Prognostic and Predictive Factors in Oncology

Mustafa Benekli, M.D.
**predictive factor** (preh-DYE-tiv FAK-tor)
A condition or finding that can be used to help predict whether a person's cancer will respond to a specific treatment. Predictive factor may also describe something that increases a person's risk of developing a condition or disease.
Prognostic factor: NCI Definition

- A situation or condition, or a characteristic of a patient, that can be used to estimate the chance of recovery from a disease or the chance of the disease recurring (coming back).
Predictive factor: NCI Definition

- A condition or finding that can be used to help predict whether a person’s cancer will respond to a specific treatment.
- Predictive factor may also describe something that increases a person’s risk of developing a condition or disease.
More Definitions...

- **Prognostic marker** - characteristic associated with prognosis or outcome, usually in terms of relative hazard of failure

- **Predictive marker** - characteristic that is associated with, and predicts, treatment response

James J. Dignam, PhD; The University of Chicago
More Definitions…

• A predictive marker is a prognostic marker that…
  – Exerts prognostic influence differentially according to treatment
  – Offers the opportunity for prospective intervention
  – May lend insight about biological aspects of the disease
More Definitions…

• **Prognostic factor** - capable of providing information on clinical outcome at the time of diagnosis, independent of therapy.
  – Such markers are usually indicators of growth, invasion, and metastatic potential.

• **Predictive factor** - capable of providing information on the likelihood of response to a given therapeutic modality.
  – Such markers are either within the target of the treatment or serve as modulators or epiphenomena related to expression and/or function of the target.

Daniel F. Hayes, MD
More Definitions…

• A **prognostic factor** may be defined as a measurable variable that correlates with the natural history of the disease.

• In contrast, a **predictive factor** is one that is associated with response to a given therapy.

Kyle T. Bradley, MD, MS
More Definitions…

• Prognostic biomarkers
  – Measured before treatment to indicate long-term outcome for patients untreated or receiving standard treatment

• Predictive biomarkers
  – Measured before treatment to identify who will benefit from a particular treatment

Richard Simon, D.Sc.
More definitions…

- **Prognostic factors** are patient and tumor factors that predict patient outcome (usually survival) and are independent of treatment.
- **Predictive factors** are clinical, cellular, and molecular markers that predict response of the tumor to treatment (either in terms of tumor shrinkage or a survival benefit from treatment).
- Prognostic factors define the effects of tumor characteristics on the patient, whereas predictive factors define the effect of treatment on the tumor.

Frances A. Shepherd, 2006
More definitions…

• A **prognostic biomarker** provides information about the patients’ overall cancer outcome, regardless of therapy.

• The presence or the absence of such a prognostic marker can be useful for the selection of patients for a certain treatment, but does not predict the response to this treatment.

CNAM Oldenhuis, 2008
More definitions…

• A biomarker with predictive value gives information on the effect of a therapeutic intervention in a patient.

• A predictive biomarker can also be a target for therapy.

CNAM Oldenhuis, 2008
Prognostic biomarkers

- Prognostic biomarkers can be separated in two groups:
  - biomarkers that give information on recurrence in patients who receive curative treatment and
  - biomarkers that correlate with the duration of (progression free) survival in patients with metastatic disease.
NIH definition of a clinical useful prognostic marker...

- NIH Consensus: A clinical useful prognostic marker must be
  - a proven independent, significant factor, that is easy to determine and interpret and has therapeutic consequences

NIH Consensus: A clinical useful prognostic marker must …

- Provide significant and independent prognostic value, validated by clinical testing
- Determination must be feasible, reproducible and widely available, with quality control
- Results should be readily interpretable by the clinician
- Measurement of the marker must not consume tissue needed for other tests, particularly routine histopathologic evaluation

### Table 1 – Biomarkers of interest: an overview of prognostic and predictive value

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Tumour type</th>
<th>Prognostic value</th>
<th>Predictive value</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LOE</td>
<td>LOE</td>
<td></td>
</tr>
<tr>
<td>ER/PR</td>
<td>BRCA</td>
<td>Yes, subgroup</td>
<td>Yes</td>
<td>Endocrine therapy</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>BRCA</td>
<td>Yes, subgroup</td>
<td>Yes</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>c-KIT</td>
<td>GIST</td>
<td>Yes, subgroup</td>
<td>Yes, subgroup</td>
<td>Imatinib</td>
</tr>
<tr>
<td>EGFR1</td>
<td>NSCLC</td>
<td>No</td>
<td>Yes, subgroup</td>
<td>Gefitinib, erlotinib</td>
</tr>
<tr>
<td>Mutated K-ras</td>
<td>NSCLC</td>
<td>Yes</td>
<td>Yes</td>
<td>Gefitinib, erlotinib</td>
</tr>
<tr>
<td>TRAIL receptors</td>
<td>CRC</td>
<td>Yes</td>
<td>Yes</td>
<td>Cetuximab, panitumumab</td>
</tr>
<tr>
<td>VEGF</td>
<td>RCC</td>
<td>Yes</td>
<td>No</td>
<td>Angiogenesis inhibitors</td>
</tr>
</tbody>
</table>

LOE: level of evidence; ER: oestrogen receptor; PR: progesterone receptor; BRCA: breast cancer; GIST: gastrointestinal stromal tumours; EGFR1: epidermal growth factor receptor 1; NSCLC: non-small cell lung cancer; CRC: colorectal cancer; TRAIL: tumour necrosis factor (TNF)-related apoptosis-inducing ligand; NK: not known; VEGF: vascular endothelial growth factor; RCC: renal cell carcinoma.

- a c-KIT exon 11 mutation.
- b c-KIT exon 9 mutation.
- c EGFR1 exon 18, 19 or 21 mutation.
Breast cancer prognostic factors

- Axillary lymph node status
- Tumor size
- Lymphatic/vascular invasion
- Histologic grade
- Histologic subtype
- ER / PR status
- Her2/neu gene amplification and/or overexpression
- Patient’s age
- Response to neoadjuvant therapy
Other potential breast cancer predictive / prognostic factors

- S-phase fraction – low is the better
- Gene expression profile
- uPA/PAI-1 overexpression
- Cathepsin D level
- Bone marrow micrometastasis
- p53 gene analysis
- Microvessel density
- DNA ploidy analysis
Breast cancer predictive factors

• ER / PR status
• Her2/neu gene amplification and/or overexpression
Prognostic markers in breast cancer
Axillary lymph node status

• Not predictive, never estimates the likelihood of response

• Prognostic, if positive indicates increased hazard from the disease or poor outcome
  – Most significant prognostic factor in breast cancer

• 5-year survival:
  – Negative ALN - 83%
  – 1-3 positive - 73%
  – 4-12 positive - 45%
  – ≥13 positive - 28%
Prognostic markers in breast cancer

Tumor size

- The most powerful prognostic factor in node negative patients
- 20-year recurrence-survival
  - Tumors <1 cm – 88%
  - Tumors 1.1 - 3 cm – 72%
  - Tumors 3.1 - 5 cm – 59%
Prognostic markers in breast cancer

Others

- Histologic subtype
  - tubular, mucinous, medullary better prognosis
- LVI
  - Recurrence rate 38% in pos vs 22% in negs
- Grade (Scarff-Bloom-Richardson)
  - Relative risk of recurrence is 4.4 if grade 3 vs grade 1
Predictive / prognostic factors in breast cancer

Estrogen/progesteron receptors

• ER and/or PR expression is an independent prognostic factor:
  – ER-negative cancers are associated with greater failure hazard
  – Patients with ER and/or PR positive tumors have a better survival than hormone receptor negative tumors
    • ER/PR positives: 5-year OS 83%
    • ER/PR negatives: 5-year OS 69%
Predictive / prognostic markers in breast cancer
Estrogen/progesteron receptors

- ER is a predictive marker for hormonal treatment
- High cellular expression of ER and PR predicts benefit from endocrine therapy in the adjuvant and metastatic setting
  - ER+ tumors respond
  - ER– tumors do not respond
- 5-year adjuvant tamoxifen
  - 26% reduction in the risk of mortality in ER+
  - Absolute mortality reduction 5.6% vs 10.9% in ALN neg vs positives.

EBCTCG Lancet 1998
Predictive / prognostic markers in breast cancer
Her2/Neu

- Amplified or overexpressed in 25-30% of BC
- HER2/neu positive tumors are more aggressive and have increased rates of recurrence and increased mortality (i.e., worse prognosis) compared to negative tumors.
- Predictive of response to trastuzumab.
- The prognostic value of HER2/neu overexpression is neutralised by targeting the prognostic biomarker
Prognostic factors in NSCLC

- Stage of disease at presentation – most important
- Performance status
- Lymphatic invasion
- PET-CT metabolic activity
- Gene expression profiling??
- Molecular markers – poor prognosis?
  - Her2 expression
  - Met expression
  - HGF expression
  - Loss of tumor suppressor genes (p53, p16, Rb gene)
Predictive and prognostic factors in NSCLC

- EGFR1 and K-ras not prognostic – controversial reports!
- EGFR1 mutations in exons 18, 19, 21 are predictive for response to TKIs (mostly non-smokers).
- K-ras mutations are predictive for treatment failure to chemotherapy and EGFR TKIs (mostly smokers).
- ERCC1 not prognostic, but predictive for lack of response to platinum-based therapy.
Predictive and prognostic factors in NSCLC

- Phase III trials of TKIs with erlotinib or gefitinib demonstrated some beneficial predictive factors:
  - Adenocarcinoma
  - Female sex
  - Asian ethnicity
  - Non-smoking

ESMO Course - Essentials of Medical Oncology - Istanbul
Predictive and prognostic factors in NSCLC

IPASS PFS data

**EGFR mutation is a predictive factor**

**Figure 1.** Progression-free-survival (PFS) for gefitinib versus chemotherapy as first-line therapy in EGFR positive and negative patients. Edited from the IPASS study [Mok et al. 2008].

Mok T, et al. NEJM 2009
Prognostic factors in colorectal cancer

• Pathologic stage at diagnosis: 5-year survival
  – Stage I (T1-2N0) - 93%
  – Stage IIA (T3N0) - 85%
  – Stage IIB (T4N0) - 72%
  – Stage IIIA (T1-2N1) - 83%
  – Stage IIIB (T3-4N1) - 64%
  – Stage IIIC (N2) - 44%
  – Stage IV - 8%
Prognostic factors in colorectal cancer
Well-documented factors

- Local extent of tumor (T stage)
- Regional lymph nodes
  - Number of lymph nodes involved
  - Number of lymph nodes examined
  - Lymph node ratio
- Presence of mesenteric metastatic deposits
- Vascular invasion
- Residual tumor after surgery (R0, R1, an R2 resection)
- Serum CEA
Prognostic factors in colorectal cancer

Other relevant factors

• Tumor grade
• Radial margins
• Microsatellite instability (MSI)
• 18q deletions (LOH of DCC gene)
• Other molecular markers:
  – Oncogenes, TSGs, apoptosis genes, growth factor genes, cyclins, adhesion molecules, MMPs, epigenetic aberrations…
  – K-ras mutations are not prognostic, but predictive of response to anti-EGFR MoAbs
KRAS mutation status in MCRC: Relation with prognosis and response prediction

ERBITUX + FOLFIRI HR=0.63 (p=0.007)
Median PFS: Wild-type (n=172) 9.9 months
vs mutant (n=105) 7.6 months

FOLFIRI HR=0.97 (p=0.87)
Median PFS: Wild-type (n=176) 8.7 months
vs mutant (n=87) 8.1 months

KRAS is a predictive factor
KRAS is NOT a prognostic factor

Summary

• Prognostic factors:
  – identify patients who have very good prognosis on standard treatment and do not require more intensive regimens
  – identify patients who have poor prognosis on standard chemotherapy who are good candidates for experimental regimens

• Predictive factors:
  – required for selection of appropriate treatment