Side effects of molecular-targeted therapies in solid cancers: a new challenge in cancer therapy management

Ahmad Awada, MD, PhD
Medical Oncology Clinic
Institut Jules Bordet
Université Libre de Bruxelles (U.L.B.)
Brussels, Belgium
1. Concept
2. Achievements on the management of side effects
3. Remaining challenges
4. New challenges with the development of molecular-targeted therapies
5. Conclusions
SUPPORTIVE CARE = Reducing the cancer-related problems and the side effects of the medicine administered to treat the disease
# SIDE EFFECTS OF CANCER THERAPY: ACHIEVEMENTS

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Preventive &amp; Therapeutic intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>• G-CSF, Anti-infectives</td>
</tr>
<tr>
<td>Anemia</td>
<td>• Epoetine</td>
</tr>
<tr>
<td>Mucositis</td>
<td>• Laser therapy, Palifermin</td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>• 5-HT3 and neurokin-1-receptor antagonists</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>• LMW Heparin</td>
</tr>
<tr>
<td>Cardiomyopathy (anthracyclines)</td>
<td>• Liposomal formulations, Dexrazonane</td>
</tr>
</tbody>
</table>

- **Febrile neutropenia**
- **Anemia**
- **Mucositis**
- **Nausea & Vomiting**
- **Thromboembolic events**
- **Cardiomyopathy (anthracyclines)**
MANAGEMENT OF SIDE EFFECTS: REMAINING CHALLENGES

• Alopecia

• Thrombocytopenia (Promising Thrombopoietin-mimetics are under investigation)

• Asthenia
# MOLECULAR TARGETS AND THERAPIES (1)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism of action</th>
<th>Main tumor indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib*</td>
<td>Small molecule</td>
<td>TK inhibitor of EGFR</td>
<td>NSCLC</td>
</tr>
<tr>
<td>(Iressa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib*</td>
<td>Small molecule</td>
<td>TK inhibitor of EGFR</td>
<td>NSCLC</td>
</tr>
<tr>
<td>(Tarceva)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab*</td>
<td>Monoclonal Antibody</td>
<td>Blocks EGFR</td>
<td>Colorectal, Head &amp; Neck, NSCLC</td>
</tr>
<tr>
<td>(Erbitux)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panitumumab*</td>
<td>Monoclonal Antibody</td>
<td>Blocks EGFR</td>
<td>Colorectal</td>
</tr>
<tr>
<td>(Vectibix)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Investigational in BC

TK : tyrosine kinase; EGFR : epidermal growth factor receptor
## MOLECULAR TARGETS AND THERAPIES (2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism of action</th>
<th>Main tumor indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Monoclonal Antibody</td>
<td>Blocks HER2</td>
<td>Breast (HER2+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastric (HER2+)</td>
</tr>
<tr>
<td>Lapatinib (Tykerb)</td>
<td>Small molecule</td>
<td>Reversible inhibition of EGFR and HER2</td>
<td>Breast (HER2+)</td>
</tr>
<tr>
<td>Neratinib</td>
<td>Small molecule</td>
<td>Irreversible inhibition of HER family</td>
<td>Breast* (HER2+)</td>
</tr>
<tr>
<td>TDM-1</td>
<td>Trastuzumab linked to anti-tubulin (mytansin)</td>
<td>Targeted chemotherapy!</td>
<td>Breast* (HER2+)</td>
</tr>
</tbody>
</table>

* Investigational

TK : tyrosine kinase; EGFR : epidermal growth factor receptor
<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism of action</th>
<th>Main tumor indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Monoclonal Antibody</td>
<td>Blocks VEGF</td>
<td>Colorectal, Breast, NSCLC, Renal</td>
</tr>
<tr>
<td>(Avastin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Small molecule multitargeted TK inhibitor</td>
<td>Inhibition of VEGFR, PDGFR and RAF</td>
<td>Renal, HCC, Breast*</td>
</tr>
<tr>
<td>(Nexavar)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Small molecule multitargeted TK inhibitor</td>
<td>Inhibition of VEGFR, PDGFR, and C-Kit</td>
<td>GIST, Renal</td>
</tr>
<tr>
<td>(Sutent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Small molecule</td>
<td>mTor inhibitor</td>
<td>Renal</td>
</tr>
<tr>
<td>(Torisel)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>Small molecule</td>
<td>mTor inhibitor</td>
<td>Renal, Breast*, neuroendocrine</td>
</tr>
<tr>
<td>(Afinitor)</td>
<td></td>
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</tr>
</tbody>
</table>

VEGF (R) : vascular endothelial growth factor (receptor)
PDGFR: platelet derived growth factor receptor

* Investigational
Molecular-targeted therapy: A New Approach in cancer therapy

- Requires oncologists to:
  - individualize treatment (e.g., HER2 amplification, K-Ras and EGFR mutations)
  - recognise expected and unexpected side effects
  - prevent and manage these side effects
« I stopped taking the medicine because I prefer the disease to the side effects of therapy »
<table>
<thead>
<tr>
<th>Side effects</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI, skin</td>
<td>Anti-EGFR; Multi-targeted kinases</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Gefitinib, mTor inhibitors</td>
</tr>
<tr>
<td>Hypomagnesemia, hypocalcemia</td>
<td>Monoclonal Antibody Anti-EGFR</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>Trastuzumab, multi TKI, others</td>
</tr>
<tr>
<td>Bleeding, thrombosis, perforation, HTA</td>
<td>Anti-VEGF(R)</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Motesanib</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Bevacizumab, multi TKI</td>
</tr>
<tr>
<td>Reversible posterior Leukoencephalopathy syndrom</td>
<td>Bevacizumab, multi TKI</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Sunitinib (Sorafenib)</td>
</tr>
<tr>
<td>Auto-immune disorders</td>
<td>Anti-CTLA-4 monoclonal antibodies</td>
</tr>
<tr>
<td>Hematological</td>
<td>Sunitinib, mTor inhibitors</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>IGFR Inhibitors (glucose), mTor inhibitors (glucose, lipid)</td>
</tr>
</tbody>
</table>
Many patients have comorbidities that may complicate targeted therapy optimization

<table>
<thead>
<tr>
<th>Comorbidity/health status</th>
<th>Potential impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-/post-surgery</td>
<td>Susceptibility to wound healing or bleeding</td>
</tr>
<tr>
<td>Hypertension</td>
<td>May compromise kidney function (mainly in nephrectomized patients)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Increased susceptibility to related side effects</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Alteration in blood glucose or cholesterol control</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Underlying conditions</td>
</tr>
<tr>
<td></td>
<td>Increased susceptibility to related side effects</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Possible link with fatigue</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Altered drug metabolism and clearance</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Altered drug metabolism and clearance</td>
</tr>
</tbody>
</table>

TARGETED THERAPIES:
CUTANEOUS TOXICITY
SKIN TOXICITY OF ANTI-EGFR: RASH AND ACNEIFORM ERUPTION

(A) papular lesions on the chest
(B) papulopustular eruption on the back
(C) follicular pustules
(D) confluent pustules on the nose

e.g., Lapatinib, erlotinib, gefitinib
Sorafenib and Sunitinib: skin toxicity (1)

- Maculopapular rash in back and extremities
- Thrombocytopenic Purpura
- Rash
Sorafenib and Sunitinib: skin toxicity (2)

- **Acral erythema (hand and foot syndrome):** Painful symmetric erythematous and oedematous areas on the palms and soles.
- Generally arises after 2-4 weeks of treatment.
- Is dose dependent.

- **Sunitinib skin toxicity** consisted of:
  - (A) Painful periungual erythema,
  - (B) Bullous lesions on the fingers,
  - (C) Plantar areas with erythema.
  - (D) Intraepidermal cleavage, on microscopic examination.
Nail toxicity of MKIs

- Include pain, fissuring and paronychial inflammation

- Soaks and cushioning provide the greatest symptomatic relief. Topical steroids are recommended

MKIs: multi-targeted kinase inhibitors
Subungual hemorrhages of MKIs

**Mechanism hypothesis**

VEGF(R) may be involved in the renewal of capillaries that sustain frequent microinjuries at the fingers. Blocking these receptors might prevent the repair of “traumatized” nail bed capillaries

(with Sorafenib or Sunitinib)

MKIs: multi-targeted kinase inhibitors
Modification of hair and skin pigmentation

- Sunitinib-induced hair depigmentation. In patients with (A) no gray hair before treatment; (B) facial hair; (C) eyelashes; (D) hair will progressively grow discolored under exposure to sunitinib; and (E) hair discoloration was reversible during the washout period.
Suggested Interventions (supportives measures, dose reduction or interruption) for Skin Toxicity: The example of Sorafenib

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMPTLY institute supportive measures</td>
<td>Topical therapy for symptomatic relief</td>
<td>Interrupt Nexavar treatment for a minimum of 7 days and until toxicity has resolved to Grade 0–1</td>
</tr>
</tbody>
</table>

- **Grade 1**: Continue Nexavar Treatment

- **Grade 2**: Consider a Nexavar dose decrease to 400mg QD for 7-28 days
  - If symptoms resolve, increase to full Nexavar dose
  - If symptoms persist, interrupt treatment for a minimum of 7 days and until toxicity resolves to Grade 0-1
  - Resume Nexavar at reduced dose of 400mg QD

- **Grade 3**: When resuming, decrease by one dose level
  - If toxicity maintained at Grade 0–1 for 7-28 days, increase by one dose level
TARGETED THERAPIES: GASTROINTESTINAL TOXICITIES
GASTROINTESTINAL SIDE EFFECTS

- Commonly seen with targeted drugs
- Nausea, vomiting, diarrhea, mucositis, gastritis, dysguesea, dysphagia, abdominal pain, gastrointestinal bleeding, perforation...
MUCOSITIS
Laser therapy: the optic fiber illuminates the lesion at a distance of 10 mm.

(A protection of the patient’s (and operator’s) eyes by sunglasses)

Athermic laser: Effective in the prevention and treatment of mucositis induced by systemic treatment and radiation.
Athermic laser: Therapeutic effect in 2 patients suffering from mucositis

Mucositis of the tongue

Grade II mucositis prior to laser

On day 6 after onset of laser therapy on every other day: no more lesions!

Mucositis of the inferior lip

Grade III mucositis prior to laser

Grade I mucositis on day 5 after onset of laser on every other day
Interstitial lung disease (ILD) : a complication of anti-EGFR and anti-mTor therapy

A 70-year-old male with stage IIIIB adenocarcinoma who had been treated with platinum-based chemotherapy was started on gefitinib, and developed a severe cough and mild dyspnea on day 30. The chest radiography showed areas of consolidation on the upper and lower field of the right lung (a), and multifocal areas of airspace consolidation were seen on the thin-section CT scan (b)
## CARDIAC DYSFUNCTION INCIDENCE WITH TARGETED AGENTS

<table>
<thead>
<tr>
<th>Targeted agents</th>
<th>Cardiac Dysfunction</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>3-18 %</td>
<td>up to 4 %</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>10 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>3 %</td>
<td></td>
</tr>
<tr>
<td>Sunitinib (sorafenib)</td>
<td>8-15 %</td>
<td>up to 10 %</td>
</tr>
<tr>
<td>Imatinib</td>
<td>2 %</td>
<td>1 %</td>
</tr>
</tbody>
</table>
Trastuzumab: cardiac dysfunction

- Her2 (ErbB2) & ErbB4 protect cardiomyocytes from apoptosis

- By blocking Her2, Trastuzumab produce cardiomyopathy characterized by:
  - decreases in LVEF
  - symptoms of CHF
Hypertension (HT)

- One of the most common AEs associated with Bevacizumab and MKIs!
- Impaired angiogenesis contribute to the development of HT
  - anti-angiogenic agents (e.g., sorafenib and sunitinib) may decrease vascular surface area and increase peripheral vascular resistance
- Sunitinib: blood pressure levels tend to normalise during 2-week treatment breaks and increases upon reinitiation of treatment
- Patients require antihypertensive medication and patients with pre-existing HT may need to adapt their antihypertensive therapy

TARGETED THERAPIES:
OTHER TOXICITIES
The most common side effect of multi TKI (62%) occur independently of endocrine dysfunction (e.g. hypothyroidism). Management restricted to dose reduction/interruption.
RENNAL TOXICITIES

- Proteinuria occurs in the range of 10-50% with bevacizumab (only 3% ≥ grade 3)

- A more serious form has been recently described: thrombotic microangiopathy
BEVACIZUMBA-INDUCED RENAL THROMBOTIC MICROANGIOPATHY

Figure 3. Hypothetical Model of Disruption of VEGF Signaling in Renal Thrombotic Microangiopathy.

The loss of function of vascular endothelial growth factor (VEGF) through genetic deletion (VEGF KO), pharmacologic inhibition, or an elevated level of circulating soluble fms-like tyrosine kinase 1 (sFlt-1) that binds VEGF is associated with damage to the glomerular endothelium characterized by swelling and thrombotic microangiopathy. VEGFR-2 denotes kinase insert domain receptor.
THYROID DYSFUNCTION

- Mainly hypothyroidism

- Associated with VEGF(R) TKI
  (sunitinib (20-85 %) > sorafinib (15-20%))

- Suggested mechanisms:
  - Drug induced atrophy of thyroid through inhibition of gland vascularity
  - VEGFR TKI inhibit thyroid peroxidase
  - Inhibition of RET ??

Wong E et al; Thyroid, 2007
• Increase in lipid and glucose

• Mainly with mTOR and IGFR inhibitors

• Should be checked at baseline and during treatment (lipid profile, HbA1c, serum glucose level)

• Treat accordingly

• Particular importance on the adjuvant setting!
REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME OF BEVACIZUMAB (MTKIs)

- Characterized by: headache, seizures, impaired vision, acute hypertension, and typical MRI findings
- Is a brain-capillary leak syndrome (induced by vasospasm + hypertension)
- Also described with some chemotherapeutic and immunosuppressive agents (e.g., Cyclosporine, tacrolimus, cisplatin, ...)
Magnetic resonance imaging obtained immediately after the onset of symptoms: confluent hyperintense T2 signal involving subcortical white matter of the occipital lobes.
Blocking cytotoxic T lymphocyte–associated antigen 4 (CTLA-4): a promising approach in melanoma
Autoantibodies or clinical manifestations of autoimmunity is associated with improvements in relapse-free survival and overall survival in patients with melanoma.

Haematological toxicities

- Haematological toxicities associated with MKIs include thrombocytopenia, neutropenia and anemia\textsuperscript{1,2}

- **Management of thrombocytopenia**
  - monitor platelet counts and look for signs of bleeding
  - direct pressure or nasal packing for epistaxis
  - avoid trauma to skin or mucous membrane

- **Management of neutropenia**
  - monitor WBC count, especially neutrophils
  - patients should report temperature elevation to ≥38°C and other signs of infection
  - avoid crowded areas and exposure to infection

- **Management of anaemia**
  - patients may report dizziness, shortness of breath and fatigue
  - prescribe iron supplements and RBC transfusions if required
Conclusions (1)

- Clinical trials and clinical practice have identified several side effects (SE) associated with molecular-targeted therapies.

- Overall, these SEs differ from those associated with chemotherapy and are mainly mechanism-based.

- Most SEs related to targeted therapies are predictable and manageable but unexpected SE could arise.

- Preventive measures for selected SE can be taken to avoid dose reduction or treatment interruption.
The treatment of side effects induced by targeted agents is often empirical.

Prompt recognition of treatment-related SEs and appropriate treatment will increase the likelihood that patients are maintained on therapy.

Good communication is vital between patients, clinicians including expert consultations, and nurses.
REMEMBER:

TO BE

AVOided!

«I stopped taking the medicine because I prefer the disease to the side effects of therapy»
THANK YOU