Innovations in bladder cancer

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Thanks to sponsorship from Synergo® as well as contributions to WebCafe in 2005, we were able to attend the conference and give this review.

Main Synergo page

Continued on separate pages, further presentations:

5. Intravesical chemotherapy: Does it work? Prof. P.F. Bassi

Department of Urology Catholic University Medical School - Rome

6. Innovative Treatments: Newer Chemotherapeutic Drugs; C Barone, Oncologia Medica ,Università Cattolica S. Cuore, Roma. 2005

7.Thermochemotherapy in bladder cancer: Overview of basic science; Synergo technique – principles of operation Dr. A Lev

8.The effect of heat dose on clinical outcome A.G. van der Heijden;University Medical Centre Nijmegen The Netherlands

9.Local hyperthermia and intravesical chemotherapy for superficial TCC of the bladder Clinical studies: An overview; R. Colombo U.O. di Urologia Istituto Scientifico Universitario “Vita e Salute” San Raffaele, Milano

10.Thermo-chemotherapy: Preliminary results of current international studies Prof. Fred Witjes Radboud UMC Nijmegen, the Netherlands Innovations in Urology: Bladder cancer Rome, December 2, 2005

11.Thermochemotherapy - Current Italian Studies Rodolfo Hurle U.O. Urologia Humanitas Gavazzeni Bergamo

{/niftybox}Synergo® II Workshop Dec. 2005- Rome Synergo® Medical Enterprises

Congress Organizer/Chairman: Prof. PF Bassi, Chairman Department of Urology, Catholic University Medical School, University Hospital "A. Gemelli"

Auditorium Centro Congressi Europa, Universita Cattlolica del Sacro Cuore, Facolta de medicina e Chirurgia "A. Gemelli"

Some of the best minds in Europe specialising in the field of uro-oncology collected together in Rome for a comprehensive look at innovations in the field of bladder cancer research.

Presentations 1-4:

1. Future directions in bladder cancer research- Genetic Markers;

Gigliola Sica -Chairman Institute of Histology and Embryology,

Faculty of Medicine Catholic University of the Sacred Heart Rome

2. Newer non-invasive diagnostic tools in bladder cancer

M J Bailey, St. George’s Hospital, London

3. ISUP-WHO tumor classification: really the gold standard?

Fabio M.Vecchio Ist. Anatomia Patologica, Università Cattolica Roma

4 .Markers of recurrence and progression Prof. Fred Witjes Radboud UMC Nijmegen, the Netherlands; Innovations in Urology: Bladder cancer Rome; December 2, 2005

1. Future directions in bladder cancer research- Genetic Markers

Gigliola Sica- Chairman Institute of Histology and Embryology

Faculty of MedicineCatholic University of the Sacred Heart Rome

Dr. Sica’s presentation focused on new, improved techniques in diagnostics which will hopefully lead to ways of lessening the costliness of a lifetime of cystoscopies and follow ups and the anxiety this brings for people with TCC. The goals are to define invasiveness and predict response, saving time and cost by tailoring individual treatments most likely to be effective.

There are at least 3 ways to look at markers:

- Neo-plastic tissue- biopsy of suspicious lesions
- Serum – blood tests
- Urine – urine marker tests

Dr. Sica talked covered advances in the field of proteonomics - the study of tissue proteins and body fluids. Whereas traditional biology deals with a single gene or protein of interest, the new, theoretical biology analyses a set of genes (the genome) or proteins (the proteome). The proteome is the group of proteins that are encoded by the genome and expressed in the same biological environment.

Ultimately we are looking for a panel of markers; more than one is needed to make testing reliable. Single markers give insufficient information on which to base individual treatment decisions.

Genetic studies being done today are attempting to identify the spectrum of genetic changes that occur during the transformation from normal tissue to cancerous tissue, and to clarify the natural history of bladder tumors with different clinical outcomes. Several known oncogenes and tumour suppressor genes are mutated in TCC. These include genes encoding several key G1 checkpoint proteins (p16, p14ARF, Rb, p53, cyclin D1). Whole genome analysis has been carried out by comparative genomic hybridization;

What can we do now?

There is no technological barrier to the detailed analysis of multiple markers in either retrospectively or prospectively collected tumour panels, and much research has already been done to assess the relationships between genetic changes and clinical parameters, particularly tumour grade and stage; Progress in the Human Genome Project along with microarray technology will lead to the identification of amplified and/or deleted genes within a relatively short time. To date however, the available genetic information on TCC has had little impact on everyday practice.

Existing tissue collections and archival resources should be used to their full potential and this will require appropriate funding for coordinating mechanisms.

What can we start doing now?

--Retrospective studies to validate and test the predictive power of marker panels.

--Prospective studies where high quality tissue samples could be collected from patients in clinical trials.

What we already know:

-Genetic alterations are necessary but not sufficient in themselves to promote progression.

-Selection and growth of transformed cells is likely to play a dominant role during the earliest stages of cancer progression

-Increases in mutation rates are thought to be more common during the later stages of the disease

Pre-malignant cells need the appropriate microenvironment for such selective expansion and progression to occur.

Moreover, transformation seems to be linked to alterations of cell structure and shape.

Markers related to progression and survival:

•Growth factors and their receptors (tyrosinkinase [TKI] receptor)

• Cytokines/interleukins

• Soluble forms of adhesion proteins

• Plasma membrane proteins

• Nuclear matrix proteins

• Nuclear matrix proteinases

• Cytoskeleton proteins

• Ca2+-binding proteins

EGF-R is a member of the TKI family, is over-expressed in 81% of primary bladder cancers and in 67% of metastases. Expression is correlated with stage, grade and survival.

HER2/neu over-expression in the development of muscle-invasive transitional cell carcinoma of the bladder - HER2 is a member of the tyrosine kinase family and encodes a 185-kDa transmembrane protein. HER2 is over-expressed in 81% of primary bladder cancers and in 67% of metastases.

Angiogenic factors elevated in the urine of TCC survivors:

Vascular endothelial growth factor (VEGF)

Basic and acidic fibroblast growth factor

Prostaglandin E2

Cyclooxygenase -2

Cytokines are signalling molecules contributing to the inflammatory response; they protect the body from pathogens and other environmental factors

IL-8 is a leukocyte chemo-attractant and induces angiogenesis. Sources of IL-8 include transitional epithelial cells, endothelial cells, mast cells, neutrophils, T cells, macrophages.

IL-8 levels :

-• are greater in subjects with TCC compared with those with successfully -treated TCC;

-• increases with TCC stage indicating that they are greater in more invasive tumous;

-• are reduced after treatment with Bacille Calmette Guerin or mitomycin.

-• An anti IL-8 antibody inhibits tumour growth in rats

IL-4 induces the activation and differentiation of B cells; inhibits macrophage activation and may be involved in cancer formation; IL-4 gene intron-3 polymorphism is associated with TCC.

E-cadherin - Abnormal expression of E-cadherin has been associated with more rapid progression and reduced survival. The soluble form (sE-cadherin, 80kDa) is elevated in TCC [among other tumors] and is found in both serum and urine.

Uroplakin II is a membrane protein which is expressed in transitional cell carcinoma and associated with differentiation/grade and seems to be useful for detection of micro-metastases

BLCA 4 – This urine marker dialogues with IL-8 NS IL-1; has been shown to be a tumor anti-coagulant

Cytokeratin 20 (CK20) is a protein which is specifically expressed in epithelial cells of the urinary and gastrointestinal tract. CK-20 immunocytology is more sensitive than standard cytology in the detection of TCC, particularly of Stage pT1, grade 2, and grade 3 tumors.

Fascin 1 -a protein which binds actin microfilaments; an association with increased invasiveness has been found. This is a very new marker with limited studies to date, but it is associated with invasiveness.

Survivin - a unique member of the inhibitor of apoptosis (IAP) protein family. Survivin is highly expressed in urine but is undetectable in non-malignant tissues, suggesting a potential role in tumor genesis.

Major proteins that are either up or down-regulated in TCC/bladder cancer:

Upregulated in urine:

Nuclear matrix protein 22

FDP

BTA stat, BTA trak

Telomerase

Hyaluronic acid and hyaluronidase

[the above urine markers are discussed further on webcafe’s diagnostic procedures-urine markers section]

Psoriasin

Defensin

Down-regulated in tissue:

Adipocyte-type fatty acid binding protein (A-FABP)

Glutathione S-transferase

Prostaglandin dehydrogenase (PGDH)

Keratin 13

Seung-won Lee et al., J. Chromatography 815:203-213, 2005.

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2. Newer non-invasive diagnostic tools in bladder cancer

M J Bailey, St. George’s Hospital, London

Screening vs. surveillance

What we know:

-Screening high risk populations such as smokers or those with exposed to known carcinogens may be feasible

- most new tumours are low-risk.

Surveillance – could cystoscopic follow-up be reduced or replaced using markers? Whole population screening is not cost effective.

Diagnostic tools - what would we like to have?

Diagnosis- Simple point of care test, must be

-Sensitive (positive when tumour present)

-Specific (negative when tumour absent)

-Affordable

Surveillance- As above, but sensitivity and cost effectiveness equations might be different

Currently used imaging tests:

IVU

Ultrasound

CT

MRI

PET

On the horizon for imaging:

Virtual cystoscopy w/ CT or MRI (however these tools are less sensitive for picking up carcinoma in situ/CIS and considered too expensive to use for initial diagnosis and staging)

Photodynamic Cystoscopy

Intravesical photosensitiser 2 hours pre-cystoscopy

Cystoscopy performed with blue light-source

Tumours fluoresce with red light [see also: hexvix]

Urine tests

Voided urine cytology

Microhaematuria

BTA stat -

BTA trak -Quantitative test for human complement related factor H; Reference lab based test; Has superseded BTA stat (qualitative POC test)

NMP 22 - Commercially available POC test; Detects nuclear matrix protein 22;

May predict recurrence

On the horizon for urinary markers:

-Telomerase detection- promising new marker

-Microsatellite instability assays-still in research phases

-Fluorescence in-situ hybridisation FISH- The Urovysion Test uses FISH to identify genetic abnormalities; DNA probes for translocation/deletion/amplification of chromosomes 3,7,9q21 and 17; FISH is a reference lab procedure; useful post-BCG

-Fibrin degradation products FDP

-Immunocyt assay -Cells stained with 3 monoclonal antibodies; Visualised with immunocytoflouresence; Lab based test, may predict recurrence, Useful in post-BCG surveillance

-HA-HAase assays

-Survivin assays

test	sensitivity	specificity	comments
VUC*	30-40%	90%	routine lab
Bard Trak	70%	70-90%	Ref.lab
NMP22	66%	80%	POC**
FISH	80%	95-100%	Ref.lab
Immunocyt	80%	70-80%	Ref.lab
HA-HAase	70-90%	90%	Ref.lab
Telomerase	75%	85%	Ref.lab
Survivin	60%	80%	Ref.lab

*voided urinary cytology, ** point of care; for an explanation of sensitivity and specificity go here

Conclusions

-Urine marker tests can be difficult to interpret if there are co-existing conditions such as stones, inflammation and infection.

-No currently available urine test is sufficiently sensitive to replace cystoscopy

-Use of NMP22 may lead to more careful inspection if positive pre-cystoscopy

-Positive urinary markers may pre-date appearance of visible tumours by several months

-Use of markers may reduce frequency of surveillance cystoscopies

-Newer urinary markers such as HA-HAase may have greater sensitivity and specificity

-Imaging modalities for the foreseeable future are too expensive and lack sensitivity, so cannot replace cystoscopy

-We already have risk-stratification which reduces the frequency of cystoscopies

-The use of blue-light cystoscopy allows detection of papillary lesions and CIS earlier than conventional cystoscopy

A suggestion for current best practice might be:

Low-risk tumours - annual cystoscopy

Intermediate-risk tumours - 3 monthly cystoscopies following course of intravesical cytotoxic agent

High-risk tumours - 3 monthly cystoscopies supplemented by cytology, NMP22 ImmunoCyt or Bard Trak following course of BCG.

Use blue-light PDD if marker positive.

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3. ISUP-WHO tumor classification: really the gold standard?

Fabio M.Vecchio Ist. Anatomia Patologica, Università Cattolica Roma

The WHO-ISUP classification of bladder neoplasia arises from a consensus of the World Health Organization and the International Society of Urologic Pathology.

Aim: to develop a universally acceptable classification system for bladder neoplasia that could be used effectively by urologists, pathologists and oncologists.

WHO-ISUP Consensus Classification (I)

Normal

Normal (may include cases formerly diagnosed as “mild dysplasia”)

Hyperplasia

Flat hyperplasia

Papillary hyperplasia

Flat lesions with atypia

Reactive (inflammatory) atypia

Atypia of unknown significance

Dysplasia (low grade intraurothelial neoplasia)

Carcinoma in situ (high grade intraurothelial neoplasia*)

* includes cases with “severe dysplasia”

WHO-ISUP Consensus Classification (II)

Papillary neoplasms

Papilloma

Inverted papilloma

Papillary neoplasm of low malignant potential

Papillary carcinoma low grade

Papillary carcinoma high grade*

Invasive Neoplasms

Lamina propria invasion

Muscolaris propria (detrusor muscle) invasion

* Option exists to add comment as to the presence of marked anaplasia

Non-invasive urothelial tumours

"The aim of classification of tumours has always been to define groups with differences in clinical outcomes that are signicant enough to be clinically relevant. Also classifications need to be sufficiently reproducible and comprehensive to be uniformely applied by all pathologists and urologists. Further, patients having a benign disease should not threatened

by an unnecessary diagnosis of cancer. And lastly, as molecular pathology research progresses, classification should reflect genetic differences between tumour categories.” (Sauter et Al., 2004) urothelial hyperplasia (flat and papillary)

Urothelial dysplasia

include reactive atypia and atypia of unknown significance

Urothelial papilloma

Inverted papilloma

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

Papillary urothelial carcinoma, low grade

Papillary urothelial carcinoma, high grade

Urothelial carcinoma in situ

Non-invasive urothelial tumours -Definitions

Urothelial hyperplasia Markedly thickened mucosa without cytological atypia

Urothelial dysplasia (low grade intraurothelial neoplasia) has appreciable cytologic and architectural changes to be preneoplastic but which fall short of carcinoma in situ (CIS). Lesions show variable loss of polarity with nuclear rounding and crowding and cytologic atypia (irregular nuclear borders, mildly altered chromatin distribution, inconspicuous nucleoli and rare mitoses).

Urothelial papilloma is composed of a delicate fibrovascular core covered by urothelium indistinguishable from that of the normal urothelium

Inverted papilloma benign urothelial tumour that has an inverted growth pattern with normal to minimal cytologic atypia of the neoplastic cells

Papillary urothelial carcinoma, low grade A neoplasm of urothelium lining papillary fronds which shows an orderly appearance, but easily recognizable variations in architecture and cytologic features

Papillary urothelial carcinoma, high grade

Papillary urothelial neoplasm of low malignant potential (PUNLMP) is a papillary urothelial tumor which resembles the esophytic urothelial papilloma, but shows increased cellular proliferation exceeding the thickness of normal urothelium. A neoplasm of urothelium lining papillary fronds which shows a predominant pattern of disorder with moderate to marked architectural and cytologic atypia

Urothelial carcinoma in situ A non-papillary, i.e. flat, lesion in which the surface epithelium contains cells that are cytologically malignant (pleomorphism, prominent nucleoli throughout the urothelium and upper level mitoses).

Accomplishments of the WHO-ISUP classification - provides a detailed histologic description of the various grades, using specific cytologic and architectural criteria; Removal of ambiguity in diagnostic categories in previous classifications. Stratification of bladder tumors into prognostically significant groups

Prognosis of Urothelial Papillary Lesions

recurrence
grade progression
stage progression
survival

papilloma
08%
2%
0%
100%

PNLMP*
27-47%
11%
0-4%
93-100%

Low Grade Papillary Carcinoma

47-71%
7%
2-12%
82-96%

High Grade Papillary Carcinoma
55-58%
not applicable
15-40%
74-90%

Montironi and Lopez-Beltran; Int. J. Surg. Pathol. 13:143-153, 2005

*papillary neoplasm of low malignant potential

Open problems of WHO-ISUP Classification

_____Papillary tumors may show heterogeneity (dissimilarites) of grade. It remains to be defined what percentage (if any) is minimally needed to place tumors in a higher category when the highest grade is focal.

_____The distinction on transurethral resection of muscolaris mucosae from muscolaris propria invasion may occasionally be difficult.

_____Do PNLMP and low grade papillary carcinoma have significative differences in clinical outcome ?

General Principles of Classification

Classification schemes are devices, often determined by consensus rather than fact. All classification schemes have limitations, both in concept and in application. Interpretative reproducibility among pathologists is inversely proportional to the number of discriminations required and the complexity of the definitions. The factors that determine how a pathology classifies any particular case have never been understood ant the result represents an individual interpretation, not a fact

Interobserver variability in interpretation

A pathologic diagnosis is an interpretation (i.e., the result of a complex integration of factors).

Interobserver variability in interpretation is inevitable and probably cannot be reduced to less than 10 percent.

Pathologists tend to have problems distinguishing lesions of similar histology, like PUNLMP and low-grade carcinoma.

The case for combining the categories of papilloma, PUNLMP and low-grade carcinoma into a single group of “low-grade neoplasm” contrasted to a category of “high-grade carcinoma” seems to have merit.

[Murphy, Grignon, Perlman 2004]

Gold standard or not, it is the most useful classification system we can use at the moment.

Classifications are arbitrary inventions, but not haphazard:

“Classifications, then, are not right or wrong; they cannot even be said to be good or bad except in relation to a purpose. The most that can be said about them is that they are useful or not useful… It was as accurate and factual for our forebears to classify whales with fishes as for us to find this classification abhorrent.” (Bohrod, 1971)

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4. Markers of recurrence and progression Prof. Fred Witjes Radboud UMC Nijmegen, the Netherlands; Innovations in Urology: Bladder cancer Rome; December 2, 2005

Experts have now published a simple calculator that can be downloaded free from the EORTC web site: www.eortc.be/tools/bladdercalculator/default.htm The following presentation discusses the details:

How to define risk groups with prognostic factors

Demographic: elderly and females do worse

Clinical signs of a worse prognosis:

---Size and multiplicity

---Recurrence rate

---Reaction to intravesical therapy

Histological signs of a worse prognosis

--Grade

--Stage

--CIS

Predicting recurrence and progression in stage Ta-T1 bladder cancer: the use of the EORTC risk tables Richard Sylvester. (EORTC Data Center, Brussels, Belgium, Ad van der Meijden, Wim Oosterlinck, Fred Witjes, KarlHeinz Kurth (for the EORTC GU Tract Cancer Group) PubMed

Individual patient data are available for 2596 stage Ta T1 bladder cancer patients entered in 7 EORTC trials from 1979 to 1989

Endpoints: Time to first recurrence; Time to progression to T2 or higher

Patients were divided into 5 groups for recurrence and progression according to their individual characteristics: Tumor size of <3 or >3cm; Prior recurrence rate <1 year or >1 year; stage Ta or T1; presence of CIS; Grade G1, G2, G3:

Factors of recurrence differ from that of progression; CIS increases risk of progression.

SCORING SYSTEM

factors

recurrence
progression

#tumors
single
0
0

multiple
4
3

size
<3cm
0
0

>3cm
3
3

prior recurrence rate
primary
0

0

<1yr
2
2

>1yr
4
2

Stage
Ta
0
0

T1
1
4

CIS
No
0
0

Yes
0
6

Grade
G1
0
0

G2
1
0

G3
2
5

Total score

0-14
0-23

Probability of Recurrence

Recurrence score
Prob. rec. 1 yr
Prob. rec. 5 yrs

0
16% (11-21)
34% (27-41)

1-4
24% (22-27)
49% (46-53)

5-7
34% (30-38)
63% (58-68)

8-11
51% (47-55)
74% (70-78)

12-14
84% (69-98)

Probability of Progression

Progression score
Probability of progression
Probable progression at 5 yrs

0
0.25% (0-0.7)
1% (0-2)

2-6
1% (0.5-2)
7% (5-9)

7-11	
5% (3-7)	
18% (14-21)	
12-16	
10% (6-15)	
39% (30-37)	
17-23	
32% (12-51)	
75% (53-97)	

T1 G3 Tumors

The prognosis of T1 G3 patients is variable

According to the total score, probability of progression varies:

- 1 year: 4% to 32%

- 5 years: 22% to 75%

CIS is the most important prognostic factor

Recurrence at 3-months cystoscopy

The prognostic importance of recurrence at 3 months is similar to that of CIS and grade 3:

3 month recurrence	Probability of Progression
no	9% (181/2070)
yes	26% (80/313)

Conclusions EORTC risk tables

Patients with superficial bladder cancer have a very variable prognosis. A simple scoring system based on 6 common clinical and pathological factors is proposed:

Number of tumors, prior recurrence rate and tumor size
Recurrence

T category, Grade progression and CIS
Progression

Remarks: pT1 substaging and staging error

Microstaging pT1 -

Clinical outcome Kaplan-Meier 3y risks for progression:

pT1a-b, no CIS - 0% (n=75)

pT1c with CIS - 42%(n=44)

Staging error in high risk SBC after cystectomy (J Urol 166, 490, 2001)

Cystectomy specimens revealed understaging errors of 40%:

78 cystectomies for high risk <pT1 TCC

31x appeared (40%) >pT2

Disease free rate 98% (<pT1) vs. 65% (>pT2, p<0.01)

Standard re TUR in high risk SBC? (Jakse et al, J Urol 165, 808, 2001)

Out of 42 patients who underwent a second TUR (for high grade pT1 +/- CIS)

- Upstaging and change of treatment in 10 (24%)

-No tumour on reTUR: 100% organ preservation

A second look TUR in T1 TCC: why (Jakse et al, Eur Urol 2004)

Conclusion 1: Prognostic risk groups can be defined even without markers; Provided a good TUR and good histology; Whenever in doubt: second look.

The main issue in high risk superficial disease is that the natural (untreated) history over 3 years will see a greater than 70% recurrence rate, and a 30-50% risk of progression in cases of CIS.

The fate of progressive patients

Those who progress from primary superficial bladder cancer had a worse prognosis than those with primary invasive tumors, 2 examples:

74 progressive pts. matched to a group of 89 primary invasive pts.

3 year bladder ca specific survival: 65% vs. 37% (p=.001) Schrier et al, Eur Urol 2004

The “BCG meta-analysis”; Death due to bladder cancer in case of progression is 64% in 2.5 years Sylvester et al, J Urol 2002

Conclusion 2: The conservative window in high risk superficial disease is small

Potential progression markers for EORTC CIS study

Ki-67 (proliferation, Anticancer res 21, 1495, 2001)

CK-20 (easy, recurrence)

pT1 sub classification

p53 mutation analysis or IHC

E-cadherin expression

EGF-R over expression

(always use a panel of markers)

P53 and Ecadherin are the most important markers at this time because:

Two distinct pathways are described

p53 mutations/17p loss are indicative for aggressive biological behaviour; “..loss of cell cycle control..”

Decreased E-cadherin expression indicative for invasivion: “.. Loss of local control..”

p53 and progression: P53 controls cell cycle

Methods to asses p53 mutations:

--Immunohistochemically (mutant p53 has increased half life)

--Mutation analysis

p53/E-Cadherin Immunohistochemistry in Bladder Cancer

E-Cadherin ~ 20 papers, reporting consistent data

P53 ~ 100 papers, reporting equivocal data (review Schmitz-Dräger)

--Lack of standardization of methods

--Lack of standardization of scoring systems

What we did in Nijmegen

Assumption: p53 mutation analysis is better but a lot of work

Retrospective pilot: 18/22 patients with p53 mutation progressed

Prospective study:

--Clinical pre-selection of high risk patients

--P53 mutation analysis

____ SSCP pre screen

____In case of shift DNA sequencing (‘manual’)

Results

105 high risk patients

Median follow up 6 years

29 p53 mutations, 76 wild type

p53 no relation with death due to TCC or progression or disease worsening

p53 related to recurrence and G3 and CIS

Conclusion 3: p53 mutations are related to recurrence but no relation to progression or death has been found. Clinical applications have yet to be confirmed. Until now, patient history and histology are the main indicators.

Take home messages:

Do a good TUR and work with a good uro-pathologist

History and histology gives useful information for recurrence and progression

Progression is the main issue

Molecular markers can be of help

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