Management of Metastatic Renal Cell Carcinoma

25th ICRO Teaching Programme

Dr. Vimal Pandita

Sr. Consultant & Head

Medical Oncology & Hematology

Max Superspeciality Hospital, Dehradun

Introduction

Renal cell cancer comprises about 3.5 to 4% of all new cancers

Clinically occult for most of its course

Approximately 30% of patients with RCC present with metastatic disease

Long-term survival rates of mRCC is dismal but has improved of late largely due to introduction of newer therapies

Introduction

Management of Stage IV disease

Prognosis models

Role of Nephrectomy

Any role of Chemotherapy or Radiotherapy

Cytokines

TKIs & antiangiogenesis agents

Checkpoint inhibitors, others

Future

Prognostic models

Prognostic models

Prognostic scoring systems have been developed to define risk groups of patients by combining independent prognostic factors for survival

Not only this helps in explaining likely prognosis to a patient, they may also help in personalizing treatment from a basket of therapeutic armamentarium

MSKCC prognostic model

Most widely used

Derived from 463 patients with mRCC enrolled in clinical trials and treated with interferon

Five variables

MSKCC prognostic model

1. Interval from diagnosis to start of treatment <1 year
2. KPS < 80%
3. Serum LDH > 1.5 times ULN
4. Corrected serum calcium > ULN
5. Hemoglobin < LLN

Score 0 = Low risk

Score 1-2 = Intermediate risk

Score 3-5 = Poor risk

SURVIVAL	
1 YEAR(%)	3 YEAR(%)
71	31
42	7
12	0

MSKCC criteria validated by independent group at Cleveland clinic

Heng's Model (IMDC)

Patients treated with VEGF targeted therapy era

Useful in previously treated and untreated patients

Improved prognostication compared to other prognostic models

6 variables

Heng's Model (IMDC)

1. KPS < 80
2. Interval from diagnosis to start of targeted therapy <1 year
3. Hemoglobin < LLN
4,5,6. Calcium, Neutrophil count, Platelet count > ULN

Heng's Model (IMDC)

score 0 = Favorable risk

score 1 - 2 = Intermediate risk

score 3 - 6 = Poor risk

SURVIVAL

Risk category	Median OS	2-Yr OS
Favourable	not reached	75%
Intermediate	27 months	53%
Poor	8.8 months	7%

IMDC model more accurate in reflecting outcomes in current era of targeted therapy

Role of Nephrectomy

Nephrectomy

Data mainly from Interferon era

Combined analysis of different trials favored surgery group

(*SWOG & EORTC*)

Median Survival 13.6 months for Surgery + IFN-a

7.8 months for IFN-a alone

Very rare reports of regression of metastatic disease following nephrectomy

Patient selection

Most likely to benefit from cytoreductive nephrectomy before systemic therapy

-- lung only metastasis

-- good prognostic features

-- good performance status

Nephrectomy

Targeted therapy era

There may be benefit (non randomized studies)

IMDC retrospective study(201 patients)

- Improved OS 19.8 vs 9.4 months

- Marginal benefit in poor risk patients

Phase III CARMENA study--ongoing

Nephrectomy

No universal approach to patient selection

> 75% tumour debulking possible

ECOG 0 or 1

No evidence of extensive liver or bone metastasis or CNS involvement

istimated overall survival <12 months or > 4 prognostic factors do not enefit

Palliative nephrectomy

Intractable pain not controlled with analgesics

Hematuria due to RCC

Systemic symptoms- Hypercalcemia, fatigue, fever

Metastasectomy

Settings:

Stage IV disease at presentation, performed with nephrectomy

Metastatic disease following nephrectomy

Persistent disease despite systemic therapy

Metastasectomy

Can yield long term DFS

Strongest predictors of LTS

- > 1yr DFI from nephrectomy to detection of metastasis
- Single vs multiple sites of metastases
- Lung vs other sites
- ECOG 0 or 1
- No prior cytotoxics or significant weight loss

Metastasectomy

Role of systemic therapy

Only surveillance is recommended

Phase III ECOG trial undergoing (pazopanib vs placebo)

Resection of residual disease after systemic therapy

Chemotherapy & Radiotherapy

Histology

Clear cell RCC

Papillary RCC

Chromophobe RCC

Introduction

RCC with sarcomatoid features

Aggressive , can occur in any histologic subtype, poor prognosis

Gemcitabine + Doxorubicin, some activity

Sunitinib + Gemcitabine

Medullary & Collecting Duct carcinomas – Gemcitabine + cisplatin/carboplatin. Paclitaxel + carboplatin

Introduction

Chemotherapy in RCC extensively studied

No single agent demonstrated response rate above 10%

Currently little to no role in mRCC

Mechanism of Chemotherapy resistance

Reduced drug accumulation due to various transport proteins

P-glycoprotein expressed on RCC cells acts as an efflux pump

Additional mechanisms

Systemic therapy

Cytokines

Interferon-a & Interleukin-2

These immunological agents retain a unique role in the armamentarium of agents used to treat widespread metastatic RCC

Their use in treating RCC was instrumental in demonstrating that biotherapies were capable of inducing complete and curative regressions of human cancer.

Introduction

Result only attained by small proportion

Factors that predict or produce dramatic, durable responses in such patients have not been clearly established, but

The fact remains that biotherapy, and specifically IL-2 is the only systemic treatment that can consistently cure some patients with metastatic RCC.

Introduction

Problems:

Low and uncertain response rates

No definite pretherapy indicators or predictive factors of response

Toxicity and treatment related mortality

Availabilty of safer drugs

VEGF-Targeted Therapy

VEGF receptor inhibitors

Sunitinib

Pazopanib

Sorafenib

Axitinib

VEGF Ligand-binding agents

Bevacizumab

Introduction

Sunitinib

Multikinase inhibitor including VEGF, PGDFR-a, c-KIT, FLT3, RET

Inhibition of angiogenesis and cell proliferation

Sunitinib vs IFN

ORR 31%

11 vs 5 months PFS, 26.4 months OS

Activity in Clear cell, non clear cell, brain metastasis and poor PS

Introduction

Pazopanib

Oral angiogenesis inhibitor-VEGF, PGDFR-a, c-KIT

Pazopanib vs placebo

ORR 30%

PFS 9.2 months vs 4.2 months (11.1 months for treatment naive)

OS not significant because of extensive crossover

Introduction

Bevacizumab

Monoclonal antibody that binds circulating VEGF

Bevacizumab + IFN-a vs IFN-a + placebo

PFS 10.2 months vs 5.5 months

Trend towards improved OS = 23.3 months

Introduction

Axitinib

Oral VEGF receptor inhibitor

Higher response rates than Sorafenib

Not compared with sunitinib or Pazopanib in 1st line

ORR 48%

PFS 15.5 months

Introduction

Sorafenib

inhibits VEGF, FLT3, PDGFR, FGFR, C-raf and B-raf

No increase in PFS vs IFN-a in first line

Mainly used in second line

mTOR pathway inhibitors

mTOR protein regulates micronutrients, cell growth, apoptosis and angiogenesis by its downstream effects on variety of proteins

Temsirolimus

Everolimus

Introduction

Temsirolimus

Activity in mRCC

Temsirolimus, temsirolimus + IFNa or IFNa monotherapy (poor risk)

Median OS 10.9 vs 7.3 months over IFNa

No benefit of combining the two

Inferior to Sorafenib as second line

Inferior to Bevacizumab in first line

NCCN – Category 1 for first line in poor risk patients

Introduction

Everolimus

mTOR inhibitor

Used as second line

PFS 4.9 months vs 1.9 months with placebo

Immune checkpoint inhibitors

Nivolumab

Anti PD-1 monoclonal antibody

PD-1 is a protein on activated Tcells with PD-L1 & PD-L2 being its ligands. When these interact, this prevents activated T cells to destroy cancer cells

Nivolumab Blocks PD-1 and thus prevents its interaction with its ligands

Introduction

Nivolumab

Phase III Checkmate 025 trial

Previously treated clear cell mRCC Nivolumab vs Everolimus

Median OS 25 vs 19.6 months

ORR 25% vs 5 %

Consistent OS benefit across all risk groups and other factors

Approach to the patient

Approach

65-75 % renal tumours are Clear cell carcinomas

Others Papillary, Chromophobe, collecting duct, medullary and oncocytomas

Initial insights into molecular pathogenesis of clear cell RCC from studies in VHL disease

VHL – C

Cerebellar and spinal hemangioblastomas, pheochromocytomas

Clear cell RCC(40-60%)

Introduction

In VHL LOH on Chr3p25 at VHL locus

Same abnormality in 75 to 80 % sporadic clear cell RCC

Implicates VHL gene in pathogenesis of clear cell RCC

This abnormality leads to overproduction of VEGF

Alternate pathway-mTOR

Treatment naive

Pazopanib, Sunitinib and Bevacizumab + IFNa

Pazopanib 800mg OD

Good and Intermediate risk

Similar in efficacy to sunitinib

Less toxic

Poor risk

Sunitinib

Temsirolimus

Prior Immunotherapy

Axitinib

Sunitinib

Pazopanib

Prior targeted therapy

Nivolumab

Cabozantinib

Axitinib

Prior targeted therapy & Immunotherapy

Clinical trial

Another targeted agent

New kids on the block

Cabozantinib

Lenvatinib