Innovations in bladder cancer p.3

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

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

Conventional treatment regimens till this point in time still show rather high recurence rates:

TUR alone: up to 80% recurrence (20y follow up)

Thousands of review articles have concluded that the average recurrent rate of TUR alone at one year is 65%; at 2 years it is 75%

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TUR + chemo prophylaxis: 25-50% (2y follow up)

Conventionally Agreed Net Benefit of +/-15% improvement

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TUR + BCG: 20-65%

* Progression rate are stable: 10-20% in 5 years

European guidelines for risk assessment:

Low risk

single, Ta,G1, < 3 cm diameter

High risk
T1, G3, multifocal or highly recurrent, CIS

Intermediate risk
all other tumors, Ta-T1, G1-G2, multifocal, > 3 cm diameter

Recurrence rates are still very high not-with-standing current improvement in TUR techniques and instillation protocols. How should we modify this fact?

Bladder instillations: some pharmaco-kinetics aspects:

Drug concentration - Wientjes et al studied the pharmacokinetics of MMC drug concentration in urine and determined that an effective MMC concentration is > 0.12 mg/ml of MMC in urine. That is, significant concentrations of Mitomycin C were found in the bladder wall, when urine Mitomycin C concentration was > 0.12 mg/ml. Wientjes et al. Penetration of MMC in human bladder. Cancer Research (1993)(53) 3314-3320.

Effective exposure time: Conclusion: 2 x 20 mg MMC = 1 x 40 mg MMC

Bladder tissue wall is equally exposed to an effective MMC drug concentration.

Questions to be addressed include the high levels at the start of the instillation

Maximum effective MMC concentration:

In-vitro experiments with:

4 human bladder cancer cell lines and

2 mouse bladder cancer cell lines

24 hours in media containing

0, 0.125, 0.25, 0.5, or 1 mg/ml of MMC

(see Wientjes et al and T.v.d. Heijden et al)

Maximum MMC effective concentration range < 0.25 mg/ml

Initial exposure of patients to higher concentrations of MMC during the first minutes of treatment, may not provide additional clinical benefit.

Maximum effective MMC concentration summary:

Dose
Time above 0.12 mg/ml

Effective AUC

C* 0.25 mg/ml

C* 0.12 mg/ml

40mg
40 min.
8.57 min*mg/ml

2x20
44 min.
8.71 min*mg/ml

C* -MMC Concentrations above 0.25 mg/ml calculated as 0.25 mg/ml

Instillations should keep chemotherapeutic agent’s concentration as steady as possible at effective level. Using the highest dose possible is not necessarily good

Effect of heat (alone) on tumour tissue: Known facts:

Heat may kill tumour cells

Heat alone destroys blood supply in tumour tissue.

Since 1980 there have been thousands of studies investigating the use of both hyperthermia, hyperthermia+radiation and hyperthermia+chemotherapy against cancers of all kinds.

Heat and chemotherapy The objective: delivery of the drug to the cell, enter the cell and combine to DNA

DIffusion Although diffusion is very common in biological systems, it is also a very slow process (on a macroscopic scale). There are several physical factors that affect the rate at which particles diffuse.

Factors:

Size of the particle (molecular weight)

Diffusion distance - In 2 mm, without HT, about 3% of bladder MMC concentration remains

Temperature

Concentration difference

Surface area

Speed of molecules

Permeability - Obviously, if a substance is not permeable through the membrane, it will not be able to diffuse through it. The more permeable a substance is, the faster diffusion through it.

For molecular weight > 200, the spontaneous permeability is close to zero.

Heat and chemotherapy - rationale:

Activation energy - the minimum energy that is necessary before a chemical reaction can occur

The activation energy provides the energy needed to break (at least partially) some bonds before others can be formed. For a bimolecular reaction mechanism, not only must the two species collide but they must also possess the activation energy for the reaction before the collision will be successful.

In summary - Having the target tissue heated will cause Chemotherapy molecules to arrive fasterand higher quantities to target cells and chemically act faster

Heating vs. RF Why does RF work better than liquid heating?

Temperature dramatically drops across the bladder

With the RF catheter used in the Synergo® method, temperature gradient across outer bladder tissues is maintained; Special thermocouples constantly measure temperature of the bladder walls

SAR- Specific Absorption Rate

This value will tell us if we have enough energy to heat the tissue. In a point where SAR is higher then 100W/Kg, the heating ability of our device enables hyperthermia.

Summay of hyperthermia + chemotherapy

Drug will arrive in higher quantities, faster and at more stable concentration.

Drug will act faster by factor of X10-100

Temperature in bladder is homogenous and measurements are therefore reliable.

Temperature outside bladder is safe

Conclusion: the application can be administered safely with high potential efficacy.

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

Untreated high risk TCC:

Within 3 years 30% invasive progression

In case of CIS even 50% progression

More than 70% recurrence

Treatment purpose of TCC:

Eradication neoplasia

Prevent recurrence

Prevent muscle invasive progression

Prevent metastatic disease

Treatment TCC according to risk

Low
Single chemo instillation

Intermediate
cycle/course of chemo instillation; thermo-chemotherapy

High
BCG (maintenance); thermo-chemotherapy

Thermo-chemo vs. chemo

Drug uptake improved

Intracellular distribution improved

Reaction chemotherapy with DNA is increased

DNA repair is inhibited

Objectives heat dose analysis

Follow up recurrences plotted as a function of treatment parameters

Empirical relationship between treatment parameters and the time to recurrence

Optimizing treatment parameters in microwave thermo-chemotherapy treatments

Materials and Methods

1994-2005: several hundred patients underwent prophylactic or ablative thermo-chemotherapy

A list of criteria was made to select those which could be used to obtain meaningful results

Criterion	Inclusion	Exclusion
Type of patient		
For efficacy only		
Not for efficacy		
Type of treatment		
Prophyactic		
Ablative		
N Treatments		
Six weekly		
Less then six weekly		
Follow up		
>one FU cystoscopy		
No FU cystoscopy		

T0 determined as first chemotherapy treatment

Video cystoscopy performed every three months

Outcome data is last cystoscopy

In case positive cystoscopy ? time to recurrence

In case of negative cystoscopy ? no recurrence

Maximum follow up time 30 months

Data Collection: Each patient two data sets:

Treatment parameters for all treatments extracted from the Synergo system

Follow up data collected from patient files including cystoscopy results

Cross-checking records for consistency

Average bladder temperature is measured throughout treatment

Threshold temperature put at 40, 41, 42 and 43ºC

Analysis ‘time over threshold’ (thermal dose)

Thermal dose represented as (XXXTDYY); 250TD42 represents 250 min over 42ºC

picture 12

Results After filtering for eligibility 124 patients included

N treatments ranged from 6 to 16 (mean 10.6)

Tumour characteristics intermediate and high risk

Patients by country:

Country
N patients
Male Female

Israel
62
50 - 12

Netherlands
14
13 - 1

Austria
6
5 - 1

France
2
1 - 1

Italy
40
31 - 9

Total
124
100 - 24

Calculations: Heat dose effect

Treatment broken down in 2 temperature ranges: below 42ºC and above 42ºC

Function showing relationship between mix of these two ranges versus clean ratio

Treating above 42ºC is 44% more effective than working below 42 ºC

Calculation can be applied by all temperature ranges

Discussion

Circulation speed was not included in analysis

It was varied very little between patients

Not a time cumulative effect

Drug-epithelium contact time variable (urine production)

RF power not included in analysis

Conclusions

Treating above 42ºC is significantly more effective than below 42ºC

Effectivity thermo-chemotherapy increases significantly by temperature increase

Temperature intensity more important than duration