Oncologia e rene

Ambulatorio integrato di Nefro-Oncologia

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WHY, WHEN AND HOW A NEPHROLOGIST SHOULD BE INVOLVED IN THE MANAGEMENT OF A CANCER PATIENT

AVOID UN-NECESSARY TREATMENT INTERRUPTIONS AND DOSE REDUCTIONS

"New drugs have brought new toxicities. Certain of these toxicities pose problems which many Clinicians …will not be familiar with … A particular concern is that the desire to avoid toxicities and uncertainty about their management may lead … to prescribe a lower than optimal dose … or to reduce dose unnecessarily …"[1]

In two retrospective studies conducted in the USA[2] and in Italy[3], the percentage of patients who discontinued treatment owing to adverse events ranged between 16% and 23%

1 Escudier B, et al. Cancer Treat Rev 2011

2. Choueiri TK, et al. BJU Int 2009;

3. Porta C, et al. BMC Cancer 2011

WHY, WHEN AND HOW A NEPHROLOGIST SHOULD BE INVOLVED IN THE MANAGEMENT OF A CANCER PATIENT

WHY

- The IRMA study showed that among 4,684 patients with cancer, 12% and 52.9% had an eGFR of < 60 ml/min/1.73m^2 or of < 90 ml/min/1.73m^2, respectively. In patients aged > 75 years the prevalence was 27.2%, and 75% respectively [1]

- The presence of acute or chronic renal failure in a patient with cancer may affect the treatment and prognosis and worsen morbidity and mortality

1. Lounay-Vacher V, et al. Cancer 2007

WHY, WHEN AND HOW A NEPHROLOGIST SHOULD BE INVOLVED IN THE MANAGEMENT OF A CANCER PATIENT

WHY

- in patient with with CKD, the doses of many drugs need to be reduce furthemore, potentially active tratments are omitted in patients with renal impairment [1]

- the relationship between kidney and cancer therapy could also be regarded as 'circular'

- patient with cancer have an increased risk of developing AKI with an incidence of 258 cases per 1000 person-year the first year after cancer diagnosis, and the survival rates are lower in patients with cancer and AKI[2]

1 Darmon M, et al,.Crit Care 2006; 2 Chrstiansen CF, et al. Eur J Intern Med 2011

… AND IN PATIENT WITH CKD TOO

CORRELATION BEETWEN GFR AND RISK TO DEVELOP RCC OR UROTHELIAL CANCER (1.190.538 PATIENTS FOLLOWED FOR 8 YEARS)[1,2]

HR FOR RCC WITH eGFR

45-59: 1.58

30-44: 1.81

<30: 2.28

Not significant associations between eGFR and other types of cancer

PATIENTS WITH A PRE-EXISTING CKD MAY HAVE A GREATER RISK OF DEVELOPING HYPERTENSION AND PROTEINURIA AND OTHERS RENAL ADVERSE EVENTS REGARDLESS OF THE DOSE

1 Rosner & Meng oral, ASCO 2012; 2Lowrance W.T. et al JASN 2014

… AND IN PATIENT WITH CKD TOO

Frequently oncologists ask nephrologists to assess the degree of kidney impairment for anticancer therapy dosage adjustment

A thoroughly knowledge of the specific metabolism of anticancer agents and of their pharmacokinetic and pharmacodynamic properties is thus mandatory to decide if, when, and at what extent to reduce treatment doses

THE ISSUE OF NEPHRECTOMIZED PATIENTS

PRE-NEPHRECTOMY ASSESMENT OF KIDNEY FUNCTION

Prevalence of CKD pre-nephrectomy:

22% of 1184 patients with solid renal tumor had CKD stage III or greater, and 40% of patients 70 years and older had CKD stage III or greater [1]

Among 662 patients scheduled for partial or radical nephrectomy, the prevalence of chronic renal failure was 26% (CKD stage III or greater)[2]

Lower preoperative GRF is independ risk factor for post-operative AKI and for worsening of CKD[3]

Patients who experienced post-operative AKI had a 4.24-fold higher risk of new-onset CKD[3]

1 Canter D et al. Urology 2011; 2 Huang C, et al. Lancet Oncology 2006; 3 Cho A et al. NDT 2011

THE ISSUE OF NEPHRECTOMIZED PATIENTS

POST-NEPHRECTOMY FOLLOW-UP OF KIDNEY FUNCTION

the eGFR prior nephrectomy is highly predictive of developing CKD after nephrectomy[1]

These patients are not sent to Nephrologist, but they are followed by Urologists (and/or Oncologists)

Multidisciplinary rounds between Urologists, Oncologists, Radiotherapists … and Nephrologist???

Patients nephrectomized for RCC with or without CKD have a greater risk of developing all types of adverse events related to therapy not just those belonging to nephrologist[2]

1 Huang C, et al. Lancet Oncology 2006; 2Kandula P, et al. Kidney Int 2011

THE ISSUE OF PATIENTS UNDERGOING DIALYSIS

dialysis patients have a higher risk of developing cancer, particularly RCC

WE SHOULD CONSIDER TWO TYPES OF PATIENTS:

- patient with cancer that develops ESRD requiring dialysis
    - mortality rate in dialysis is 25% in the first six months and 20% in first year
    - ethical problem

- patient undergoing hemodialysis that develops cancer
    - dose and timing of treatment
    - surgery
    - pain therapy
    - end of life issues

THE ISSUE OF PATIENTS UNDERGOING DIALYSIS

IN PATIENT UNDERGOING HEMODIALYSIS THAT DEVELOPS CANCER UNNECESSARY DOSE ADJUSTMENTS SHOULD BE AVOIDED

- dose and timing of treatment

There are few data in the literatur… on dialysis, just case re… about classic C…

Di… …st of the drugs because the… …nbranes

Inde… …ergoing dialysis are often denied active oncological treatm… …ithout a real knowledge of the pharmacokinetic of anticancer agents in dialysis, as well as of the potentialities of these agents

Too often patients with CDK or on dialysis are UNDERTREATED

1 Janus, N. et al. CANDY (CANcer and DialYsis) study. Ann Oncol. 2013

WHY, WHEN AND HOW A NEPHROLOGIST SHOULD BE INVOLVED IN THE MANAGEMENT OF A CANCER PATIENT

WHEN

ALL TYPES OF CANCER:

- patients with CKD during oncological follow-up, or during oncological treatment
- patients who develop kidney disease (without significant waiting time) during tratement with nephrotoxic and no nephrotoxic agents
- before starting a potentially nephrotoxic treatment especially if present risk factors (e.g. hypertension, diabetes..)
- patients on dialysis

IN NEPHRECTOMIZED PATIENTS

- pre-surgery
- during follow-up (as needed) and pre-therapy
- during therapy (each time is needed – without significant waiting time)

WHY, WHEN AND HOW A NEPHROLOGIST SHOULD BE INVOLVED IN THE MANAGEMENT OF A CANCER PATIENT

HOW

DEDICATED NEPHRO-ONCOLOGICAL OUTPATIENT AMBULATORY (IN STRICT COOPERATION WITH ONCOLOGISTS)

- the prevalance of both cancer and CKD are growing up, patients with cancer can survival longer, so there is an increasing demand for physician who can provide long-term management

- the increasing number of therapies require an expertise of onco-nephrologists who must be knowledgeable about the array of new chemotherapeutic agents and their potential effects on kidney function

WHY, WHEN AND HOW A NEPHROLOGIST SHOULD BE INVOLVED IN THE MANAGEMENT OF A CANCER PATIENT

MANAGEMENT OF RENAL DISEASE IN CANCER PATIENTS

Management of:

- patients with risk factors
- patients with CKD
- patients on hemodialysis
- transplant patients
- patients with RCC or nephrectomized for RCC

Management of:

- renal involment in cancer
- paraneoplastic glomerulonephritis
- renal toxicities of classic CT
- renal toxicities from new target therapies

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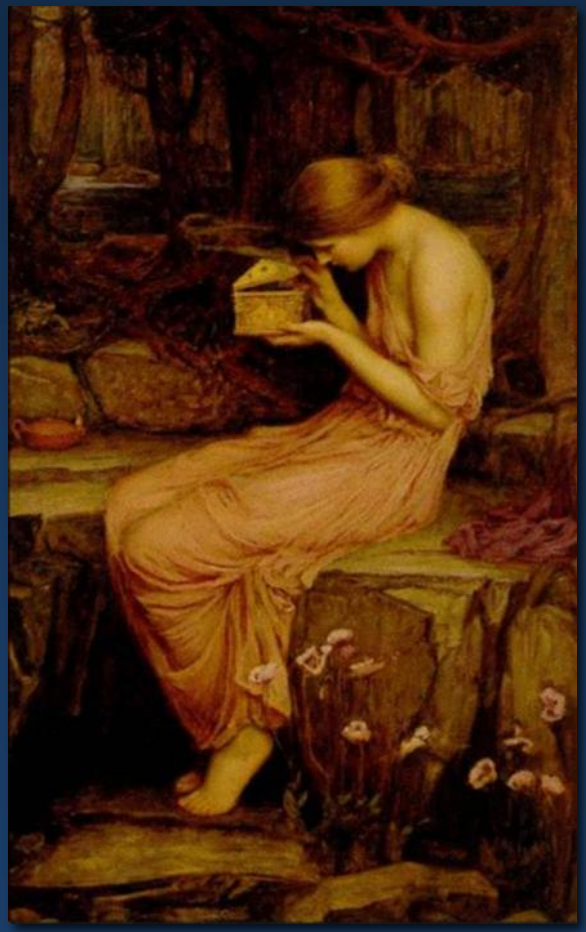
NEW DRUGS, NEW TOXICITIES…



John William Waterhouse, "Pandora", 1896

"After decades of use of common cytotoxic drugs, not only oncologists, but also internists, emergency physicians and general practitioners, have become well aware of the main toxicities of these agents

Consequently, our ability to promptly and correctly treat these side effects has allowed us to provide our cancer patients an adequate quality of life

As newer, molecularly targeted, anticancer drugs are entering clinical practice, a wide array of previously unrecognised and ill defined side effects of these drugs are increasingly observed…

… toxicities that we must recognise and learn to manage"[1]

1. Porta C, et al. Clin Exp Med 2007;7:127

IMPROVEMENTS …
OR EMERGING PROBLEMS?

Agents targeting VEGF/VEGFRs
- Bevacizumab
- ziv-Aflibercept
- Sunitinib
- Pazopanib
- Axitinib

B-RAF inhibitors ± MEK inhibitors
- Vemurafenib
- Dabrafenib
- Trametinib

EGFR inhibitors
- Gefitinib
- Erlotinib
- Afatinib
- Cetuximab
- Panitumumab

HER2-targeting agents
- Trastuzumab
- Lapatinib
- Pertuzumab
- T-DM1

Other multikinase inhibitors
- Sorafenib
- Imatinib
- Regorafenib
- Vandetanib

mTOR inhibitors
- Temsirolimus
- Everolimus

Bone targeting agents
- Denosumab

Novel ormonal agents
- Abiraterone
- Enzalutamide

Novel chemoterapeutics
- Nab Paclitaxel
- Olaparib
- Trabectedina

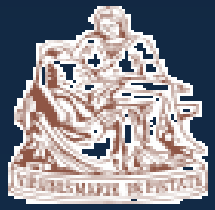
Other agents
- Ipilimumab
- Crizotinib
- Catumaxomab

SUMMARY OF PRODUCT CHARACTERISTICS

An integrated analysis of all clinical trials showed that the pharmacokinetic characteristics of …are not influenced by…or renal function. To date, have been studied only patients with adequate renal function (serum creatinine ≤ 1.5 times the upper limit of normal)…

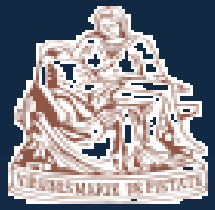
The results of a population pharmacokinetic model (data from subjects with baseline ClCr ranging from 30 ml/min and 150 ml/min) indicated that it is unlikely that renal insufficiency has a clinically relevant effect on the pharmacokinetics of … No dosage adjustment is required in patients with creatinine clearance greater than 30 ml / min.

Caution is advised in patients with creatinine clearance less than 30 ml / min as there is no experience in this population



TRYING TO GET ORDER OUT OF CHAOS …

Drug	Renal function impairment allowed in pivotal trial?	Renal excretion	More frequent renal AEs reported	Suggestions for the management of patients with mild to moderate CKD	Indications for the manage-ment of severe CKD patients	Indications for patients on dialysis
Bevacizumab	No	No	Hypertension, proteinuria	No need for dose reductions	No data (no need for dose reductions)	No issues
Cetuximab	No	No	Hypomagnesemia, other electrolyte disorders	No need for dose reductions	No data (no need for dose reductions)	No issues
Sunitinib	No	16%	Hypertension, proteinuria	No need for dose reductions	No data (no need for dose reductions)	No issues
Pazopanib	No	<4%	Hypertension, proteinuria	No need for dose reductions	No data (no need for dose reductions)	No issues
Axitinib	No	23%	Hypertension, (proteinuria)	No need for dose reductions	No data (no need for dose reductions)	No issues
Trastuzumab	No	No	Hypertension, AKI (with cisplatin)	No need for dose reductions	No data (no need for dose reductions)	No issues
Ipilimumab	No	No	Autoimmune nephritis, (DRESS syndrome?)	No need for dose reductions	No data (no need for dose reductions)	No data



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WHAT DOES IT MEAN ...

MANAGEMENT OF TARGET THERAPIES

RENAL TOXICITIES

- proteinuria
- hypertension
- electrolyte disorders
- acute kidney injury
- thrombotic microangiopathies

PATIENT WITH CKD

PATIENTS ON HEMODIALYSIS

TRANSPLANT PATIENTS

PATIENTS WITH RCC OR NEPHRECTOMIZED FOR RCC

WHAT ARE WE DOING IN CREMONA FROM MAY 2011

NEPHRO-ONCOLOGICAL AMBULATORY

- This Ambulatory takes place within an oncology outpatient ward, in order to allow closer interaction between specialists and easier access to patient's data
- One day a week (morning and afternoon) with time reserved for emergencies
- Reservations made directly to the front office of the oncology ward (also CUP)
- Same electronic medical record used in Nephrology Unit
- recipe mutidisciplinare consulting

WHAT ARE WE DOING IN CREMONA FROM MAY 2011

NEPHRO-ONCOLOGICAL AMBULATORY

- Nephrologist reference for cancer patients (consultant)
- Protocols for screening and follow-up of cancer patients according to different class of anticancer drugs
- Protocols for screening and follow-up of patients exposed to contrast medium and oncological drugs-induced nephrotoxicity (e.g. Cisplatin)
- Protocol for management of RCC patients

WHAT ARE WE DOING IN CREMONA FROM MAY 2011

NEPHRO-ONCOLOGICAL AMBULATORY

UNITS INVOLVED

- Oncology
- Radiotherapy
- Urology
- Breast Unit
- Surgery
- Hematology

WHAT ARE WE DOING IN CREMONA FROM MAY 2011

NEPHRO-ONCOLOGICAL AMBULATORY

Outpatients but also inpatient during therapy or during recovery

WHICH PATIENTS:

- cancer patients with pre-existing CKD in or not oncological treatment (even before the start of the treatment)
- patients who develope any renal Aes (any)
- cancer patients that should start a potentially nephrotoxic treatment
- RCC patients with CKD, undergoing or not active oncological tretament

what are we doing in Cremona from May 2011

TREATMENT-RELATED TOXICITIES OUTPATIENT

- proteinuria
- hypertension
- electrolyte disturbances
- calcium-phosporous metabolism disease
- anemia in patient with CKD and cancer
- management of tanticancer therapies in ESRD or on dialysis

TREATMENT-RELATED TOXICITIES INPATIENT

- TMA requiring dialyss
- AKI requiring dialysis

WHAT ARE WE DOING IN CREMONA FROM MAY 2011

FAST ACCESS TO

- Biopsy in patients with proteinuria
- Acid-base status for electrolyte disturbances
- Renal Artery Doppler Ultrasound and Renal US
- Hypertension Ambulatory with ABPM
- Dedicated Nutritional Ambulatory for cancer patients

WHAT ARE WE DOING IN CREMONA FROM MAY 2011

WE HAVE FOLLOWED

- 349 CANCER PTS WITH CKD ON ACTIVE CANCER TRETAMENT
- 92 UNTREATED CANCER PATIENTS WITH CKD
- 80 PATIENTS NEPHRECTOMIZED FOR A LOCALIZED RENAL CELL CARCINOMA
- 47 PATIENTS NEPHERCTOMIZED FOR A METASTATIC RENAL CELL CARCINOMA

PRELIMINARY RESULTS (POSTER SIN e ASN)

- percentage of patients who discontinued treatment owing to renal adverse events < 1% (in two studies in USA[2] and Italy[3], it ranged between 7% and 10%)
- 0% CIN
- 10 patients between 349 developed AKI but all re-start therapy
- 6 patients started dialysis without discontinue therapy

;

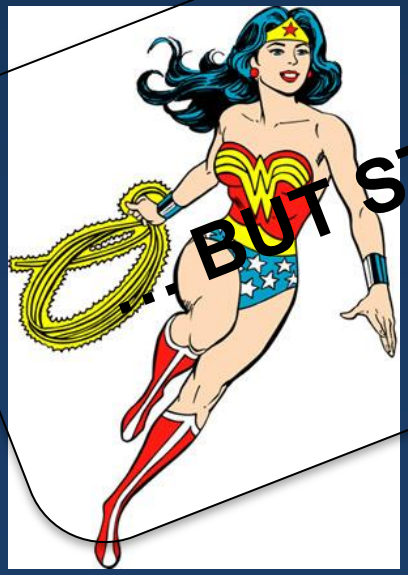
3. Porta C, et al. BMC Cancer 2011

CONCLUSION

NEPHROLOGISTS SHOULD DO THEIR OWN WORK,
taking into account that the tumor and its treatment is at the center of the stage

- ask oncologists for each patient's prognosis
- do not consider the kidney di per se more important than the tumor
- PLEASE, DO NOT TRY TO BE AN ONCOLOGIST

...BUT STRONGLY IN COLLABORATION



ONCOLOGISTS SHOULD DO THEIR OWN WORK,
but they should also understand when and how referring patients to his/her nephrological counterpart

- not too late for patient (potentially unuseful)
- not too late for the symptoms (potentially harmful)
- PLEASE, DO NOT TRY TO BE A NEPHROLOGIST

Thank you for your kind attention!!!

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