ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XXIV, N 4, 12 SECTIO DDD 2011

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Molecular-oriented treatment of metastatic kidney cancer

Leczenie ukierunkowane molekularnie przerzutowego raka nerki

INTRODUCTION

Molecular approach to the treatment of metastatic kidney cancer

According the latest trials results, chemotherapy and hormone treatment of metastatic kidney cancer seems to be ineffective. The reviews of most recent study results give the following conclusions:

- Response to the treatment within the limits of statistical error – 5%,
- Chemotherapy lacks effectiveness – high expression of P170 protein which is coded by genes from multi-drug immune gene family,
- The analysis of the effectiveness of these drugs resulted in failure:
  - modeling the functions of the P170 protein – vinblastines, cyclosporine A, tamoxifen,
  - inducing apoptosis: paklitaxel, docetaxel, epothilone –ixabepilone, patupilon,
  - bioorganometallic compounds – titanocene bichloride,
  - other – irinotecan, capecitabine gemcitabine
- Allogenic bone marrow or blood stem cells transplant –the response is linked to "transplant against kidney cancer" reaction - applied only in clinical trials on experimental basis.

Renal cell carcinoma accounts for approximately 2-3% of total number of cancers that adults are suffering from. It takes 7th place among the most common cancers among men and 9th place among the most common cancers among women (Fig. 1-4). Men are more likely to be affected– gender ratio of cases M:W=2:1. The cancer is usually diagnosed in 6th and 7th decade of lifetime

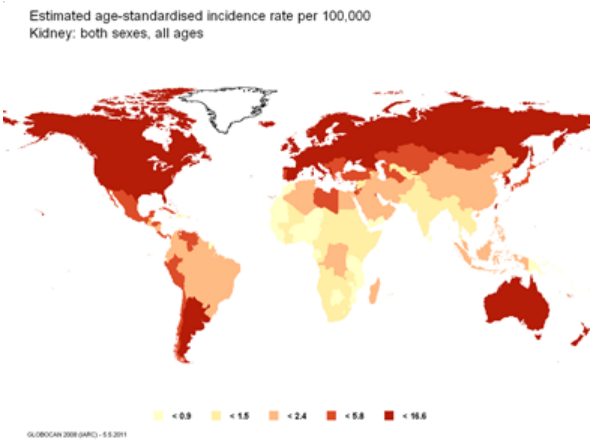

Figure 1. Estimated kidney cancer incidence rate with regard to both sexes [3,8].

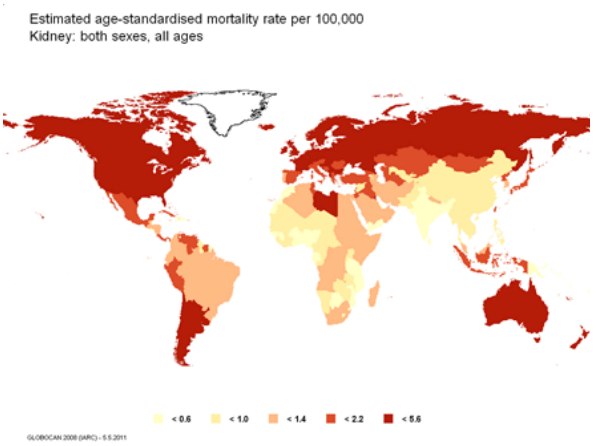

Figure 2. Estimated kidney cancer mortality rate with regard to both sexes [3,8].

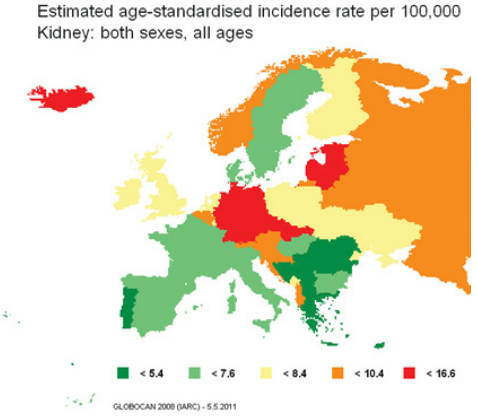

Figure 3. Estimated kidney cancer incidence rate in Europe with regard to both sexes [3,8].

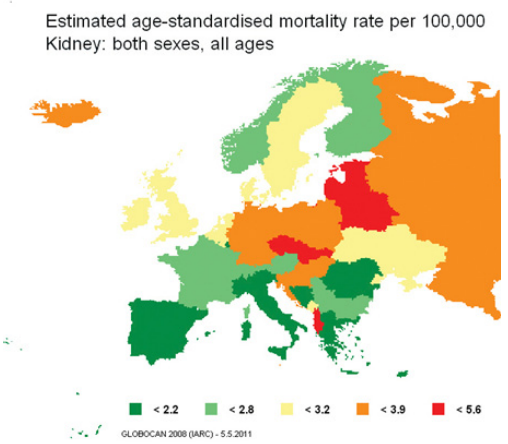

Figure 4. Estimated kidney cancer mortality rate in Europe with regard to both sexes [3,8].

In Poland in 2007 there were 3886 new kidney cancer cases, including 223 in Lubelskie Voivodship.

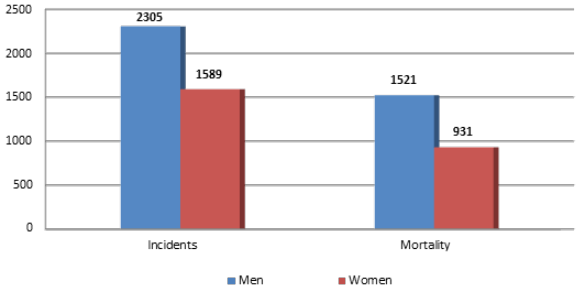

Figure 5. Estimated kidney cancer incidence in Poland with regard to both sexes

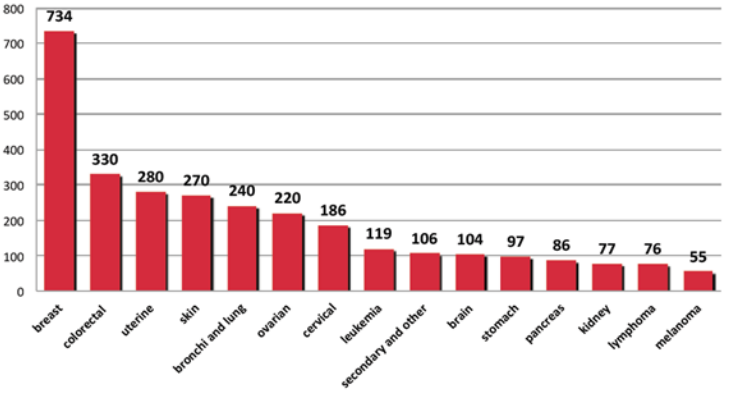

Figure 6. Number of new cancer cases among women in Lubelskie Voivodship in 2007

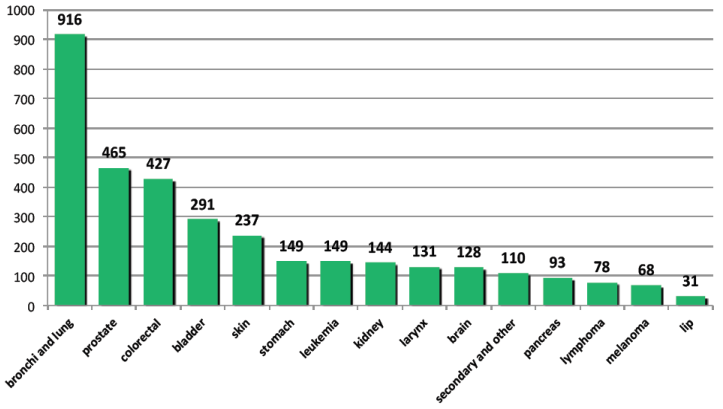

Figure 7. Number of new cancer cases among men in Lubelskie Voivodship in 2007

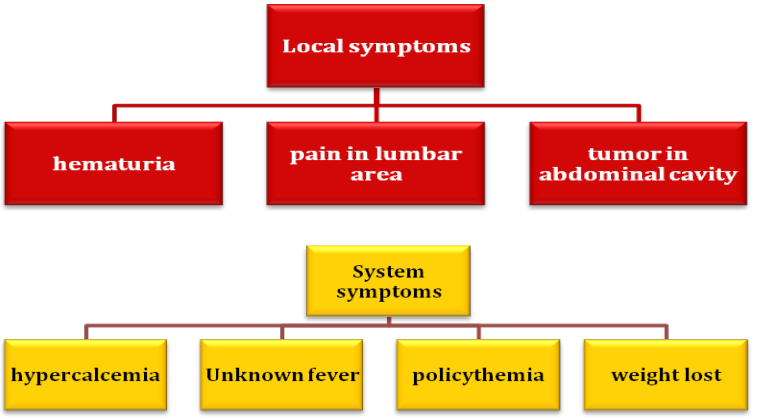

Figure 8. Local and system symptoms of the kidney cancer

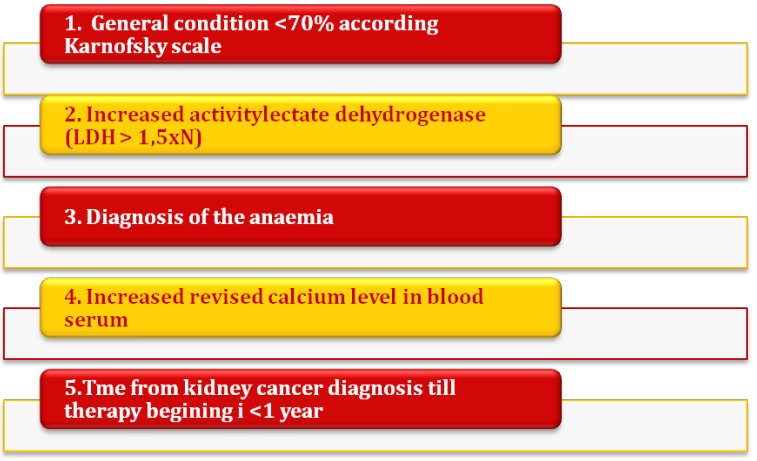

Fig. 9. The five detrimental risk factors according MSKCC Scale

TREATMENT CHARACTERISTICS – EVIDENCE AND RECOMMENDATIONS LEVELS

Credibility level could be specified as follows:

1. Evidence gathered from meta-analysis based on numerous properly designed and controlled trials. Clinical trials were randomized both with low false positive and with false negative error levels (high significance).
2. Evidence gathered from at least one well designed experimental trial. Clinical trials were randomised both with high false positive and/ or negative errors (low significance).
3. Evidence gathered from well designed, partially experimental, controlled trials conducted on one group. Analysis done before/after, cohort method and control trials series.
4. Evidence from well designed non- experimental trials such as comparative-descriptive trials and correlation cases.
5. Evidence gathered from the case description.

Recommendation levels are as follows:

A. There is first level evidence which is determined according to numerous types of trial levels II, III and IV.
B. There is evidence on level 2, 3 or 4 and conclusions are generally coherent.
C. There is evidence on level 2, 3 or 4 but results are not coherent.
D. There is small or non-systematic empirical evidence.

The majority of clinical trials was conducted on patients with tumors characterized by clear cell histology First line treatment on patients with low or average risk according to MSKCC: sunitinib or bevacizumab + interefron-alfa ot pazopanib; on patients with high risk level: temsirolimus [1, A]. Second line treatment on patients with the history of cytokines treatment failure: sorafenib or pazopanib [1, A]. Treatment on patients with the history of tyrosine kinase inhibitors treatment failure: everolimus [1, A]. Information about cases of patients with tumors characterized by non-clear cell histology is insignificant. Sunitinib or sorafenib are offered as therapeutical alternative despite limited effectiveness; Temsirolimus as an alternative drug based on analysis of stage III trial [III, B]. Prodecure algorithm according to ESMO has been presented in the Table 1.

Table 1. Prodecure algorithm according to ESMO

First line of treatment			
Hystologic Type	**Risk Groups**	**Standard**	**Options**
Clear cell renal carcinoma	Good, average prognosis	Sunitinib, Bevacizumab + IFN, Pazopanib	High dose Il2
	Bad prognosis	Temsirolimus	Sunitinib
Second line of traetment			
Clear cell renal carcinoma	After cytokines	Sorafenib, Pazopanib	Sunitinib
	After TKIs	Everolimus	
Non-clear cell renal carcinoma			Temsirolimus, Sorafenib, Sunitinib

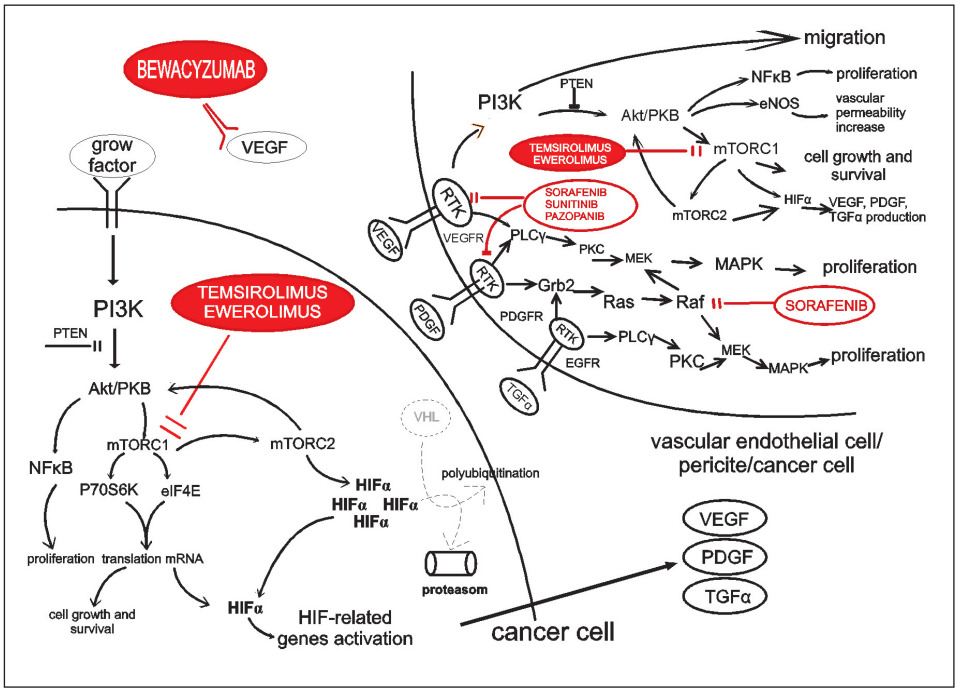

Figure 10. Mechanisms involved in neoangiogenesis and carcinogenesis of renal cancer cells and treatment target points

Tyrosine Kinase Inhibitor (TKI) - sunitinib, sorafenib and pazopanib (Fig 10):

- Treatment oriented toward molecular intra-cellular elements on the signal transmission channels; non-selective. Competitive inhibition of ATP joining needed to lead phosphorytation through kinase. Wide inhibition spectrum – benefit → blocking many channels linked to angiogenesis theoretically more efficient than inhibition of one of the channels only. Higher level of selectiveness – benefit → reduction of undesirable actions linked to treatment. hydrophobic nature
- Good absorption from digestive system after and oral application
- Ability to diffuse through the cell membrane inside the cell
- Pharmacokinetics of these drugs is not significantly related to body mass, therefore the dose is fixed, independently from height and weight.

Monoclonal antibodies – bevacizumab (Fig.10):

6. Recombined, humanized monoclonal antibody coupled to VEGF and deactivating its biological functions
7. Associated with interferon-α
8. Both bevacizumab and small doses of interferon-α express anti-angiogennic activity
9. VEGF inhibits maturation and functions of dendrite cells
10. Simultaneous use of VEGF inhibition and interferon-α, which stimulates maturation and production of cytokines performed by subpopulation of cells, may reverse to certain extent the state of immuno-suppression in case of advance kidney cancer.

mTOR Kinase inhibitors - temsirolimus, everolimus (Fig. 10):

- Selective inhibition of mTORC1 protein structure
- Inhibition of signal transmission in response to the growth factors from PI3K/Akt/mTOR cascade which is engaged in control of the progress of cellular cycle and apoptosis
- Indirect influence of rapamycine analogs on creation of mTORC2 structure (regulator of PI3K/Akt/mTOR path) which appears during the cell long-term exposure to these substances
- Suppression of mTORC1 and mTORC2 decreases the level of HIF-α transcription and contributes to debilitation of angiogenesis mechanisms.

Interferon – α only used for treatment on patients with: previous nephrectomy, positive prognosis (low risk according to MSKCC), the kidney cancer metastasis limited to lungs.

Total survival time median (months): nephrectomy + Interferon-α 11.1 (95% CI, 5.4–9.5; $p = .05$). Nephrectomy 8.1. 6 randomized trials: Interferon - α – improvement OS o 2.6 months (metastasis to lungs and/or soft tissues, ECOG 0 or 1, no weight lost) [6,9].

Comparison of the effectiveness of sorafenib (400 mg p.o. 2x per day, n=97) and interferon-α (9 mln j.m. s.c. 3x per week, n=92): Objective response to treatment: 47% vs. 12%; PFS Median : 11 months vs. 5 months; OS Median : 26.4 months vs. 21.8 months (statistically significant differnces discovered after secondary analysis done with regard to stratification factors).

Comparison of the effectiveness of bevacizumab associated therapy (10 mg/kg iv every 2 weeks) with IFN-α (9 mln j.m. s.c. 3x per week) (n=327) vs. placebo + IFN-α (n=322) [7]. Objective response to treatment: 31% vs. 13% PFS Median :10.2 month vs. 5.4 months OS Median : 23.3 months vs. 21.3 months (no statistical significance).

Comparison of temsirolimus effectiveness (25 mg i.v. 1x per week, n=209) and interferon-α (3 mln j.m. s.c. → 9 mln j.m. s.c. 3x per week, n=207) and association of exchanged drugs (15 mg i.v. 1x per week + 3-6mln j.m. s.c. 3x per week n=210) Patients with bad prognosis

Objective response to treatment: 8.6% vs 4.8% vs. 8.1% (no statistical significance)

PFS Median: 5.5 months vs. 3,1 months vs. 4.7 months, OS Median: 10.9 months vs. 7.3 months vs. 8,4 months (statistically significant differences in total years lived).

Comparison of the effectiveness of everolimus (10 mg p.o., n=277) and placebo (n=139) [14,15]. Objective response to treatment: 1% vs. 0%, PFS Median: 4.9 months vs. 1.9 months, OS Median: 14.8 months vs. 14.4 months (no statistical significance).

Comparison of effectiveness of pazopanib (800 mg p.o., n=155) and placebo (n=78) [11]

Objective response to treatment 32% vs 3%, PFS Median: 11.1 months vs. 2.8 months, OS Median: data haven't been published yet.

CONCLUSIONS

Introduction of new drugs oriented toward the molecular treatment improved the prognosis for the patients suffering from metastatic renal cell carcinoma. During the period of molecular treatment statistically significant prolongation of the survival time has been achieved. It is crucial to identify new prognostic and prediction factors in order to adequately select patients who will benefit from the use of new drugs and medicines

Implementation of the optimal sequence of available targeted drugs can contribute to prolongation of the total survival time among patients suffering from metastatic renal cell cancer

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ABSTRACT

According the latest trial results, chemotherapy and hormone treatment of metastatic kidney cancer seems to be ineffective. The most recent study results show that the response to treatment is on the level of statistical error – 5%, chemotherapy lacks effectiveness. The analysis of the effectiveness of specified drugs resulted in failure.

The paper presents the treatment characteristics – treatment and recommendation levels of metastatic kidney cancer, as well as effectiveness of different treatment algorithms.

In conclusion we stated that the introduction of new drugs oriented toward the molecular treatment improved the prognosis for the patients suffering from metastatic renal cell carcinoma. During the period of molecular treatment statistically significant prolongation of the survival time has been achieved.

Keywords: metastatic kidney carcinoma, therapies, hormone treatment, prognostic factors

STRESZCZENIE

Wyniki najnowszych badań wskazują, że leczenie hormonalne przerzutowego raka nerki wydaje się nieefektywne. Ostatnie doniesienia wskazują, ze odpowiedź na leczenie kształtuje się na poziomie błędu statystycznego – 5%. Publikacja przedstawia charakterystykę schematów leczenia, zalecenia odnośnie do poszczególnych poziomów w porównywanych algorytmach. W konkluzji wskazuje się na znaczenie wprowadzenia nowych leków w leczeniu chorych z przerzutowym rakiem nerki dla wydłużenia okresu całkowitego przeżycia.

Słowa kluczowe: przerzutowy rak nerki, terapie, leczenie hormonalne, czynniki prognostyczne