“Onco-Nefrologia: presente e futuro”

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Why, when and how a nephrologist should be involved in the management of a cancer patient
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Management of:
- renal involvement in cancer
- renal toxicities of classic CT
- renal toxicities from new immune and targeted therapies
- electrolyte disorders
- paraneoplastic glomerulopathies
- thrombotic microangiopathies
- tumor lysis syndrome
- ...

Management of cancer in:
- patients with CKD
- patients on hemodialysis
- transplant patients
- patients with RCC or nephrectomized for RCC
- patients with risk factors
Onco-Nephrology: a decalogue

1) acute kidney injury and chronic kidney disease in cancer patients
2) nephrotoxic effects of anti-cancer therapy, either traditional chemotherapeutics or novel molecularly-targeted agents
3) paraneoplastic renal manifestations
4) management of patients nephrectomized for a kidney cancer
5) renal replacement therapy and active oncological treatments
6) kidney transplantation in cancer survivors and cancer risk in ESRD patients
7) oncological treatment in kidney transplant patients
8) pain management in patients with cancer and kidney disease
9) development of integrated guidelines for onco-nephrology patients
10) clinical trials designed specifically for onco-nephrology
...The presence of acute kidney injury (AKI) or chronic kidney disease (CKD) in cancer patients has a negative impact on many aspects of patient care.

The presence of kidney impairment quite often affects a patient’s cancer treatment and overall prognosis.

The main questions in this setting are:

• the difference between acute and chronic kidney disease and their measurement

• the management of oncological drugs in patient who develop AKI or with pre-existing CKD
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\(^1\). This is particularly true for the elderly, who have the highest cancer incidence rates and 10-fold higher AKI rates compared with the non-elderly population.

Data from 3558 patients in M.D. Anderson Cancer Center showed that 12% of patients develop AKI after admission and 55% cases accrued > 48 hours after admission (increasing mortality, length of stay and costs).

Kidney cancer, liver cancer and multiple myeloma have the highest 1-year risks of AKI at 44%, 33% and 31% respectively\(^1\).

In patient with mild AKI 8-week mortality is 13.6% compared with patients with no AKI (3.8%); in patients requiring RRT mortality is 61.7% over the same frame\(^2\).

Nephrectomy is associated with 33.7% risk of AKI and predicts the future development of chronic kidney disease at 1 year\(^2\).

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\(^2\) Lam AQ, et al. *CJASN* 2012
AKI in cancer patients

AKI MAY PRECLUDE OPTIMAL CANCER TREATMENT
• requiring dose reductions/interruptions of the antitumor treatment
• by contraindicating potentially curative or life-prolonging treatments

AKI MAY DEVELOP DUE TO
• the presence of the cancer itself (obstruction, compression or infiltration)
• hemodynamic, metabolic or immunological causes
• directly caused by nephrotoxic anticancer treatments or contrast medium
• multiple concomitant causes often contributing to its genesis
• in patients treated with anticancer drugs, AKI often occurs due to indirect effects of the anticancer treatment

In patients treated with novel anticancer targeted drugs, AKI often occurs due to indirect effects of the anticancer treatment, and only rarely due to a direct toxic effect on the kidney
Chronic kidney disease in cancer patients

The IRMA study showed that among 4,684 patients with cancer,

- 12% and 52.9% had an eGFR of < 60 ml/min/1.73m² or of < 90 ml/min/1.73m², respectively
- In patients aged > 75 years the prevalence was 27.2%, and 75% respectively

France: 12.0% and 11.8% for eGFR<60 ml/min/1.73mq
Belgium: 16.1% for eGFR<60 ml/min/1.73mq
United States: 22% for eGFR<60 ml/min/1.73mq
Japan: 25% for eGFR<60 ml/min/1.73mq

Australia: for every 10 mL/min reduction in eGFR, there was an increase in cancer-specific mortality of 18%. This excess cancer mortality varied with site, with the greatest risk for breast and urinary tract cancer deaths, eGFR<60 mL/min/1.73m² appears to be a significant risk factor for death from cancer

The IRMA study clearly demonstrates that CKD is also quite prevalent in cancer patients

Finally, some very effective anticancer agents may be avoided as a potential option in CKD patients due to the lack of specific information on their pharmacokinetic properties in this setting

...taking into account that evidence is lacking for the majority of these patients, usually excluded from registrative clinical trials...
Frequently oncologists ask nephrologists to assess the degree of kidney impairment for anticancer therapy dosage adjustment.

In patients with CKD, the doses of many drugs need to be reduced furthermore, potentially active treatments are omitted in patients with renal impairment.\footnote{Darmon M, et al., Crit Care 2006;}

A thorough 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 presence of chronic renal failure in a patient with cancer may affect the treatment and prognosis and worsen morbidity and mortality.
Correlation between CKD and cancer

Correlation between eGFR and risk to develop RCC or urothelial cancer (1,905,538 patients followed for 8 years)\textsuperscript{1,2}

HR for RCC with eGFR

- 45-59: 1.58
- 30-44: 1.81
- <30: 2.28

no significant associations between eGFR and other types of cancer

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

\textsuperscript{1} Rosner & Meng oral, ASCO 2012; \textsuperscript{2} Lawrence WT. et al. JASN 2014
The relationship between kidney and cancer could be regarded as ‘circular’\(^1\), indeed, if on one hand the presence of the tumor or of an oncological treatment may directly or indirectly deteriorate renal function, on the other hand the presence of renal disease in cancer patients may worsen prognosis, increase mortality, and have impact on the bioavailability and/or safety profile of oncological drugs.

In patients with CKD, the doses of a number of oncological drugs need to be reduced, not to take into account the fact that, too often, potentially active treatments are omitted in patients with renal impairment.\(^2\)

**Too often patients with CDK or on dialysis are UNDERTREATED**

**AVOID UNNECESSARY ONCOLOGICAL TREATMENT INTERRUPTIONS AND DOSE REductions**


“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”

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<th>Agents targeting VEGF/VEGFRs</th>
<th>HER2-targeting agents</th>
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<td>Bone targeting agents</td>
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<td>Denosumab</td>
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<td>Other agents</td>
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What does it means..

**MANAGEMENT OF ANTICANCER THERAPY**

**AVOID UN-NECESSARY TREATMENT INTERRUPTIONS AND DOSE REDUCTIONS**

**RENAL TOXICITIES**
- proteinuria
- hypertension
- electrolyte disorders
- acute kidney injury
- thrombotic microangiopathies
- AKI or worsening pre-existing CKD
- glomerulopathies
- interstitial nephritis

**PATIENT WITH CKD**

**PATIENTS ON HEMODIALYSIS**

**TRANSPLANT PATIENTS**

**PATIENTS WITH RCC OR NEPHRECTOMIZED FOR RCC**

**PATIENTS WITH RISK FACTORS FOR KIDNEY DISEASE**

**AVOID UN-necessary treatment interruptions and dose reductions**
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
Daily problem

THE DECISION TO CONTINUE, DISCONTINUE OR CHANGE A TREATMENT IS A DAILY PROBLEM
GUIDELINES DOES NOT EXIST
LACK OF DATA IN LITERATURE

THE DECISION DEPENDS STRONGLY ON THE EFFECTIVENESS OF THERAPY

Effective treatment
WHEN STOP OR DISCONTINUE OR CHANGE AN EFFECTIVE TREATMENT DUE TO THEIR RENAL SIDE EFFECTS?

Not effective treatment
STOP TREATMENT

CKD, by itself, is not a reason to reduce or even to deny target therapies, at least in the absence of others comorbidities
Glomerulopathies and paraneoplastic manifestations in cancer patients

... Various forms of paraneoplastic kidney injury occur as a result of non-direct, distant toxicities of malignancy that are unrelated to drug-induced nephrotoxicity.

These rare events, which include:

• paraneoplastic glomerulonephritis (membranous, minimal change, focal segmental glomerulosclerosis, IgA nephropaty, etc.)
• paraneoplastic electrolyte/acid–base disturbances
• thrombotic microangiopathies (TMA)
• glomerular diseases associated with hematopoietic stem cell transplantation (whose incidence appears to be increasing)
• glomerular diseases associated with lymphomas and mieloma
• glomerulopathies and TMA due to therapy

They represent a complex differential diagnosis and often pose a difficult issue for clinicians...

The question in this setting is cancer screening: why, when, what and for whom
Management of patients nephrectomized for kidney cancer

Kidney cancer remains the only malignancy where either total or partial nephrectomy is indicated. This includes not only localized, curable tumours, but also incurable, metastatic malignant disease. It has been clearly demonstrated that patients who have undergone nephrectomy are at increased risk of developing AKI, de novo CKD, especially in the presence of certain co-morbidities, or of worsening a pre-existent CKD, which is highly prevalent in these patients prior to nephrectomy.

The question in this setting is why, when, and how a nephrologist should be involved in managing of nephrectomized patients?
Of 300,000 RCC survivors in the United States, at least 45,000 have an underlying kidney disease, most commonly diabetic nephropathy or hypertensive nephrosclerosis.

Partial nephrectomy, which is considered nephron-sparing, may also cause AKI or worsen underlying CKD, depending on the amount of non-neoplastic parenchyma removed but also depending on the condition of residual parenchima.

A modification of the College of American Pathologist “kidney cancer protocol and checklist” established the status of non-neoplastic kidney as a required parameter for reporting (… “Medical” nephropathy...)
RCC ...
when a nephrologist should be involved

PRE-NEPHRECTOMY ASSESSMENT 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 independent 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 \(^3\)

**POST-NEPHRECTOMY FOLLOW-UP OF KIDNEY FUNCTION**

the eGFR prior nephrectomy is highly predictive of developing CKD after nephrectomy

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**DURING THERAPY**

The 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

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How a nephrologist should be involved

PROTOCOLS FOR MANAGEMENT OF RCC PATIENTS

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

MULTIDISCIPLINARY ROUNDS BETWEEN
Urologists, Oncologists, Radiotherapists and Nephrologists to discuss complicated cases

GUIDELINES ON MANAGEMENT OF RCC PATIENTS

• AURO 2012
• AIOM 2015-2016-2017
Renal replacement therapy and active oncological treatments

... One of the more challenging areas of onc nephrology is the appropriate management of cancer patients that require renal replacement therapy (RRT) for either AKI or ESRD, a patient population characterized by low survival rates.

Decisions about anticancer drug choices and dosing are often not supported by pharmacokinetic or pharmacodynamic data, making therapeutic decisions difficult...

The questions in this setting are:

• when and if it’s ethical starting dialysis in cancer patients, the importance of prognosis;
• how to manage cancer therapies in cancer patients undergoing dialysis
What about patients under dialysis

There is paucy of information regarding issues surrounding the optimal management of dialysis patients, especially those needing chemotherapy

1) the absence of renal function in hemodialysis (HD) patients may necessitate drug dosage reduction. Therefore, drug prescription must be cautiously checked before administration with appropriate dosage adjustment whenever necessary to ensure efficacy while avoiding overdosage and related side effects

2) drug clearance by dialysis session, volume of distribution, molecular size, protein binding, must be taken into account for appropriate chemotherapy timing administration to avoid drug removal, which may result in a loss of efficacy

These two main considerations must not be considered as a contraindication to chemotherapy in ESKD patients, but more as a need for an individualized prescription according to available recommendations
Renal replacement therapy and active oncological treatments

There are few data in the literature on patients treated with oncogocal drugs while on dialysis, just case reports or small case series:

- even more data are present for cytotoxic therapy (e.g. cisplatin), there is no uniformity regarding the dose and time of administration

- dialysis does not affect the plasma concentration for most of the target therapies because they are not dialysated by commonly used membranes, and will not appear in the dialysate. No data for immune checkpoint inhibitors

- unnecessary dose adjustments should be avoided, its crucial to consider anticancer drugs in these patients as far non-dialysis patients using available specific drug raccomandation in order to: adjust dose and avoid premature elimination during dialysis session

- indeed, patients under dialysis are often denied active oncological treatment without a real knowledge of the pharmacokinetic of anticancer agents in dialysis, as well as of the potentialities of these agents

Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY (CANcer and DialYsis) study


Once diagnosed, cancer in a dialysis patient should be treated as in the non-dialysis patient, with appropriate consideration of the renal clearance, dosing, and dialyzability of chemotherapeutic agents
DIALYSIS PATIENTS HAVE A HIGHER RISK OF DEVELOPING CANCER, PARTICULARLY RCC

WE HAVE TO CONSIDER TWO TYPES OF PATIENTS:

PATIENT UNDERGOING HEMODIALYSIS THAT DEVELOPS CANCER
- dose and timing of treatment
- pain relief
- surgery

PATIENT WITH CANCER THAT DEVELOPS CKD REQUIRING DIALYSIS
- mortality rate in dialysis in first year
- ethical problem
- quality of life
- patient’s wishes

What about patients under dialysis
Kidney transplantation in cancer survivors and cancer risk in ESRD patients

Another setting that requires a close working relationship between the nephrologist and oncologist is in the evaluation for transplantation of an ESRD patient with a previously treated malignancy.

The question of how long to wait before placing such an ESRD patient on the transplantation list can be difficult.

• What is a sufficient length of time to consider a patient as cured and able to receive a graft and undergo immunosuppression therapy?

• Even more complex is dealing with the flip side of this issue — is the patient with a previously treated malignancy a suitable kidney donor?

• In such a scenario, are all malignancies considered the same in this regard?
Without a doubt, pain is probably the worst experience a cancer patient must endure.

Despite the availability of a number of highly active analgesic drugs, the use of certain drugs can be problematic in cancer patients with either acute or chronic kidney disease.

How should we treat pain in cancer patient with kidney disease?
Development of integrated guidelines for Onco-Nephrology patients

The lack of Onco-Nephrology guidance for clinicians has multiple explanations and includes:

• **selection bias of randomized controlled phase III trials**, where patients are enrolled only if they have a conserved kidney function

• **difficulty in interpreting the nature and incidence of renal adverse events** from these trials

• **lack of uniformity in the definition of kidney impairment** between oncological trials, summary of product characteristics and nephrologic classification

• **availability of only case reports** or small case series for patients undergoing dialysis
Clinical trial design specific to Onco-Nephrology

It is imperative that we together begin to design and conduct randomized, controlled clinical trials (and other trial design) aimed at addressing many of the issues and questions raised here.

Only then can we provide evidence-based care to this complicated group and ultimately improve their outcomes.
Beyond the decalogue...

- CIN in cancer patients
- Electrolyte disturbances
- Urothelial tumors
- TMA due to therapy
- Hematologic disorders and their treatments in patients with kidney disease
- Acute kidney injury in Hematopoietic Stem Cell Transplant
- Radiation Nephropathy
- Tumor Lysis Syndrome
- Anemia and use of ESAS in cancer patients
- Bone, kidney and cancer (PTH, Vitamin D, calcium and phosphorous metabolism)
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 disease more important than the tumor
• PLEASE, DO NOT TRY TO BE AN ONCOLOGIST

ONCOLOGISTS SHOULD DO THEIR OWN WORK, but they should also understand when and how referring to his/her nephrological counterpart
• not too late for patient (potentially useless)
• not too late for the symptoms (potentially harmful)
• no nihilism towards nephrologic patients
• PLEASE, DO NOT TRY TO BE A NEPHROLOGIST

... BUT STRONGLY IN COLLABORATION
WE MUST CREATE DEDICATED ONCO-NEPHROLOGICAL OUTPATIENT AMBULATORIES, IN STRICT COOPERATION WITH ONCOLOGISTS

Since the prevalence of both cancer and CKD is growing up, and patients with cancer survive longer, there is an increasing demand for physicians who can provide a long-term, integrated, management of these patients.

Furthermore, the increasing number of active anticancer agents require a specific onco-nephrological expertise, with dedicated physicians who must be aware of the array of new anticancer agents, and of their potential impact on kidney function.

In the US, the “Comprehensive Cancer Centers” have already adopted Nephrologists as a structured part of their multidisciplinary team.
What are we doing in Cremona from May 2011

NEPHRO-ONCOLOGICAL AMBULATORY
NEPHRO-ONCOLOGICAL AMBULATORY

Outpatients but also inpatient during therapy or during recovery

WHICH PATIENTS:
• treated or untreated cancer patients with pre-existing CKD
• patients who develope renal AEs (any)
• cancer patients that should start a potentially nephrotoxic Tx, especially if risk factors are present
• RCC patients, undergoing or not active oncological Tx
• transplanted patients who develop cancer
• patients on dialysis who develop cancer
TREATMENT-RELATED TOXICITIES
OUTPATIENT

- proteinuria
- hypertension
- electrolyte disturbances
- calcium-phosphorous metabolism
- anemia in patients with CKD and cancer
- management of anticancer Tx in CKD, ESRD, or on dialysis
- use of contrast medium in CKD
- TMA
- AKI
- TLS

What are we doing in Cremona from May 2011
... and what we should do in Italy

NEPHRO-ONCOLOGY SERVICE, I.E.

• Nephro-Oncology 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
• Protocol for management of RCC patients
• Multidisciplinary consultation for GU cancers
... and what we must do
... The future...

Consensus Statement

Cardio-Oncology Training: A Proposal From the International Cardioncology Society and Canadian Cardiac Oncology Network for a New Multidisciplinary Specialty

Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

International Cardioncology Society Tackles Heart Problems in Cancer Patients

Collaboration between 2 specialties focuses on mutual challenges for patients
Onco-nephrology is an evolving subspeciality that focuses on the complex relationships existing between kidney and cancer ... they represent only the tip of the iceberg and likely underestimate the actual depth of collaboration that is possible for the two specialties ...”

Society involved
Thank you for your kind attention!!!