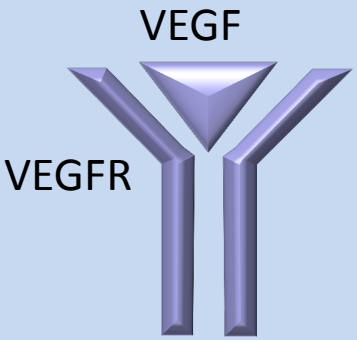
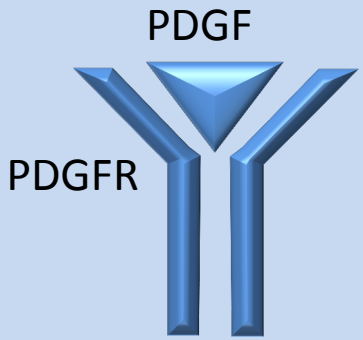


www.bingimages.com

Tyrosine kinase inhibitors

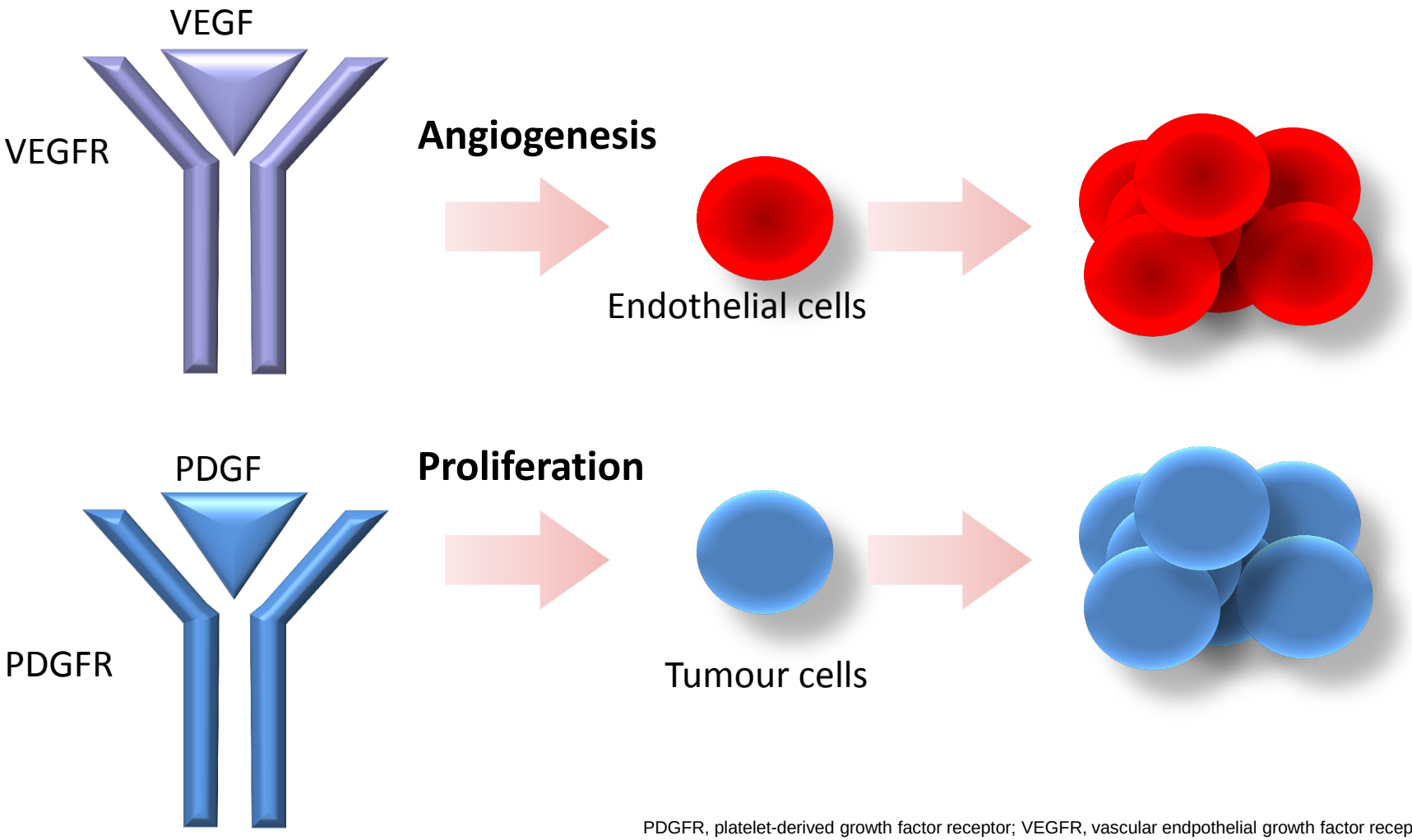
Cellular proliferation, angiogenesis and metastatic processes are controlled by molecules called ‘protein tyrosine kinases’

- Tyrosine kinases are signalling molecules
- There are lots of different tyrosine kinases, and they are important for different processes, for example:

Vascular endothelial growth factor receptor (VEGFR)	**Platelet-derived growth factor receptor (PDGFR)**
Important for angiogenesis	Important for proliferation
	

Larkin JMG and Eisen T. Ther Clin Risk Manag 2006;2:87–98; Wilhelm SM, et al. Cancer Res 2004;64:7099–109.

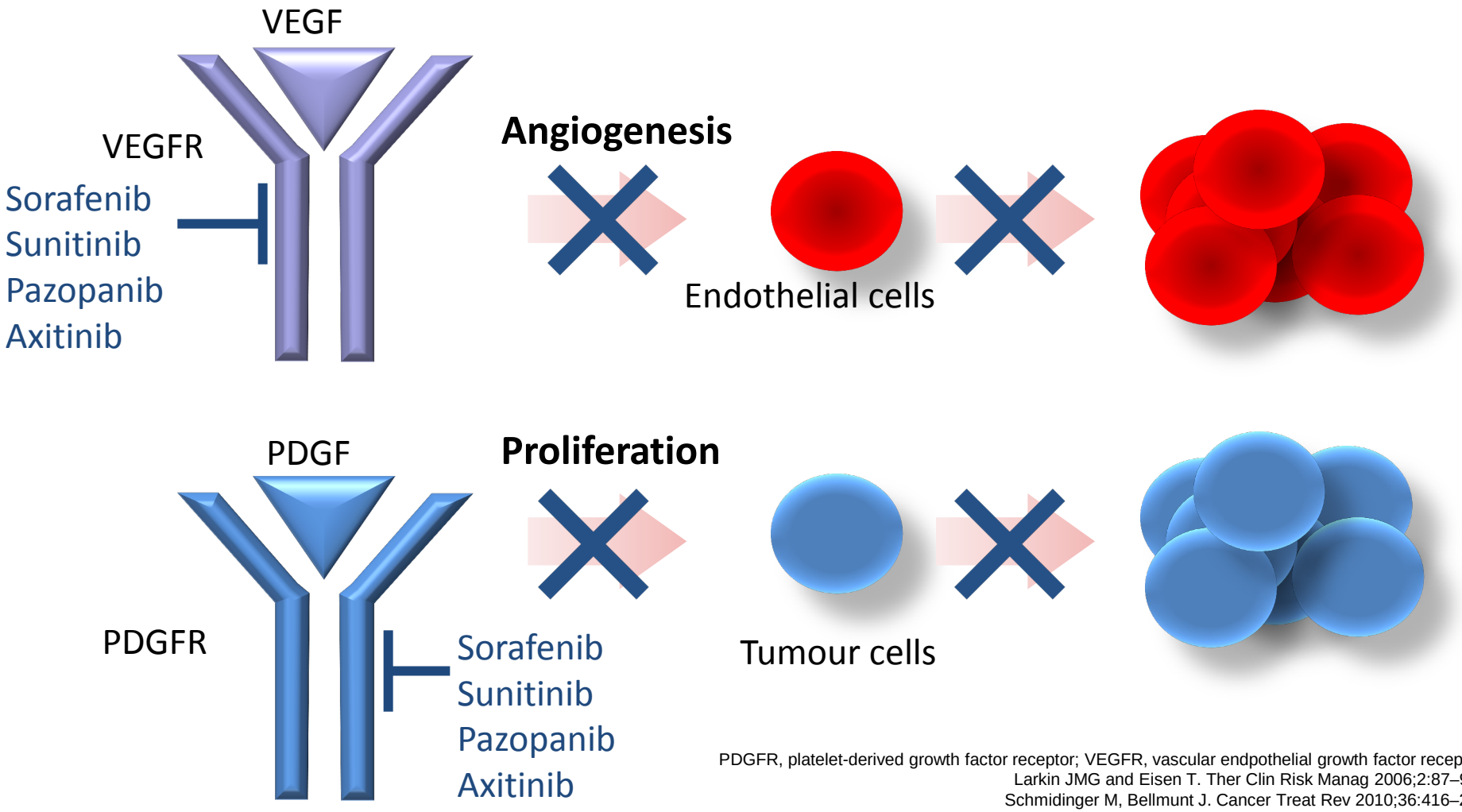
How do tyrosine kinase inhibitors treat tumours?



PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endpothelial growth factor receptor

Larkin JMG and Eisen T. Ther Clin Risk Manag 2006;2:87–98; Wilhelm SM, et al. Cancer Res 2004;64:7099–109.

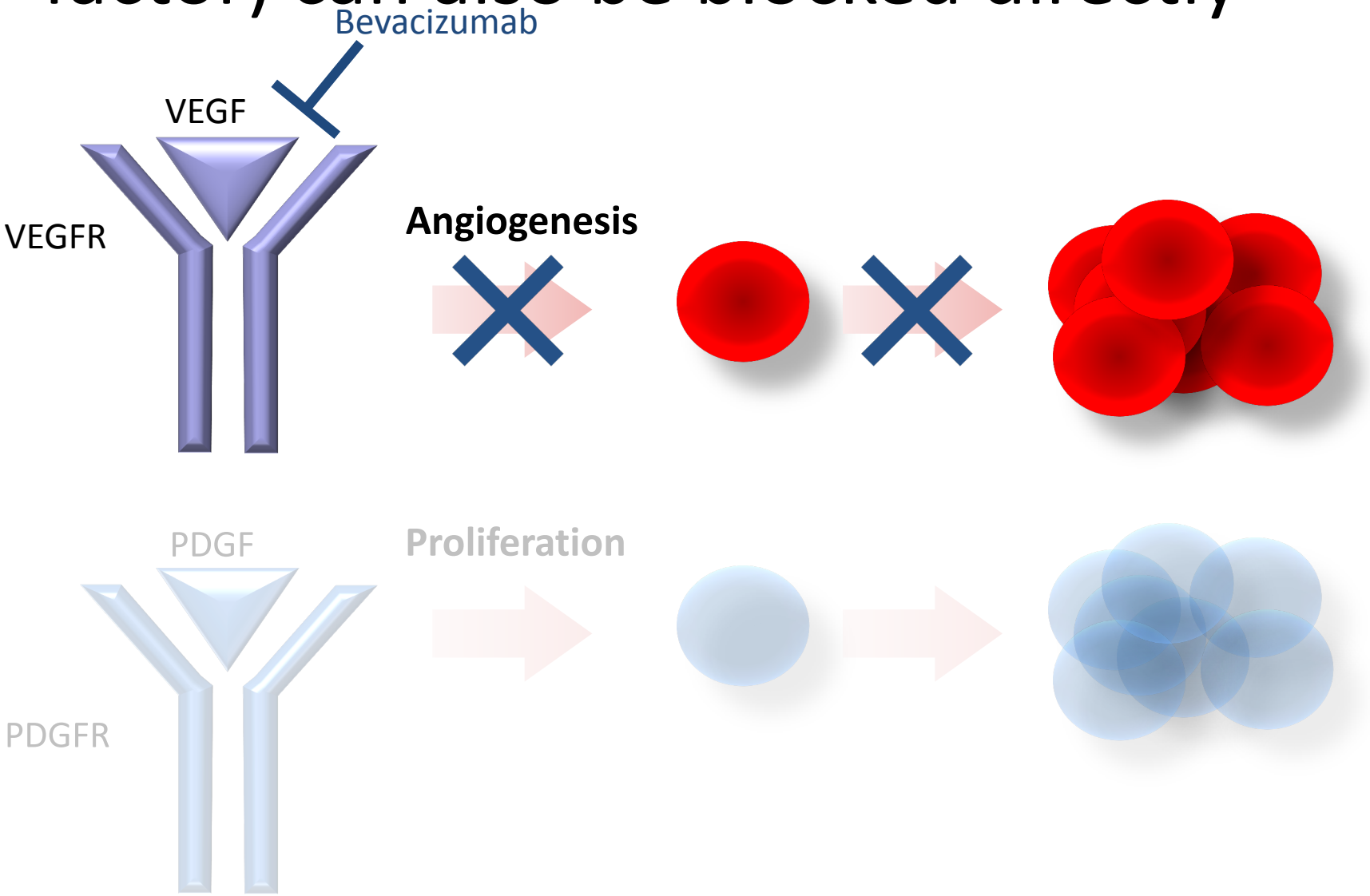
How do tyrosine kinase inhibitors treat tumours?



PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endpothelial growth factor receptor

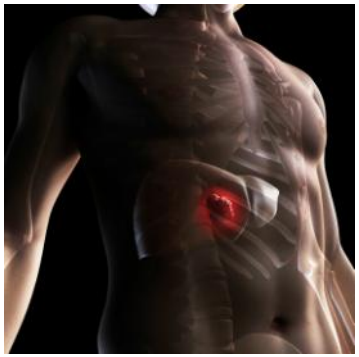
Larkin JMG and Eisen T. Ther Clin Risk Manag 2006;2:87–98;
Schmidinger M, Bellmunt J. Cancer Treat Rev 2010;36:416–24;
Wilhelm SM et al. Cancer Res 2004;64:7099–109; Kumar R et al. Mol Cancer Ther 2007;6:2012–21

VEGF (vascular endothelial growth factor) can also be blocked directly



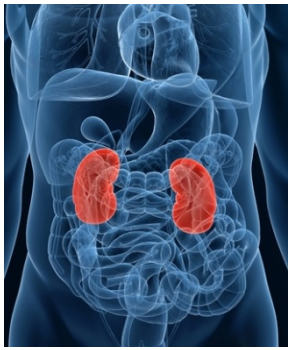
Schmidinger M, Bellmunt J. Cancer Treat Rev 2010;36:416–24.

Which cancers are treated with targeted agents?



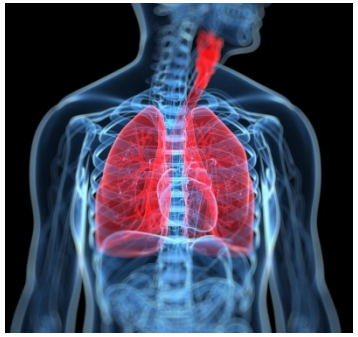
Liver
- Sorafenib

pNET
- Examples include:
  - Sunitinib
  - Everolimus



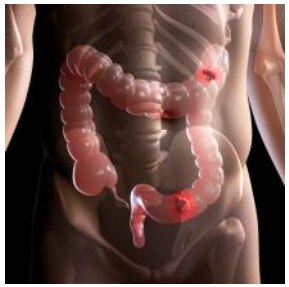
Kidney
- Examples include:
  - Sorafenib
  - Sunitinib
  - Everolimus
  - Axitinib

Lung
- Examples include:
  - Bevacizumab
  - Erlotinib
  - Gefitinib
  - Crizotinib



Breast
- Examples include:
  - Lapatinib
  - Trastuzumab

GIST
- Sunitinib
- Imatinib



Colorectal
- Bevacizumab
- Cetuximab
- Panitumumab

GIST, gastrointestinal stromal tumour.

Health Canada. Nexavar® PM; Health Canada. Sutent® PM; Health Canada. Avastin® PM; Health Canada. Afinitor® PM; Health Canada. Tarceva® PM; Health Canada. Herceptin® PM; Health Canada Tykerb PM; Health Canada Xalkori PM; Health Canada. Gleevec® PM; Health Canada Iressa PM; Health Canada. Erbitux® PM; Health Canada. Vectibix® PM.

Targeted therapies are administered by different routes and on different schedules...

Routes of administration

- **By mouth**
  - Sorafenib
  - Sunitinib
  - Pazopanib
  - Everolimus

- **By IV i**
  - Bevacizu
  - Temsirol

Dosing schedules

- Every week
- Every 2 weeks
- Once daily
- Twice daily
- Once daily with a break every 4 weeks
- Etc...

European Medicines Agency. Nexavar® SmPC, January 2012; European Medicines Agency. Avastin® SmPC, May 2012; European Medicines Agency. Torisel® SmPC; November 2011; European Medicines Agency. Sutent® SmPC, March 2012; European Medicines Agency. Votrient® SmPC, June 2012; European Medicines Agency. Afinitor® SmPC, April 2012; US Food and Drug Adminstration. Inlyta® PI, January 2012.

Targeted therapies for cancer are generally well tolerated

- The side effect profiles of targeted therapies are different to those usually seen with cytotoxic drugs
- Common side effects associated with targeted therapies can include:[1]
  - Skin reactions
  - Heart problems
  - Clotting disorders
  - Hypertension
  - Diarrhoea
  - Fatigue

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

Common side effects of targeted therapies

Drug class	Common side effects
Tyrosine kinase inhibitors Sorafenib (Nexavar®) Sunitinib (Sutent®) Pazopanib (Votrient®) Axitinib (Inlyta®) Erlotinib (Tarceva)	Hand–foot skin reaction (HFSR) Rash Fatigue Hypertension Diarrhoea Anorexia
Anti-VEGF mAb Bevacizumab (Avastin®)	Hypertension Haemorrhage Gastrointestinal perforation Poor wound healing
mTOR inhibitors Temsirolimus (Torisel®) Everolimus (Afinitor®)	Infections Pneumonitis Metabolic disorders Fatigue Rash Asthenia Anaemia

mAb, monoclonal antibody; mTOR, mammalian target of rapamycin.

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113; European Medicines Agency. Nexavar® SmPC, January 2012; European Medicines Agency. Avastin® SmPC, May 2012; European Medicines Agency. Torisel® SmPC; November 2011; European Medicines Agency. Sutent® SmPC, March 2012; European Medicines Agency. Votrient® SmPC, June 2012; European Medicines Agency. Afinitor® SmPC, April 2012; US Food and Drug Adminstration. Inlyta® PI, January 2012.

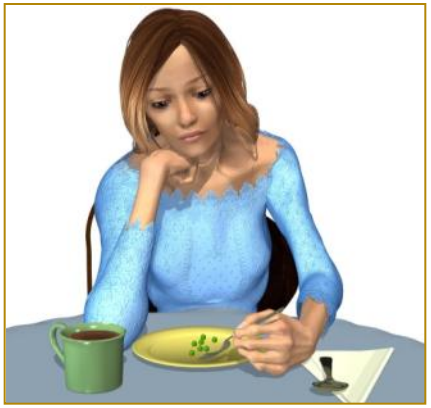
Common non-dermatological side effects

Fatigue

Hypertension

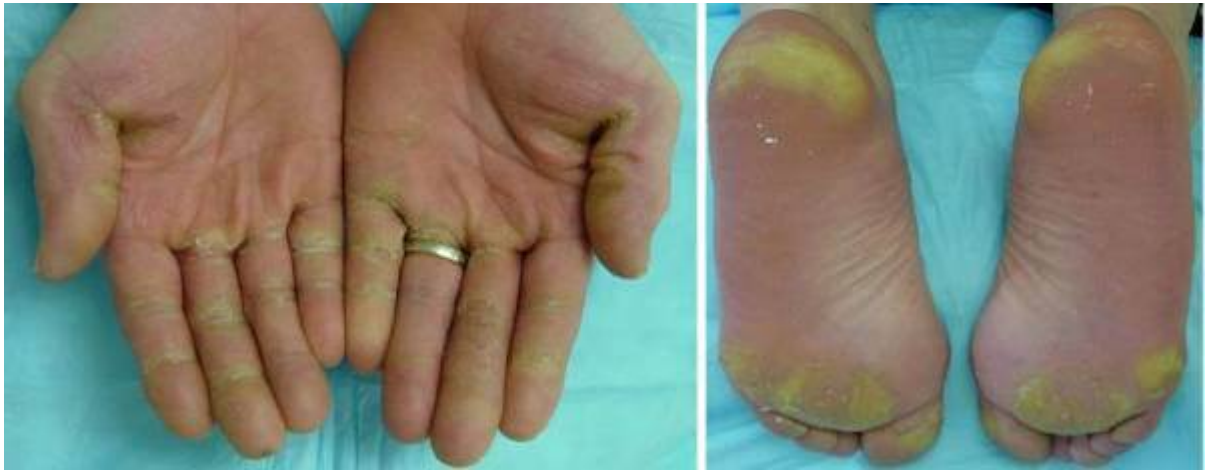
Diarrhoea

Anorexia/weight loss

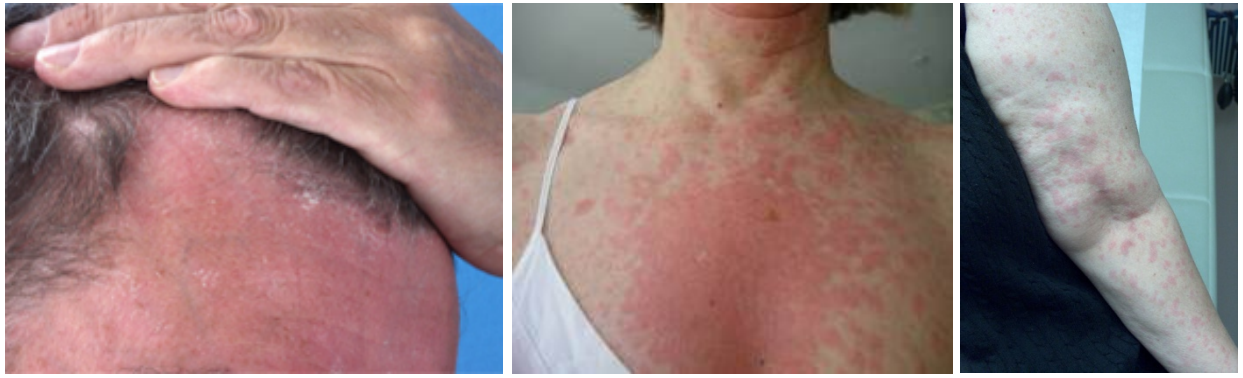


Common dermatological side effects

Hand–foot skin reaction (HFSR)*



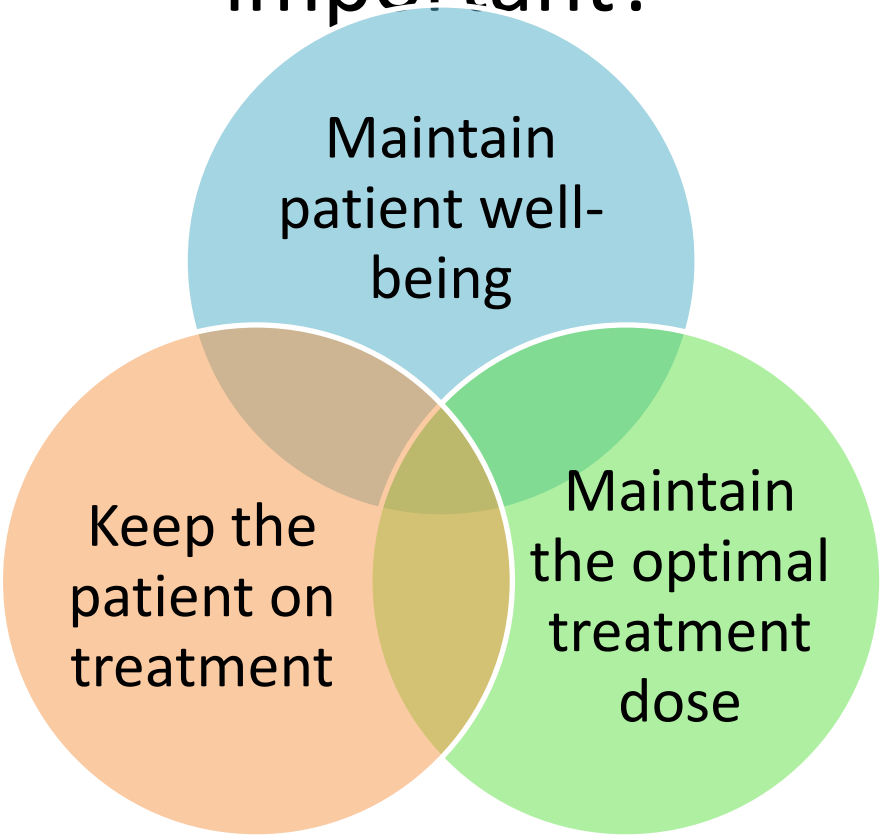
Rash†



*Photographs reproduced from Lacouture ME, et al. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. Ann Oncol 2008;19(11):1955–61, by permission of the European Society of Medical Oncology.

†Facial rash reproduced with permission from C. Robert - Dermatology - IGR Villejuif; chest rash reproduced with permission from MA Healthcare Ltd, from Edmonds K, Spencer-Shaw A. BJN 2010:19;58–60; arm rash reproduced with permission from Elizabeth Manchen, RN, MS, OCN.

Why is side effect management so important?



Maximum benefit from treatment
Minimum discomfort from side effects

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

It is important to remember…

…Preventing and managing side effects allows patients to continue on active treatment

Management of non-dermatological side effects

Fatigue, hypertension, diarrhea and anorexia

R.EU.ONC.08.2012.0493

Cancer-related fatigue is…

...a distressing feeling of physical, emotional and/or mental exhaustion related to cancer or cancer treatment

It is not proportional to the patient's activity levels

It interferes with usual functioning[1]

National Comprehensive Cancer Network. Cancer-related fatigue. V.1.2012. http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed July 2012.

Fatigue and targeted agents

- The **causes** of treatment-related fatigue are **unclear**[1,2]
- Targeted agents inhibit key tumour-sustaining targets[2]
  - But most also affect other key biological processes
- **More research is needed** to understand the mechanisms behind fatigue with different targeted agents[2]

Targeted agents associated with fatigue[3]
Bevacizumab (Avastin®)
Sorafenib (Nexavar®)
Sunitinib (Sutent®)
Pazopanib (Votrient®)
Temsirolimus (Torisel®)
Everolimus (Afinitor®)

1. National Comprehensive Cancer Network. Cancer-related fatigue. V.1.2012. http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed July 2012. 2. Larkin JMG et al. Oncologist. 2010;15:1135–1146. 3. Eisen T et al. J Natl Cancer Inst 2012;104:93–113 .

Frequency of fatigue with targeted agents

- Fatigue rates are generally similar regardless of which targeted agent patients receive

	Bevacizumab (Avastin®)	Sorafenib (Nexavar®)	Sunitinib (Sutent®)	Pazopanib (Votrient®)	Temsirolimus (Torisel®)	Everolimus (Afinitor®)
Fatigue frequency reported in the SmPC	++	++	++	++	++	++

++ = reported at a frequency of ≥10% of patients in the Canadian PM for each agent.

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113; . Afinitor® PM; Avastin® PM, May 2012; Nexavar® PM; Sutent® PM; Torisel® PM, Votrient® PM.

Grading fatigue

Grade	Description
1	Fatigue relieved by rest
2	Fatigue not relieved by rest, limiting instrumental activities of daily living (e.g. going shopping, preparing meals)
3	Fatigue not relieved by rest, limiting self care activities of daily living (e.g. bathing, feeding self)

US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012.

How should fatigue be explained to patients?

Weak

No energy

Weary

Exhausted

Physical or mental weariness

Easily tiring

Tiredness

Decreased capacity or complete inability to function normally

Difficulty concentrating

Larkin JMG et al. Oncologist. 2010;15:1135–1146

How to recognize fatigue

- Fatigue is **subjective** – it is experienced and reported **differently by each patient**

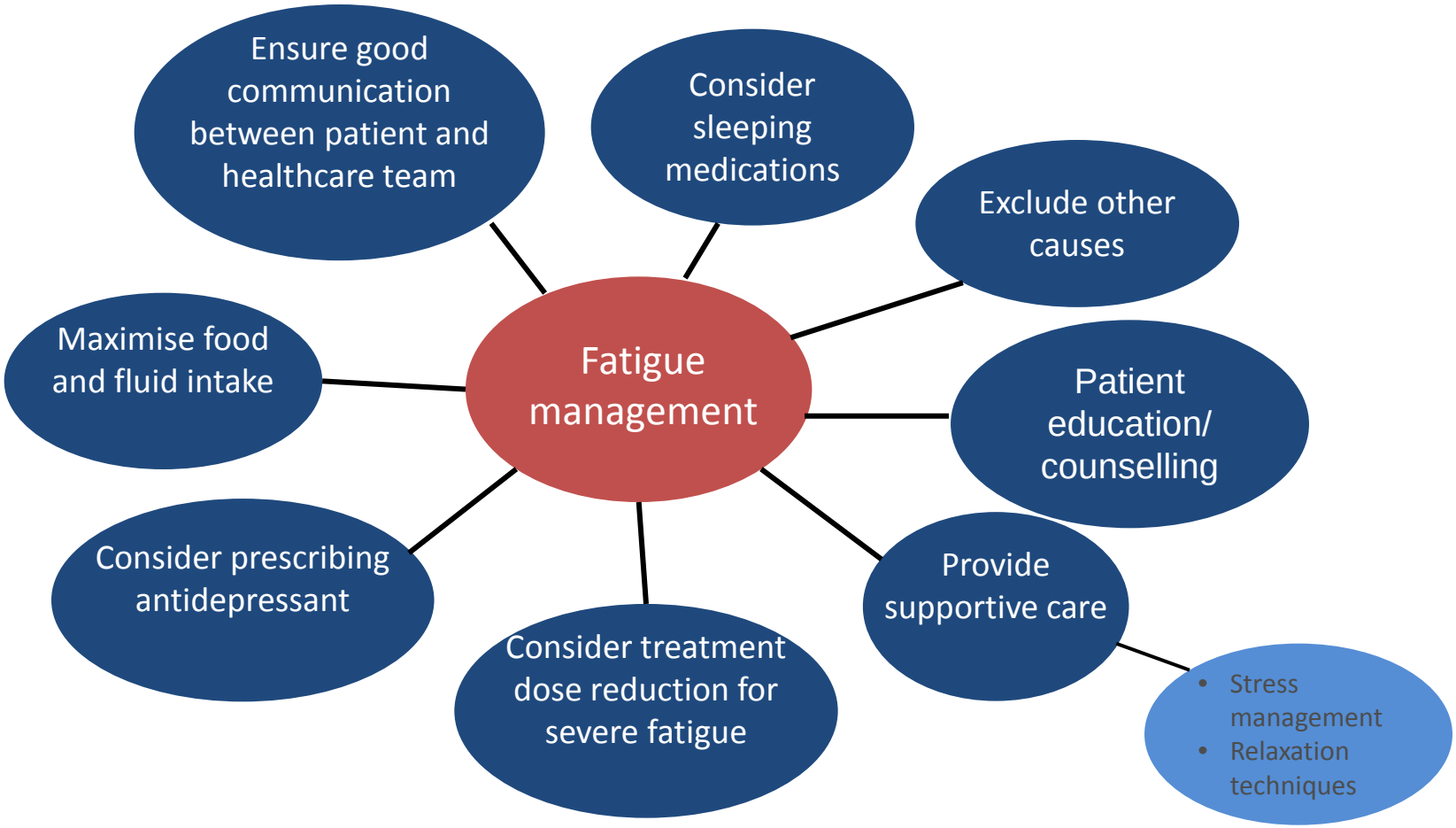
- Fatigue **often occurs with other symptoms**, e.g. pain, distress, anaemia, sleep disturbances, depression
  - It can be **physical**, **psychological** and **emotional**

- Look for signs of **decreased physical**, **social** or **mental functioning**

National Comprehensive Cancer Network. Cancer-related fatigue. V.1.2012. http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed July 2012.

Managing the symptoms of fatigue

Best implemented by a multidisciplinary team – nursing, medical, social work, physical therapy, nutrition



National Comprehensive Cancer Network. Cancer-related fatigue. V.1.2012. http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed July 2012. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

Practical suggestions

- Self-monitor fatigue levels using a patient diary
- Suggest energy conservation methods
  - Set priorities and plan ahead
  - Delegate
  - Schedule activities at time of peak energy
- Advocate labour-saving devices (e.g. electrical appliances, using escalators and elevators)
- Stay as active as possible, because that will help you to sleep better

Practical suggestions

- Maintain normal work and social schedules
- Take breaks as needed but limit daytime naps to <1 hour
- Use distraction techniques (e.g. games, music, reading, socializing)
- Tell your doctor or nurse if you cannot tolerate activity or your fatigue worsens

Fatigue: summary

- Fatigue is **very common** in patients with cancer
- **Targeted agents** are associated with fatigue...
- ...but **other causes** of fatigue should also be assessed
- Fatigue can be **proactively managed** by preparing patients for it, and adjusting life style
- **Dose reductions** may be implemented for severe fatigue

What is hypertension?

Hypertension is high blood pressure
(more than 140/90 mmHg)

US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012.

Frequency of hypertension with targeted agents

- Hypertension has been reported with all of the targeted agents approved for the treatment of solid tumours
  - Incidence is lower with the mTOR inhibitors than with the kinase inhibitors and bevacizumab

	Bevacizumab (Avastin®)	Sorafenib (Nexavar®)	Sunitinib (Sutent®)	Pazopanib (Votrient®)	Temsirolimus (Torisel®)	Everolimus (Afinitor®)
Hypertension frequency reported in the SmPC	++	++	++	++	+	+

+, reported at a frequency of ≥1 to <10%; ++, reported at a frequency of ≥10% of patients in the Canadian PM for each agent.

mTOR, mammalian target of rapamycin; PM, product monograph.

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113; Afinitor® PM. Avastin® PM. Nexavar® PM. Sutent® PM. Torisel® PM; Votrient® PM.

How to recognize hypertension

- Repeated elevation in BP to **more than 140/90 mmHg**[1]
  - Monitor BP regularly
- Hypertension is **usually symptomless**[2]
- **Severe hypertension** can cause symptoms such as:[2]
  - Headache
  - Sleepiness
  - Confusion
  - Blurred vision

1. US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed July 2012. 2. Net Doctor. http://www.netdoctor.co.uk/diseases/facts/hypertension.htm. Accessed July 2012.

Proactive management of hypertension

Get hypertension under control before starting targeted therapy[1]

Monitor BP weekly during the first 6–12 weeks of treatment[1]

Continue to check BP regularly after week 6–12[1]

May require coordination with primary care physicians and practice nurses

BP, blood pressure.

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113;

Hypertension: summary

- Hypertension is **common** with targeted agents
- Check patients' BP **before and during treatment**
- Hypertension associated with targeted agents can be **easily managed** with antihypertensive therapy
- Dose of targeted therapy can be **reduced or interrupted** if required

BP, blood pressure.

What is diarrhea?

- Diarrhea is characterized by **frequent and watery bowel movements**[1]

- Even mild to moderate diarrhea can **significantly affect patient quality of life** by impairing mobility and independence[2]

1. US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012.2. Bellmunt J, et al. Crit Rev Oncol Hematol 2011;78:24–32.

Frequency of diarrhea with targeted agents

- Rates of diarrhea are generally similar between different targeted agents

	Bevacizumab (Avastin®)	Sorafenib (Nexavar®)	Sunitinib (Sutent®)	Pazopanib (Votrient®)	Temsirolimus (Torisel®)	Everolimus (Afinitor®)
Diarrhea frequency reported in the SmPC	++	++	++	++	++	++

++, reported at a frequency of ≥10% of patients in the Canadian PM for each agent.

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113; . Afinitor® PM; Avastin® PM; Nexavar® PM; Sutent® PM; Torisel® PM, Votrient® PM.

Grading diarrhea

A disorder characterized by frequent and watery bowel movements

Grade	Description
1	• Increase of **<4 stools/day** over pretreatment
2	• Increase of **4–6 stools/day**
3	• Increase of **≥7 stools/day** or incontinence • **Hospitalization** • Limiting **self-care** activites of daily living (such as bathing, feeding self)
4	• **Life threatening** • Urgent intervention indicated
5	• **Death**

ADL, activities of daily living.

US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012.

Proactively manage diarrhea

Early recognition and reporting of diarrhoea is important

Maintain regular patient contact

Explain that a healthy diet can help prevent diarrhoea

Tell patients that diarrhoea might occur

Encourage patients to keep a diary of their bowel movements

Make sure patients know the possible consequences of diarrhoea

Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84;

Managing the symptoms of diarrhea

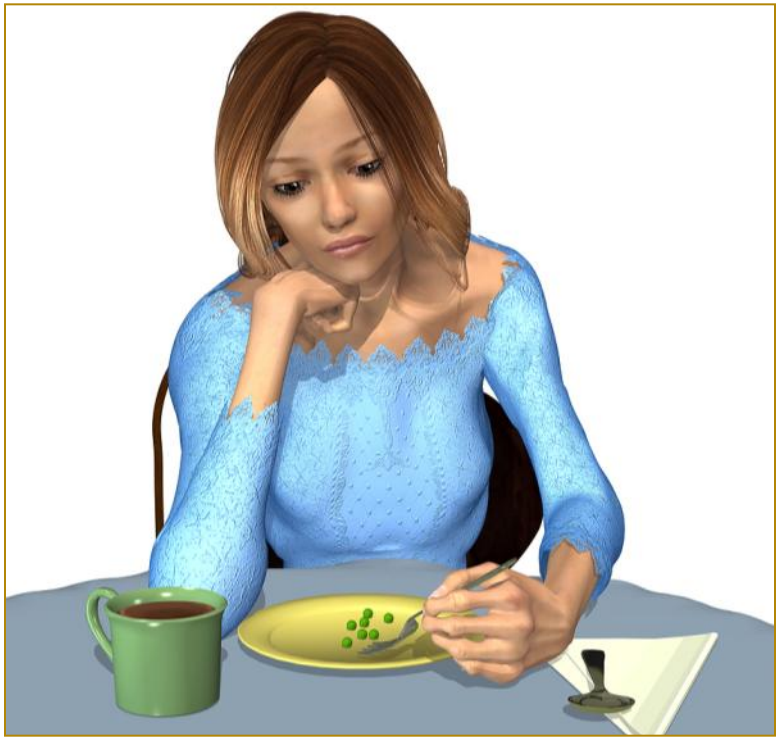
- Treat with **loperamide**
- Maintain **fluid** and **electrolyte** balance
- Introduce **dietary changes**
  - Small, frequent meals
  - Simple, plain food
  - No caffeine or alcohol
  - Dietary supplements
- **Severe diarrhea** should be managed aggressively in a **hospital**
- Moderate or severe diarrhea may require **dose reduction or treatment interruption**

Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84

What is anorexia?

Anorexia is a disorder characterized by loss of appetite

Severe anorexia can cause substantial weight loss



US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed August 2012.

Anorexia and weight loss in patients with cancer can be related to...

- The cancer itself
- Cancer treatment
- Altered metabolism
- Reduced food and drink intake
- Underlying liver disease in patients with hepatocellular cancer
  - Patients with liver disease may suffer from protein energy malnutrition – even in compensated liver disease (20–40%)

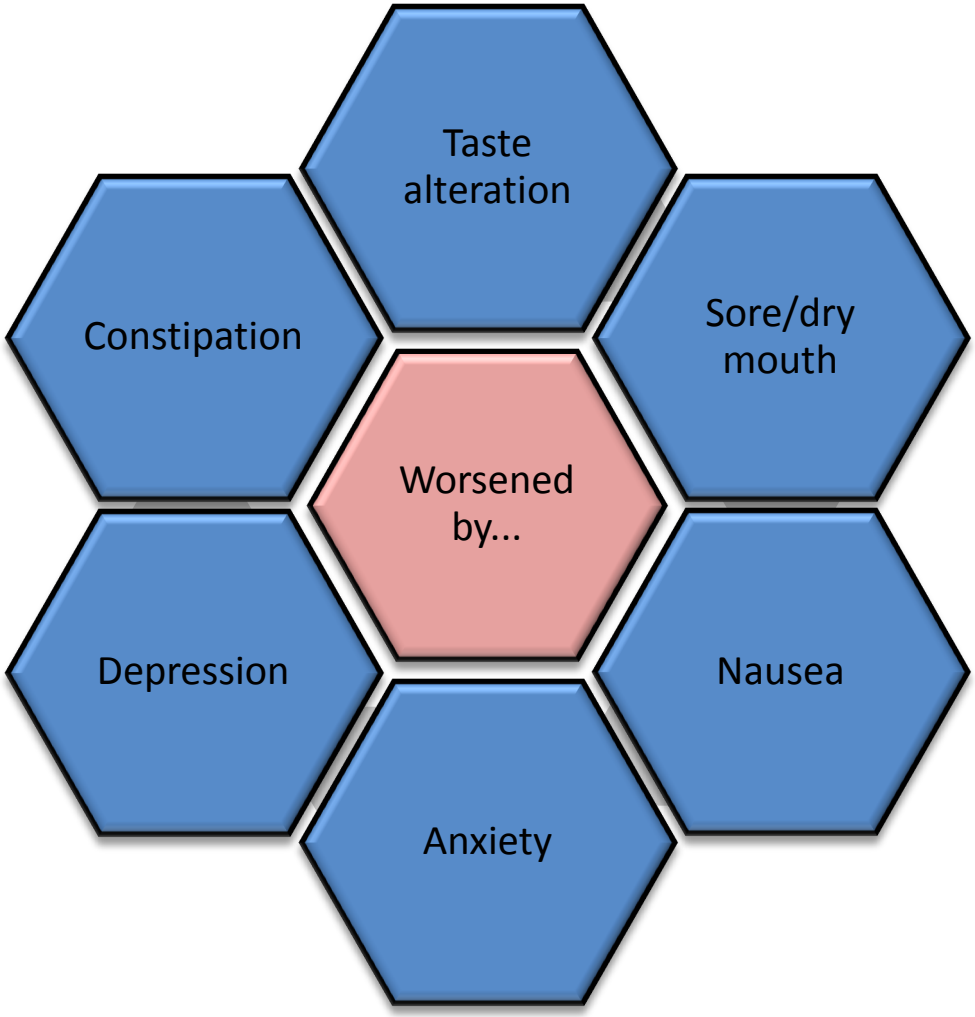
How to recognize anorexia

- Anorexia symptoms can include **weakness**, **fatigue**, **depression**, **tooth loss**, and **organ damage**

- Patients may report
  - **decreased quality of life**
  - that they are finding it **harder to perform routine, daily tasks**

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

Other side effects/cancer symptoms can make anorexia and weight loss worse



How should anorexia be explained to patients?

Anorexia is
loss of appetite

It can be improved by changing what you eat, and when you eat

Anorexia can also be treated with drugs that improve your appetite

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

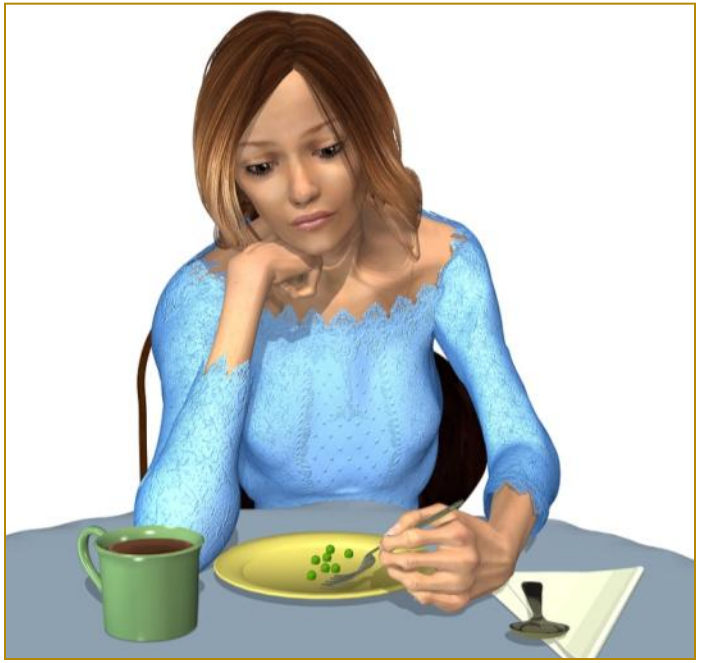
Anorexia: recommendations to patients

- Eat **small, frequent meals**[1]
- Eat **high energy** or **high protein** foods, and have snacks[1]
- Eating **pineapple** might help if anorexia is related to **taste changes**, or **lack of saliva**[2]
- Eating/drinking **peppermint** or **ginger** might help if anorexia is **related to nausea**[3]

1. National Cancer Institute. Appetite fact sheet. http://www.cancer.gov/cancertopics/coping/chemo-side-effects/appetite.pdf Accessed August 2012.
2. MacMillan Cancer Support. Carer practicalities. http://www.nhs.uk/ipgmedia/national/Macmillan%20Cancer%20Support/Assets/Carers-practicalities(MCS).pdf Accessed August 2012. 3. MacMillan Cancer Support. Controlling Nausea and Vomiting. http://www.macmillan.org.uk/Cancerinformation/Livingwithandaftercancer/Symptomssideeffects/Othersymptomssideeffects/Nauseavomiting.aspx Accessed August 2012.

Anorexia and weight loss: summary

- Anorexia and weight loss are **very common** in patients receiving targeted agents
- Anorexia can be **distressing for patients**
  - **reminder** of **illness**
  - can **reduce quality of life**
- **Appetite stimulants**, changing **diet and eating habits**, and **dose adjustments** can help manage anorexia and weight loss



Management of dermatological side effects

Hand–foot skin reaction and rash

R.EU.ONC.08.2012.0494

What is hand–foot skin reaction (HFSR)?

Group of symptoms affecting the hands and/or feet

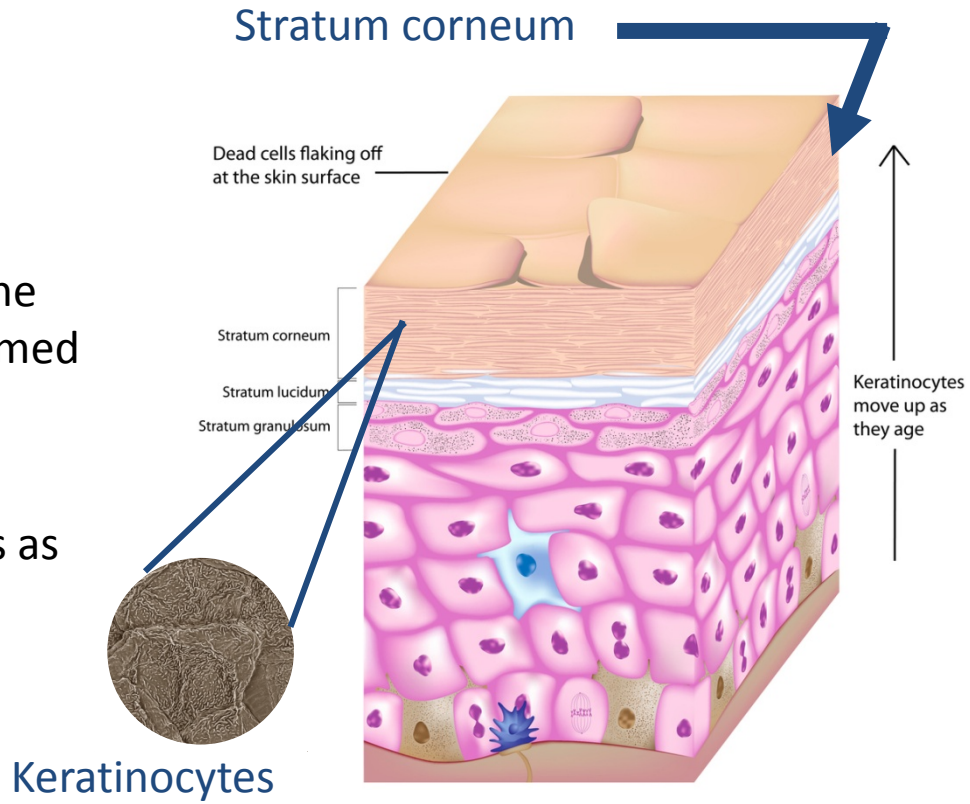
Hand–foot skin reaction can:

- cause considerable pain
- affect patient quality of life
- lead to treatment discontinuation

Lacouture ME et al. Ann Oncol 2008;19:1955–61; Autier J et al. Arch Dermatol 2008;144:886–92; Porta C et al. Clin Exp Med 2007;7:127–34.

What causes hand–foot skin reaction (HFSR)?

- Particular cells in the epidermis (called keratinocytes) become overactive
- The top layer of the epidermis, the stratum corneum, becomes inflamed and thickened (hyperkeratotic)
- Hand–foot skin reaction presents as
  - Hyperkeratosis (skin thickening)
  - Redness (erythema)
  - Blisters
  - Peeling
  - Bleeding
  - Swelling (oedema)



1. Lacouture ME et al. Ann Oncol 2008;19:1955–61; US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012.

Keratinocyte image courtesy of Thomas Deerinck, NCMIR/Science Photo Library

Hand–foot skin reaction (HFSR) and targeted agents

Hand–foot skin reaction (HFSR) with targeted agents is different from hand–foot syndrome (HFS) associated with cytotoxic chemotherapy

	Hand–foot skin reaction	Hand–foot syndrome
Generally characterized by...	...**erythema** (skin redness) and **skin thickening** (hyperkeratosis) at **pressure points** (e.g. fingers, toes, heels)	... **redness** and **swelling** that may progress to **blistering** and **ulceration**
Which agents is it seen with?	**Targeted agents**, e.g. sorafenib (Nexavar®), sunitinib (Sutent®)	**Cytotoxic agents**, e.g. capecitabine (Xeloda®), doxorubicin(Caelyx®, Myocet®), 5-FU

Lacouture ME,et al. Oncologist 2008;13:1001–11; Saif MW. Expert Opin Drug Saf 2011;10:159–69.

Hand–foot skin reaction (HFSR) rates vary between targeted agents

- Hand–foot skin reaction (HFSR) occurs most frequently in patients treated with the tyrosine kinase inhibitors sorafenib and sunitinib

	Bevacizumab (Avastin®)	Sorafenib (Nexavar®)	Sunitinib (Sutent®)	Pazopanib (Votrient®)	Temsirolimus (Torisel®)	Everolimus (Afinitor®)
HFSR frequency reported in SmPC	+	++	++	+	–	+

–, not reported or reported at a frequency of <1%; +, reported at a frequency of ≥1 to <10%; ++, reported at a frequency of ≥10% of patients in the Canadian PM.

Eisen T, et al. J Natl Cancer Inst 2012;104:93–113; . Afinitor® PM; Avastin® PM, May 2012; Nexavar® PM; Sutent® PM; Torisel® PM, Votrient® PM.

When does hand–foot skin reaction (HFSR) occur?

- Based on studies of sorafenib:
  - Hand–foot skin reaction usually appears within the **first 6 weeks** of treatment
  - Symptoms can occur all at the same time, or one after another
  - Hand–foot skin reaction tends to decrease in intensity during the course of treatment

Hutson TE et al. Eur J Cancer 2010;46:2432–40; Autier J et al. Arch Dermatol 2008;144:886–92; Lacouture ME et al. Ann Oncol 2008;19:1955–61; Porta C et al. Clin Exp Med 2007;7:127–34.

How should hand–foot skin reaction (HFSR) be explained to patients?

Common side effect of kinase inhibitors

Severe HFSR may require dose reduction or interruption

Prevention is better than cure

Needs to be treated as soon as possible

Early signs
Numbness
Tingling
'Pins and needles'

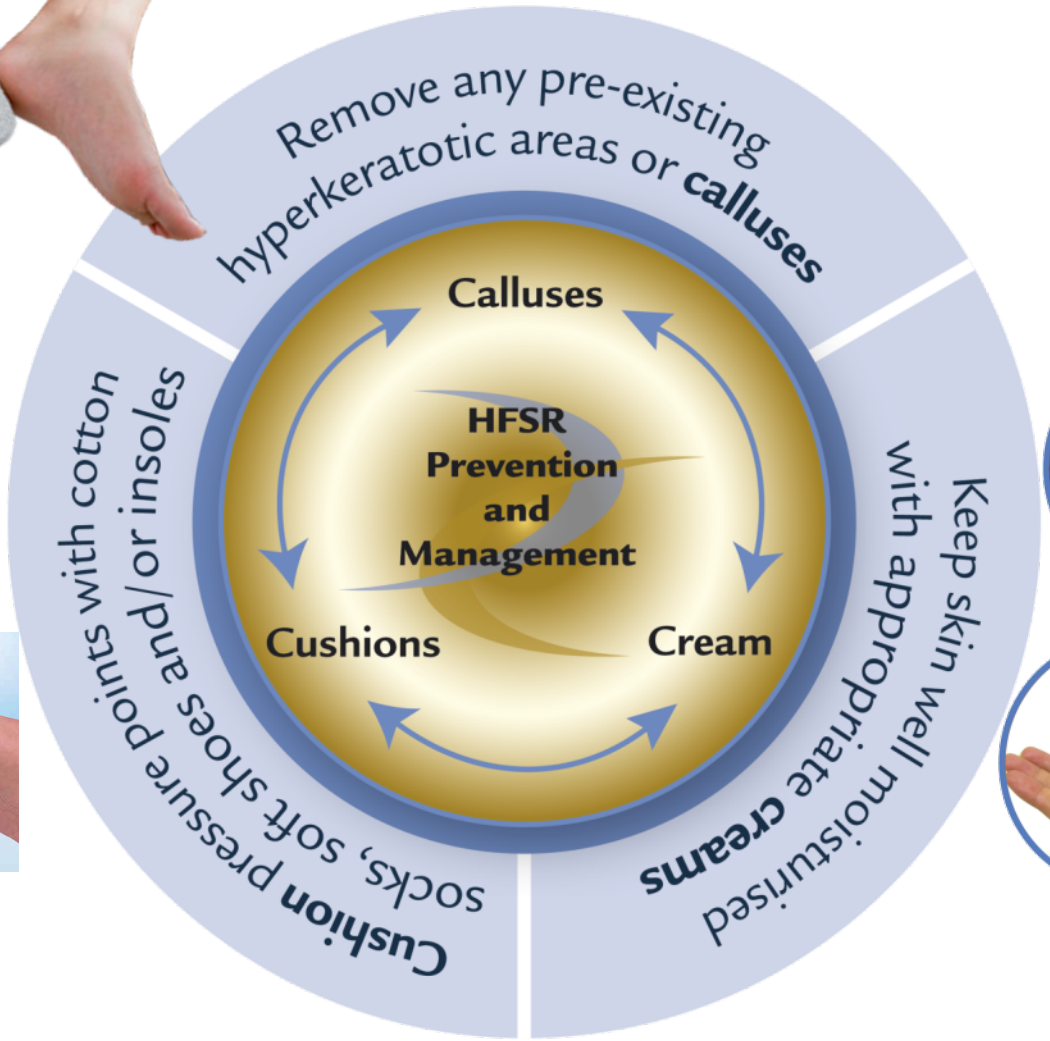
Secondary signs
Pain
Redness
Swelling

Late signs
White blisters
Severe pain
Dried skin
Cracked skin

Lacouture ME, et al. Ann Oncol 2008;19:1955–61; Autier J, et al. Arch Dermatol 2008;144:886–92; Porta C, et al. Clin Exp Med 2007;7:127–34; Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

PREVENTING HAND–FOOT SKIN REACTION (HFSR)

Preventing hand–foot skin reaction (HFSR): the three ‘Cs’



HFSR, hand–foot skin reaction.

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113. 2. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

Preventing hand–foot skin reaction (HFSR): removing calluses

- Patients will not normally consider ‘hard skin’ to be a medical condition
- Explain that the new appearance of hard skin is **a sign of a skin problem that needs to be treated** (when taking targeted agents)
- Patients should **seek help straight away**

Perform a hand/foot check-up: if there are areas of hard skin, a pedicure may be helpful

Before pedicure

After pedicure

A foot bath with Epsom salts can help soften hard skin

HFSR, hand–foot skin reaction.

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113. 2. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

Preventing hand–foot skin reaction (HFSR): using creams

Emollient (moisturising) creams

- Help stop the skin becoming dry and cracking
- Use several times daily to keep the skin soft and supple

Keratolytic creams

- Reduce the content of keratin in the skin and thus soften callouses
- Contain substances such as salicylic acid, sulphur or urea
- Use only on affected areas

In HCC patients treated with sorafenib, prophylactic urea cream three times daily:[3]

- reduced the incidence of HFSR
- delayed HFSR occurrence

HFSR, hand–foot skin reaction.

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.
2. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84. 3. Ren Z, et al. J Clin Oncol 2012;30 (suppl):Abstract 4008.

Preventing hand–foot skin reaction (HFSR): weekly monitoring

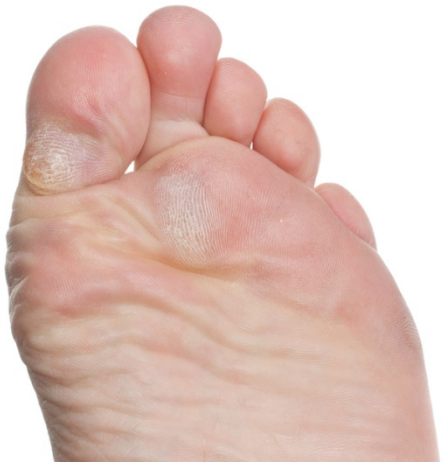
- Weekly clinic visits are useful during the first 6 weeks of therapy

This monitoring checklist is one option to help follow up the signs and symptoms of hand–foot skin reaction:

While taking an oral kinase inhibitor, patients should call their doctor or oncology nurse if they answer yes to any of the following questions:		
Is the skin on your feet red or discoloured?	❑ YES	❑ NO
Does the skin on your feet feel painful?	❑ YES	❑ NO
Do you have cracked or peeling skin on your feet?	❑ YES	❑ NO
Do you have thickened or calloused skin on your feet?	❑ YES	❑ NO
Do you feel numbness or tingling on your feet?	❑ YES	❑ NO
Do your feet feel swollen?	❑ YES	❑ NO
Is the skin on your hands/fingers red or discoloured?	❑ YES	❑ NO
Does the skin on your hands/fingers feel painful?	❑ YES	❑ NO

Recommendations to patients: report hard skin immediately

The appearance of hard skin when taking targeted agents is a sign of a skin problem that needs to be treated – seek help straight away



1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113. 2. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

Recommendations to patients: cushion the feet

Wear loose, comfy shoes when going out and slippers in the house

Avoid tight fitting clothing (socks, tights) or tight shoes that put pressure on the feet

Cushion shoes with insoles

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113. 2. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

Recommendations to patients: don't stress the skin

Take warm not hot showers; don't rub the skin

Wear cotton gloves/socks to prevent injury and keep palms/soles dry

Avoid detergents and products with alcohol (e.g. disinfectant gels)

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113. 2. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

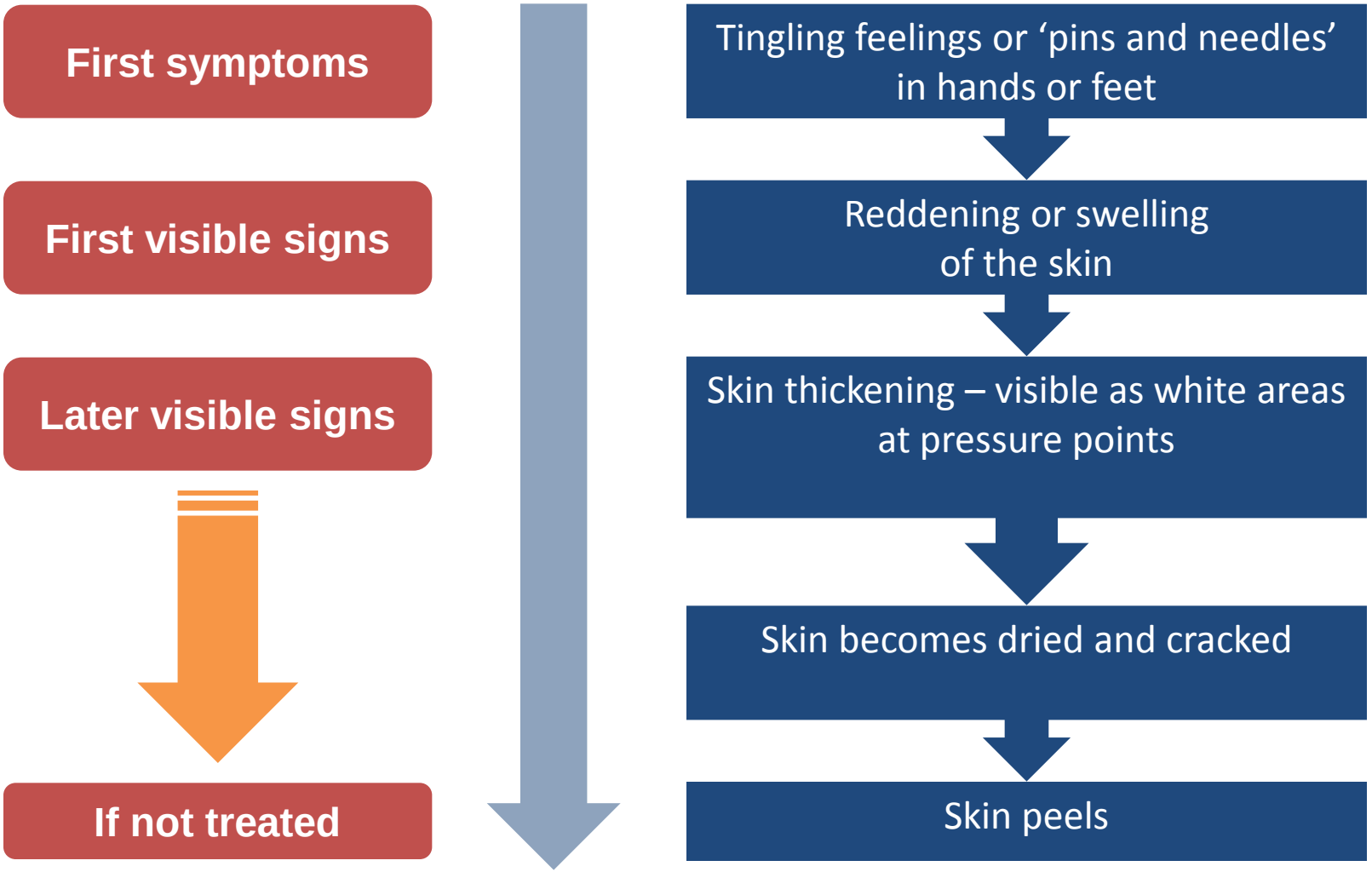
Recommendations to patients: avoid using tools that need pressure

Avoid any jobs that require repetition of pressure, e.g. chopping food or vacuuming

Avoid using tools that involve pressure, e.g. using a hammer, shovel or screwdriver

1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113. 2. Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

How to recognize hand–foot skin reaction (HFSR) in patients

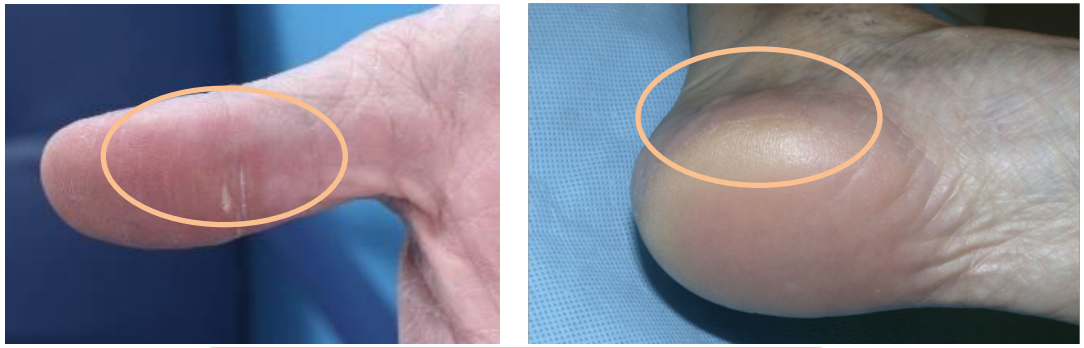


Lacouture ME et al. Ann Oncol 2008;19:1955–61; Autier J, et al. Arch Dermatol 2008;144:886–92; Porta , et al. Clin Exp Med 2007;7:127–34; Edmonds K, et al. Eur J Oncol Nurs 2012;16:172–84.

Grade 1 hand–foot skin reaction (HFSR)

Does not disrupt patient's normal activities

- Minimal skin changes or dermatitis without pain
- Does not disrupt patient's normal activities



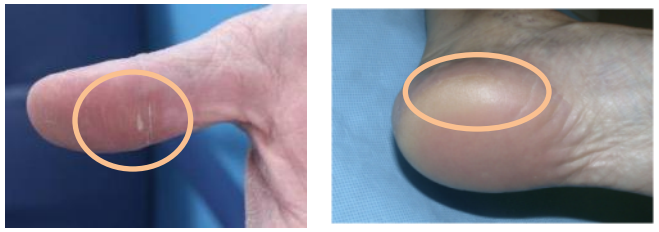
- Dysaesthesia (abnormal sensation)
- Painless swelling
- Erythema (redness)
- Discomfort

Photographs reproduced with permission from Manchen et al. J Support Oncol 2011;9:13–23. Copyright Elsevier 2011

US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012; Anderson R, et al. Oncologist 2009;14:291–302.

Treating Grade 1 hand–foot skin reaction (HFSR): general measures includes dose adjustments

Grade 1 hand–foot skin reaction



CREAMS

- Urea- or salicylic acid-containing creams may be used on hyperkeratotic areas
- Topical steroids may be used on inflamed areas[1]

FOLLOW-UP

- A 2-week follow-up in the clinic is recommended[2]
- Consider a dermatology referral for patients with unique skin presentations or those who fail to respond[3]

HFSR, hand–foot skin reaction.

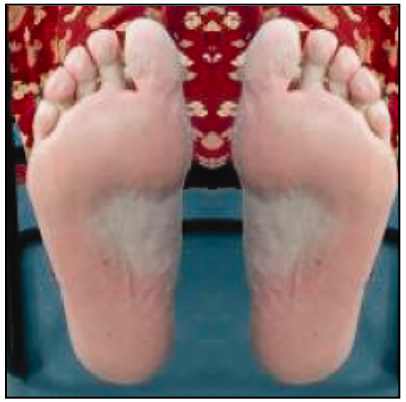
1. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113; 2. Lacouture ME, Oncologist 2008;13:1001–11; 3. Anderson R, et al. Oncologist 2009;14:291–302.

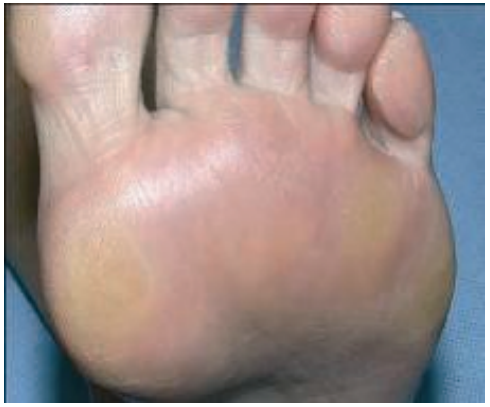
Grade 2 hand–foot skin reaction (HFSR)

Affects patient's normal activities

- Skin changes with pain
- Affects patient's normal activities (e.g. going shopping, using the telephone, preparing meals)

- Peeling
- Blisters
- Bleeding
- Oedema
- Painful erythema
- Swelling
- Hyperkeratosis (skin thickening)
- Discomfort
- Paraesthesia (numbness, tingling, 'pins and needles')

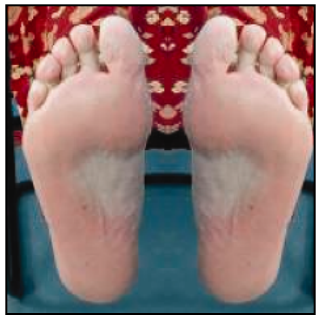




US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012; Anderson R, et al. Oncologist 2009;14:291–302.

Treating Grade 2 hand–foot skin reaction (HFSR): general measures includes dose adjustments

Grade 2 hand–foot skin reaction



CREAMS

- Apply clobetasol 0.05% ointment to erythematous areas twice daily[1]
- Use topical analgesics, including lidocaine 2%, to manage pain[1]

MEDICATION

- Consider dose reduction until symptoms subside[1–3]

FOLLOW-UP

- 1st, 2nd, 3rd occurrence: use creams and consider dose reduction[1]
- 4th occurrence: decide whether to discontinue treatment based on clinical judgment and patient preference[1]

HFSR, hand–foot skin reaction.

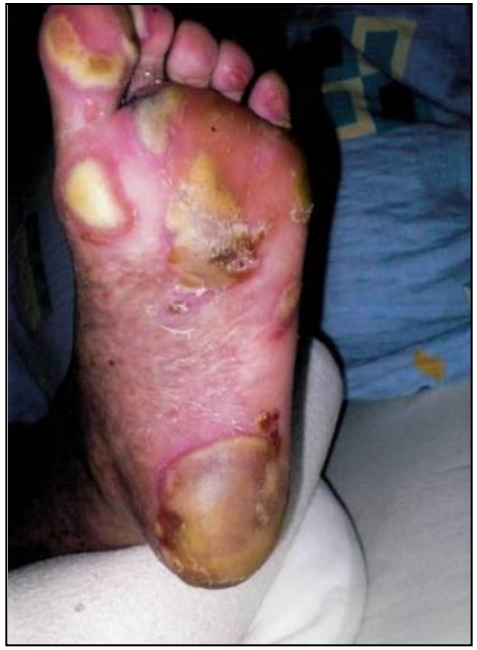
1. Lacouture ME, et al. Oncologist 2008;13:1001–11; 2. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113; 3. Anderson R, et al. Oncologist 2009;14:291–302.

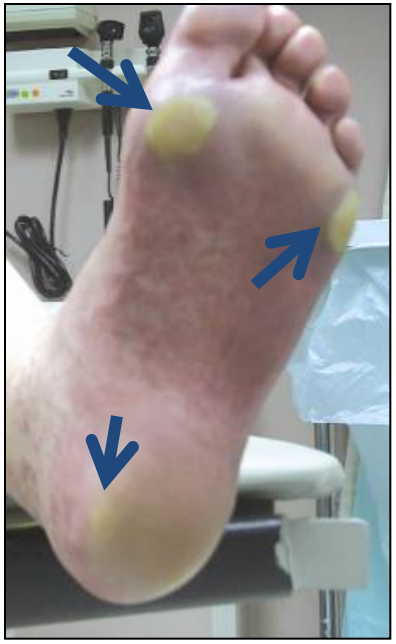
Grade 3 hand–foot skin reaction (HFSR)

Patient unable to work or perform self-care daily activities

- Severe skin changes with pain
- Patient unable to work or perform self-care daily activities (e.g. bathing, dressing and undressing, feeding self, taking medications)

- Moist desquamation (skin peeling)
- Ulceration
- Blistering
- Bleeding
- Oedema
- Hyperkeratosis
- Severe pain
- Severe discomfort
- Paraesthesia (numbness, tingling, 'pins and needles')





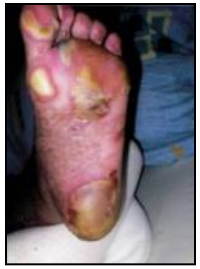
US Department of Health and Human Services. NCI-CTCAE v4.03 2010; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Last accessed July 2012; Anderson R, et al. Oncologist 2009;14:291–302.

Left photograph reproduced with permission from Dr Joerg Trojan;

Right Photographs reproduced with permission from Manchen et al. J Support Oncol 2011;9:13–23. Copyright Elsevier 2011.

Treating Grade 3 hand–foot skin reaction (HFSR): general measures include dose adjustments

Grade 3 hand–foot skin reaction



CREAMS

- Use topical therapy to relive symptoms[1,2]
- A combination of cortisone cream and topical antibiotic may be used for severe HFSR[2]

MEDICATION

- Implement dose interruption until symptoms subside[1–3]
- Systemic treatment to reduce symptoms, e.g. pyridoxine, may help[2]

FOLLOW-UP

- 1st, 2nd occurrence: creams and dose interruption. When restarting, use a lower dose[1]
- 3rd, 4th occurrence: decide whether to discontinue treatment based on clinical judgment and patient preference[1]

HFSR, hand–foot skin reaction.

1. Lacouture ME, et al. Oncologist 2008;13:1001–11;
2. Anderson R, et al. Oncologist 2009;14:291–302; 3. Eisen T, et al. J Natl Cancer Inst 2012;104:93–113;

Hand–foot skin reaction (HFSR): summary

- **Hand–foot skin reaction prevention is possible**
  - Preventative measures are a necessary part of sorafenib treatment in particular

- Hand–foot skin reaction may be a nuisance to the patient but it is **not life-threatening**

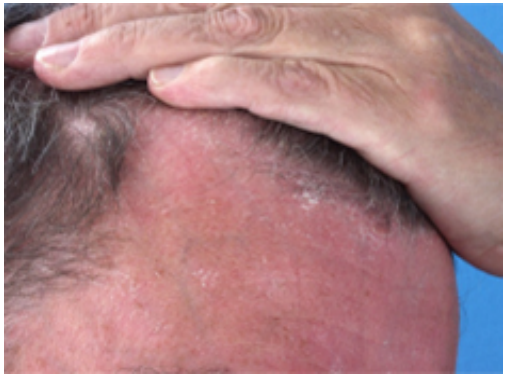
- The goal is to **keep patients on treatment** – at the standard dose, if possible – so that they can **obtain the maximum benefits** of treatment

What types of rash are associated with targeted agents?

- Rash associated with targeted agents may present differently in different patients

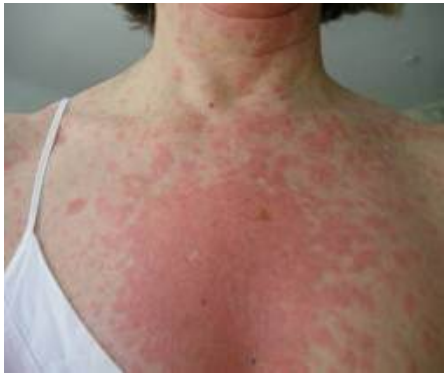
Facial rash*

Tingling or burning of scalp

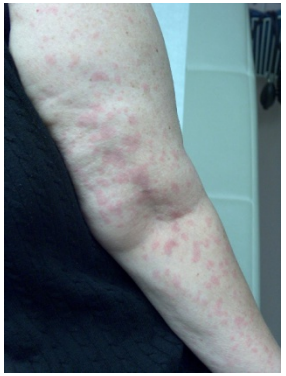


Maculopapular rash†

May be pruritic (itchy)



Body rash‡



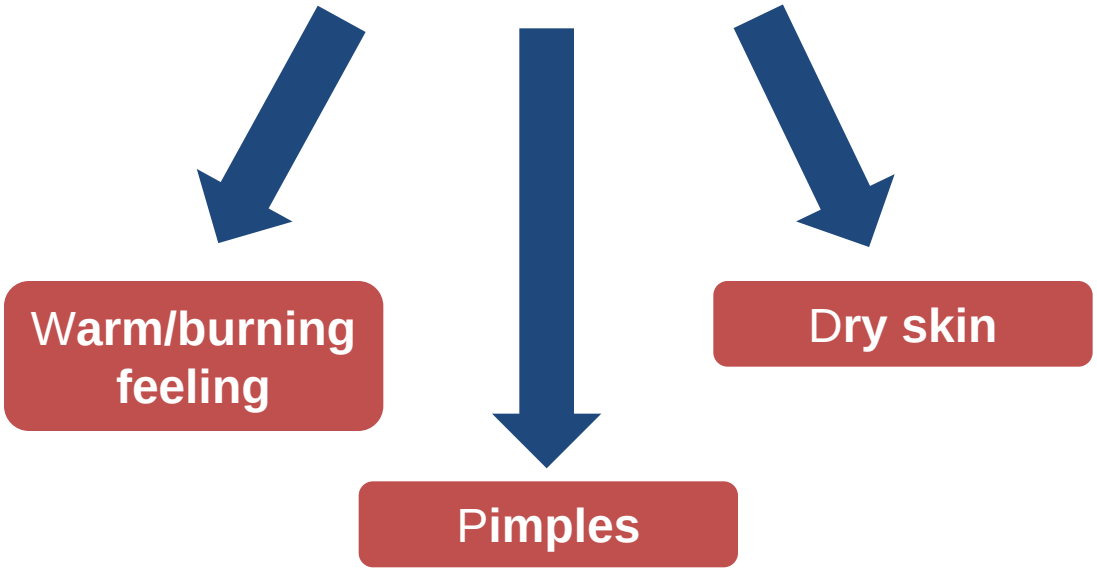
*Reproduced with permission from C. Robert - Dermatology - IGR Villejuif;
†Reproduced with permission from MA Healthcare Ltd, from Edmonds K, Spencer-Shaw A. BJN 2010:19;58–60; ‡Reproduced with permission from Elizabeth Manchen, RN, MS, OCN.

Espers P, et al. Clin J Oncol Nurs 2007;11:659–66;
Kirkali Z. BJU Int 2011;107:1722–32;
Wood LS. Community Oncol 2006;3:558–62.

How to recognize rash in patients

- Have **regular contact** with the patient, particularly **during the first few weeks** of treatment

- Look out for the **first signs of rash**



Espers P, et al. Clin J Oncol Nurs 2007;11:659–66; Kirkali Z. BJU Int 2011;107:1722–32;
Wood LS. Community Oncol 2006;3:558–62; Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

How should rash be explained to patients?

- Rash can be **common** but it is **manageable**
- Usually **mild** and **reversible**
- Patients can take steps to **reduce discomfort** and **avoid making the symptoms worse**
- Discuss the **signs and symptoms** of rash with patients
- Encourage patients to **care for their skin**

Espers P, et al. Clin J Oncol Nurs 2007;11:659–66; Kirkali Z. BJU Int 2011;107:1722–32;
Wood LS. Community Oncol 2006;3:558–62; Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

Rash: recommendations to patients

Avoid hot showers

Use mild soaps and laundry detergents

Use moisturising cream on skin

Wear loose clothing

Rash

Use anti-dandruff shampoo to relieve scalp discomfort

Avoid direct sunlight

Wear high SPF sun cream

Use anti-dandruff shampoo as a body was to relieve itching

Espers P, et al. Clin J Oncol Nurs 2007;11:659–66; Kirkali Z. BJU Int 2011;107:1722–32;
Wood LS. Community Oncol 2006;3:558–62; Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

How to manage rash symptoms

- Use **topical hydrating creams**

- Consider **antihistamine** treatment to relieve pruritus (itching)

- **Supportive measures**, such as loose clothing, may also help relieve symptoms

- Rarely, **dose modification** may be required

Espers P, et al. Clin J Oncol Nurs 2007;11:659–66; Kirkali Z. BJU Int 2011;107:1722–32;
Wood LS. Community Oncol 2006;3:558–62; Eisen T, et al. J Natl Cancer Inst 2012;104:93–113.

Rash: summary

- Rash is a **common side effect** with targeted agents – usually **mild** and **reversible**
- **Topical hydrating creams** and supportive measures e.g. loose clothing, may help alleviate symptoms
- Itching may be relieved by **antihistamine** treatment
- Dose reduction or interruption is **rarely required**

Case

Case

- Mr. G is a 67 year old patient who was started on Sunitinib for metastatic pancreatic neuroendocrine cancer
- 3 weeks later he called his nurse to say he was feeling fatigue, SOB and had mild bilateral leg swelling, mild headache
  - Sent to emergency at a peripheral hospital
- CT scan was negative for PE, Dopplers negative for DVT

Case cont.

- Blood pressure was 172/98.
- Mild CHF, cardiac workup negative.
- Started Amlodipine 5 mg daily
- Restarted his Sunitinib the next day, called his nurse to give up date
- After speaking to oncologist decision was to hold off on restarting Sunitinib until BP under control
- Able to safely restart on full dose two weeks later

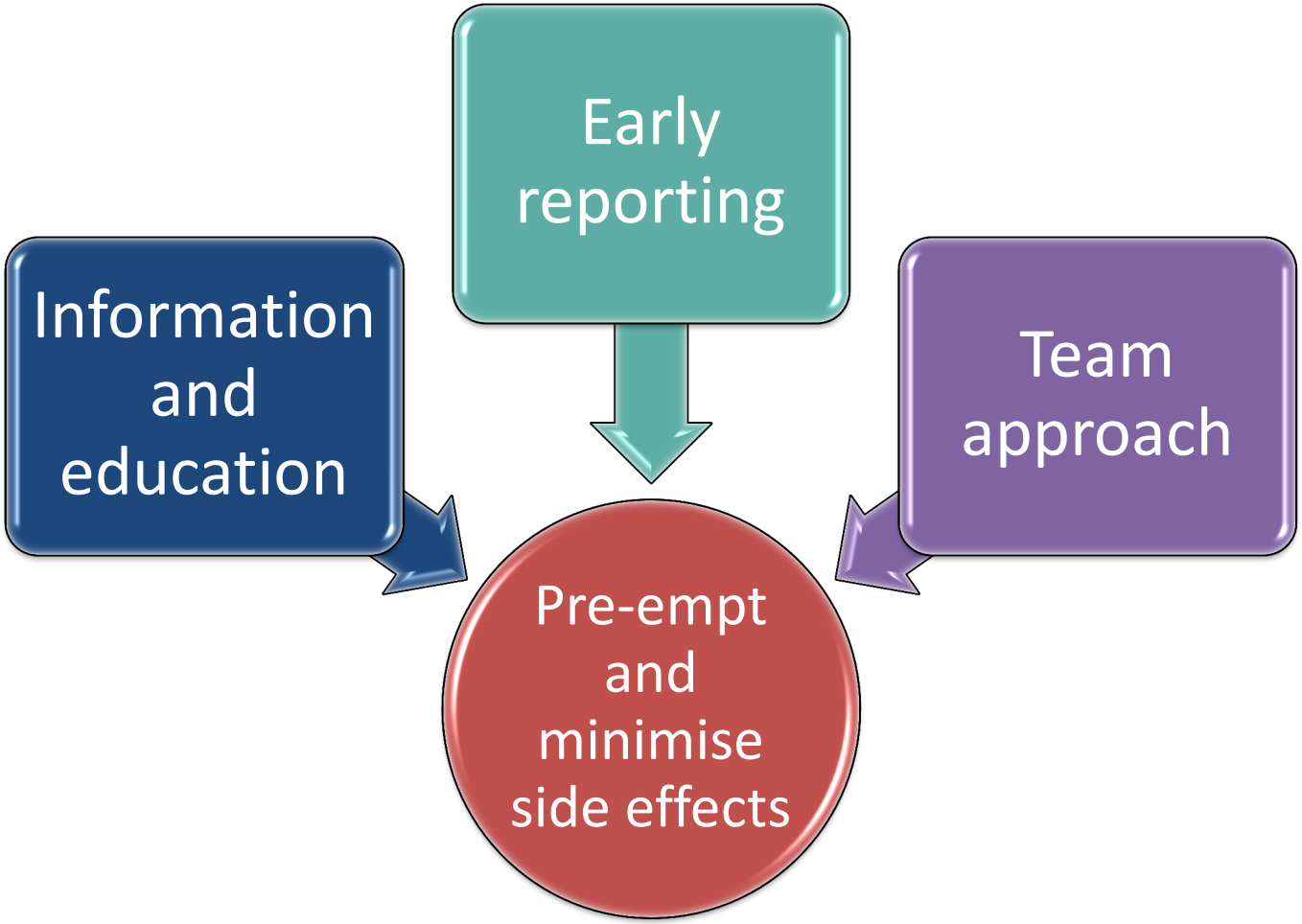
Case

- Mrs. S is a 52 year old lady on Sorafenib for advanced hepatocellular carcinoma
- She is seen in clinic for severe Grade 3 hand-foot skin reaction
- She failed to report the early signs that started three weeks earlier
- “I was scared the dose would be reduced”
- She needed to come of drug for four weeks and restart with a dose reduction

Conclusions

- Targeted agents aim to inhibit proliferation, angiogenesis or induce apoptosis of cancer cells
- Have common side effects including fatigue, anorexia, diarrhea, hypertension, and skin reactions
- Nurses play a key role in preventing and managing side effects allowing patients to continue on active treatment

Conclusions




© Photos8.com

Thanks

Questions