SIMPOSIO

Strategie terapeutiche nelle metastasi laterocervicali da focus ignoto.

La radio-chemioterapia in relazione ai biomarkers.

Giovanni Pavanato

Radioterapia Oncologica - Rovigo

ROMA 2012

17-20 novembre

Ergife Palace Hotel

Review Article

Exploring Biomarkers in Head and Neck Cancer

Corey J. Langer, MD

Table 1. Most Relevant Biological Alterations in Head and Neck Cancer by Frequency[2]

Alteration	Rate
FGFR3	19%
CDKN2A	18%
H-RAS	10%
PIK3CA	10%
K-RAS	1%-4%
Other markers	
ERCC1 high levels	71%-73%
HPV-positive	18%-38%

Abbreviation: HPV, human papillomavirus.

Cancer, 2012

Table 3. Summary of Key Implications About Candidate Biomarkers in SCCHN

Marker	Implications
ERCC1 expression	Expression may be relevant for response to platinum therapy, needs further validation.
ERCC1 polymorphisms	May be relevant to outcomes after radiotherapy treatment, needs further validation.
RRM1	Expression may be relevant to response to gemcitabine. It may also correlate with ERCC1 expression, and other DNA repair-related markers, unclear relevance.
β-Tubulin	Expression of certain isotypes may influence response to taxanes, needs further validation.
HPV	Strong prognostic factor, warrants dedicated trial designs. No specific treatments for the HPV-positive population yet.
K-RAS mutations	Low prevalence, no predictive value documented.
EGFR	Expression is universal in SCCHN; overexpression is a negative prognostic factor after RT. Gene copy amplification (by FISH) is not predictive of outcomes after cetuximab treatment.
EGFRvIII	May affect sensitivity to cetuximab, not yet validated in the clinic.
EGFR kinase domain mutations	Low prevalence, unclear relevance.

Abbreviations: FISH, fluorescent in situ hybridization; HPV, human papillomavirus; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck.

Corey J et al, Cancer 2012

CURRENT OPINION

New promising molecular targets in head and neck squamous cell carcinoma

Julie E. Bauman[a], *Loren S. Michel*[b], *and Christine H. Chung*[c]

KEY POINTS

- HNSCC is a genetically heterogeneous group of tumors caused in large part by mutagenic exposure to tobacco and alcohol, and human papillomavirus.
- The biologic heterogeneity poses a significant barrier to the development of molecularly targeted therapies for these tumors.
- Improved treatment will require the simultaneous development of novel therapeutics and corresponding biomarkers to guide their application.

Curr Opin Oncol, 2012

Table 1. Promising molecular targets and novel agents in development

Target	Targeted agent	Class
HPV	Chalcone-derivates	Proteasome inhibitors
	Bortezomib	
EGFR	Cetuximab	Monoclonal antibodies
	Panitumumab	
	Nimotuzumab	
	Zalutumumab	
	Erlotinib	Tyrosine kinase inhibitors (TKI)
	Gefitinib	
	Afatinib	Multi-TKI
	Lapatinib	
	Dacomitinib	
	Vendetanib	
MET	E7050	Multi-TKI
	Foretinib	
PI3K/AKT/mTOR	BEZ235	Multikinase inhibitors
	MK-2206	
	Everolimus	
	Rapamycin	
	Temsirolimus	
TP53	PRIMA-1	Protein interaction and ubiquitination modulators
	CP-31398	
	RITA	
	Nutlin-3	
NOTCH1	PF-03084014	Gamma secretase inhibitor
DNA damage repair	Olaparib	PARP inhibitors
	ABT-888	
Hypoxia	Nimorazole	Hypoxia modulators
	Pimonidazole	
	Tirapazamine	
	SN30000	

Curr Opin Oncol, 2012

Human Papilloma Virus (HPV)

- Prognostico in SCC orofaringe
- DNA virale con oltre 100 caratteri genotipici
- Genotipo 16 ha predilezione per mucosa orofaringe
- > 90% del DNA isolato
- Capacità tunorigenica dovuta a 2 oncoproteine virali E6 e E7 (potenziali targets terapeutici in SCC orofaringe HPV-correlati).

Curr Opin Oncol, 2012

Epidermal growth factor receptor (EGFR)

- Famiglia ErbB/HER recettori glicoproteina trans-membrana tirosina chinasi (RTK)
- Attivazione EGFR determina proliferazione cellulare, invasione, angiogenesi e metastasi
- EGFR over-expression è presente nella maggior parte di HNSSC ed è associata a stadio avanzato, ridotto relapse-free e OS.
- Cetuximab anticorpo monoclonale chimerico contro EGFR (prima target therapy approvata)
- Aumenta OS in LAD se associata a RT
- Aumenta OS nelle forme ricorrenti e metastatiche se associato a CT (CDDP-FU)

Curr Opin Oncol, 2012

C-MET

- C-MET e/o il proprio ligando (HGF) sono over-espressi nel 80% dei HNSCC
- E' oncogenico e causa aumento mobilità, invasione/metastasi e angiogenesi
- In studi pre-clinici l'inibizione di c-MET sinergizza con CDDP o erlotinib
- Forte razionale per uno svuluppo farmacologico specifico

Curr Opin Oncol, 2012

DNA Damage Repair – ERCC1

- Excision repair cross-complementing
- La over-espressione di ERCC1 può conferire resistenza intrinseca alla CT platinum-based
- ERCC1 e XPF (complementation group F): possibili biomarkers predittivi per CDDP
- Possibile sviluppo di target therapy mirata

Curr Opin Oncol, 2012

Clin Transl Oncol (2009) 11:340-348
DOI 10.1007/s12094-009-0367-1

EDUCATIONAL SERIES Blue Series

MOLECULAR AND CELLULAR BIOLOGY OF CANCER

Cervical lymph node metastases of squamous cell carcinoma from an unknown primary site: a favourable prognosis subset of patients with CUP

Nicholas Pavlidis · George Pentheroudakis · George Plataniotis

Table 1 Location of neck nodes and possible site of primary tumour

Level	Neck nodes involved	Possible primaries
I	Submandibular nodes	Mouth floor, lips, anterior tongue
II	Jugulodigastric/upper jugular nodes	Epipharynx, base of tongue, tonsils, nasopharynx, larynx
III	Middle jugular nodes	Supraglottic larynx, inferior pyriform sinus, post-cricoid region
IV	Inferior jugular nodes	Hypopharynx, subglottic larynx, thyroid, oesophagus
V	Supraclavicular	Lungs, thyroid, breast, gastrointestinal system

Table 2 Nodal staging in patients with SQ-CUP

Nodal disease	Nodal characteristics
N1	Single ipsilateral node <3 cm
N2a	Single ipsilateral node 3–6 cm
N2b	Multiple ipsilateral nodes <6 cm
N2c	Bilateral or contralateral nodes <6 cm
N3	Lymph node >6 cm

Pavlidis N et al, Clin Transl Oncol, 2009

CUP - Epidemiologia

- Gruppo molto eterogeneo
- Nel 3-5% non evidenza di T primitivo
- 80% presenta anche altre metastasi sistemiche (subset a pessima prognosi)
- 20% a prognosi favorevole (adenocarcinoma linfonodi ascellari o adenopatie da carcinoma squamoso del collo o inguinali)

Prognosi favorevole: SQCCUP

- Comportamento biologico simile al primitivo occulto
- Medio-lunga SV
- 5% (1-10%) di tutte le neoplasie del testa-collo
- Età media: 57-60 anni
- 80% maschi
- Alcolisti e tabagisti

SQCCUP - HPV

- Alta incidenza ca. squamoso orofaringe in infezioni croniche da HPV (sierotipi 16 e 18)
- Pazienti più giovani (media 5 anni), non bevitori, non fumatori
- Miglior risposta alla RT
- SV più lunga

SQCCUP - HPV

- L’impatto di questa nuova forma epidemiologica su incidenza e prognosi delle metastasi linfonodali a partenza occulta non è stato ancora chiarito
- La detezione di DNA-RNA HPV con PCR nei linfonodi da SQCCUP promette di determinare in futuro l’identificazione di un primitivo occulto dell’orofaringe

CUP – Biologia Molecolare

- Eterogeneità: aberrazioni molecolari multiple responsabili di diversi comportamenti di differenti CUP sub-sets
- SQCCUP: rarità (estrapolazione di dati dagli studi sulle neoplasie a partenza conosciuta)

SQCCUP – Biologia Molecolare (dati su popolazioni non selezionate)

- Oncoproteina RAS
- HER2
- EGFR
- COX2

} 12-60% dei casi

- BCL2 40%
- P53 50%

La loro esatta incidenza e il significato biologico nei SQCCUP sono ignoti e non provato il loro potenziale targeting con terapie specifiche mirate

SQCCUP- Fattori prognostici

- Variabili tumore-correlate

1. Stadio linfonodale
2. Spread extra-capsulare

- Buon PS, età giovane, basso volume linfonodale coinvolto, no spread, basso grado
- Trattamento con intento curativo

SQCCUP - Trattamento

- Chirurgia
- Radioterapia
- Chemio-radioterapia
  - Dimostrata efficacia nelle neoplasie localmente avanzate
  - Ad oggi non esistono studi randomizzati sulla efficacia della CT-RT nei SQCCUP

Table 4 Outcome of SQCCUP patients managed with combinations of surgery, irradiation and chemotherapy

Investigators	Number of patients	Therapy	N2/N3 status (%)	5-year survival
Jesse 1973	184	S	45/38	All patients, 53%
		RT	75/36	
		S+RT	55/31	
Colletier 1988	136	S + RT	78/13	60%
De Braud 1989	41	S and/or RT, CRT in 16 pts	39/56	Median OS 24 months
Marcial-Vega 1990	72	RT or S+RT	54/20	45%
Harper 1990	69	RT or S+RT	NR	66%
Maulard 1992	113	S+RT	40/19	38%
Reddy 1997	52	RT or S+RT	71/29	51%
Grau 2000	277	S and/or RT	49/34	36%
Friesland 2001	51	RT or S+RT	55/30	41%
Argiris 2003	25	CRT or S+CRT	76/24	75%
Shehadeh 2006	37	S+CRT	58/22	1-year OS 95%

Pavlidis N et al, Clin Transl Oncol, 2009

SQCCUP

Shehadeh NJ et al, Head & Neck, 2006

- 37 pts
- Chirurgia su N + CDDP/RT collo bilaterale e mucose
- 64 Gy sedi coinvolte del collo/ 50 Gy collo non coinvolto + mucose
- FU 42 mesi 89% pts viventi
- 46% mucosite severa; 30% xerostomia
- Risultati preliminari/necessità di studi più ampi

SQCCUP – identificazione del primitivo

- Solo nel 10% (r 5-30) dei casi evidenza del T primitivo
- Compare entro i primi 2 anni dal trattamento (se dopo 5 anni II neoplasia)
- Sedi più frequenti: rinofaringe, base lingua, tonsilla e seno piriforme.

Shehadeh NJ et al, Head & Neck, 2006

CUP – profilo molecolare

- Recenti studi hanno dimostrato la possibilità che nel 70-85% dei casi di CUP possa essere identificato un profilo molecolare “assegnabile” ad un tessuto di origine
- PCR-microarray
- Tumori testa-collo “biologicamente assegnati”: 5-10%

Shehadeh NJ et al, Head & Neck, 2006

SQCCUP – profilo molecolare

- Non è noto se un SQCCUP assegnato ad uno specifico T primitivo del testa-collo si comporti realmente come un tipico T metastatico della stessa sede!!!
- Le due entità possono essere "sostenute" da lesioni genetiche o epigenetiche differenti

Shehadeh NJ et al, Head & Neck, 2006

SQCCUP – profilo molecolare

- La speranza è che la classificazione molecolare di un SQCCUP seguito da un trattamento specifico per sede di T possa migliorare l'outcome
- Validazione in studi prospettici: pts con SQCCUP a prognosi sfavorevole randomizzati a trattamento empirico o in base al profilo molecolare

Shehadeh NJ et al, Head & Neck, 2006

Table 6 Primary tumour identification and CUP patient outcome in time

Decade	Patient number	No. of studies	Mean 5-year survival (range)	Appearance of primary
1960–69	256	3	26.5% (16–34)	–
1970–79	1084	9	29% (9–54)	18%
1980–89	449	4	40% (21–60)	16.5%
1990–99	1235	13	49% (27–60)	10.5%
2000–08	1113	12	55% (36–79)	11%

Pavlidis N et al, Clin Transl Oncol, 2009

Tumor Biol. (2012) 33:707–721
DOI 10.1007/s13277-012-0350-2

RESEARCH ARTICLE

Targeted therapy in head and neck cancer

S. K. Kundu · M. Nestor

Table 1 Current treatment options and targeted biological treatment options under development

Different treatment options for HNSCC			
Current clinical treatment options for HNSCC	A. Surgical treatment		
	Total surgery		
	Partial surgery		
	B. Non-surgical treatment		
	Radiotherapy alone		
	Chemotherapy alone		
	Chemoradiotherapy alone or following surgery		
	Biological targeting agents:		
Targeted biological treatment options under development	Targeting agent	Drug name	Clinical development phase
	EGFR inhibitors, MAbs	Cetuximab, Panitumumab, Zalutumumab	Phase III (cetuximab FDA approved)
	EGFR tyrosine kinase inhibitors	Gefitinib, Erlotinib	Phase III
	VEGFR inhibitors	Bevacizumab, Vandetanib	Phase III, Phase II
	Multiple kinase inhibitors	Sorafenib, Sunitinib, Lapatinib	Phase II
	Src kinase inhibitor	Dasatinib	Phase II
	PARP inhibitors	Iniparib, Olaparib	Preclinical phase in HNSCC
	Proteasome inhibitor	Bortezomib	Phase II
	Histone acetylation inhibitors	Vorinostat, Romidepsin	Phase II
	mTOR inhibitors	Everolimus, Temsirolimus	Phase II
	COX inhibitor	Celecoxib	Phase I
	CDK inhibitors	Seliciclib, Flavopiridol	
	Heat shock protein inhibitor	Tanespimycin	Phase I

Tumor Biol, 2012

Molecular Classification of Cancers of Unknown Primary Site

F. Anthony Greco[1] and *Mark G. Erlander*[2]

1 Sarah Cannon Cancer Center, Nashville, Tennessee, USA

2 bioTheranostics, Inc., San Diego, California, USA

..the ability to diagnose and classify unknown primary cancer more precisely would allow for more site-specific or targeted therapy, and likely improve patient outcomes.

Mol Diagn Ther, 2009

Molecular Classification of Cancers of Unknown Primary Site

F. Anthony Greco[1] and *Mark G. Erlander*[2]

1 Sarah Cannon Cancer Center, Nashville, Tennessee, USA
2 bioTheranostics, Inc., San Diego, California, USA

Table I. Summary of selected gene expression studies in human cancers of known primary sites

Original study	No. of samples	Gene expression platform	Tissue compatibility	No. of cancers classified	Accuracy (%)	Commercial entity
Tothill et al.[14]	Training set: 229 tumors; validation set the same but using leave-one-out cross-validation	Microarray (10 500 cDNAs)	Frozen	14	89	None
Talantov et al.[15]	Training set: 260 tumors; validation set: 48 tumors	Real-time RT-PCR (10 genes)	FFPE	6 plus 'other' cancers	76	www.veridex.com
Rosenfeld et al.[16]	Training set: 253 tumors; validation set: 83 tumors	Real-time RT-PCR (48 micro-RNAs)	FFPE	22	86	www.rosettagenomics.com
Monzon et al.[17]	Validation set: 477 tumors	Microarrays (1550 genes)	Frozen	15	89	www.pathworkdx.com
Pillai et al.[22]	Validation set: 352 tumors	Microarrays (1550 genes)	FFPE	15	89	www.pathworkdx.com
Ma et al.[21]	Training set: 481 tumors; validation set: 119 tumors	Real-time RT-PCR (92 genes)	FFPE	39	87 in 32 tumor types	www.biotheranostics.com

cDNA = complementary DNA; **FFPE** = formalin-fixed, paraffin-embedded; **RT** = reverse transcriptase.

In summery, the primary site prediction for CUP has been examined by several of the molecular tests. Given the occult, clinically undetactable nature of the primary sites in most CUP patients, it is extremely difficult to verify the accuracy of molecular assays or IHC stains in predicting the true primary site.

Annals of Oncology 20 (Supplement 4): iv154–iv155, 2009
doi:10.1093/annonc/mdp159

Cancers of unknown primary site: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

E. Briasoulis[1], N. Pavlidis[1] & E. Felip[2]
On behalf of the ESMO Guidelines Working Group*

[1]*Department of Medical Oncology, University of Ioannina, Ioannina Ipiros, Greece;* [2]*Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain*

Table 2. Therapy of cancer of unkown primary site

CUP subtype	Proposed treatment
Poorly differentiated carcinoma, predominantly nodal disease	Platinum-based combination chemotherapy
Poorly differentiated neuroendocrine carcinomas	Platinum plus etoposide combination chemotherapy
Peritoneal carcinomatosis of a serous histologic type adenocarcinoma in female	Similar to FIGO III ovarian cancer: optimal surgical debulking followed by platinum chemotherapy
Isolated axillary nodal metastases in female	Identical to patients with breast cancer and similar nodal involvement
Squamous carcinoma involving cervical lymph nodes	Irradiation for N1–2 disease. For advanced stages induction chemotherapy with platinum-based combination or chemoradiation is indicated
Adenocarcinoma with bone metastases and elevated prostate-specific antigen in males	Hormonal therapy as for prostate cancer
Liver, bone or multiple-site metastases of adenocarcinoma	Low toxicity chemotherapy of palliative orientation or best supportive care

Conclusioni - 1

1. L'impiego della associazione radio-chemioterapica concomitante è ormai uno standard nel trattamento dei tumori localmente avanzati del distretto cervico-cefalico, sia come trattamento esclusivo che dopo chirurgia

2. La "target therapy" e la sua integrazione col trattamento radioterapico rappresentano anch'esse ormai uno standard con solide basi biologiche

3. La tossicità dei trattamenti integrati può essere rilevante

Conclusioni - 2

4. **Il futuro della "target therapy" appare promettente per la possibile disponibilità di molti agenti biologici attivi su *target* diversi, anche per le neoplasie della testa e del collo, in tutti i casi, comprese le forme CUP, in cui sia possibile identificare un primitivo (caratterizzazione biologica)**

5. **L'oncologo radioterapista inevitabilmente dovrà possedere le conoscenze necessarie per gestire la complessità dei trattamenti integrati con chemioterapia e con i nuovi agenti biologici.**

Personalized Health Care – Fantasy or Reality?

Grazie per l'attenzione!