7141 POSTER

Costs of adverse events management associated to the treatment of first-line metastatic renal cell carcinoma with bevacizumab + interferon alpha-2a compared with sunitinib in Spain

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Background: Both the combination of bevacizumab (BEV) + interferon alpha-2a (IFN) and sunitinib (SUN) have shown to prolong the time to progression-free survival when compared to interferon alpha alone in patients with metastatic renal cell carcinoma (mRCC). However, the type and frequency of adverse events (AEs) differ between these two options. The objective of the study was to evaluate the costs associated with the management of AEs in the current clinical practice when using BEV+IFN or SUN for mRCC, from the Spanish public hospitals perspective.
Methods: An economic decision analytic model was developed to compare the costs related to the management of all grade 3/4 AEs in patients with mRCC. Type and frequency of 40 AEs were collected from published trials (BEV+IFN: Escudier B. Lancet 2007; 370: 2103−11. SUN: Motzer RJ. N Engl J Med 2007; 356:115−24). The estimation of resources used related to the management of AE was made through an Oncology Expert Panel. Cost evaluation (€2009 values) included direct medical costs: outpatient visits, diagnostic and laboratory tests, hospitalizations, surgery, and medication. Unitary cost data were collected from the Spanish Database of Health Costs (e-Salud) and the Spanish Catalogue of Medicinal Products.
Results: Average cost of managing grade 3/4 AEs per patient was €568 for BEV+IFN and €940 for SUN, which represents a 40% cost saving with BEV+IFN (€371 per patient). The main drivers (representing approximately 83% of all costs) for SUN costs were related to the management of laboratory abnormalities, anaemia, mucosal inflammation, decline in ejection fraction, diarrhoea, thrombocytopenia, rash, epixtasis, and vomiting. In comparison, the main costs for BEV + IFN were associated to the management of gastrointestinal perforation, bleeding, proteinuria, venous thromboembolic event, anorexia and anaemia. The difference in costs between the two regimens was mainly due to a greater number of AE for SUN than for BEV+IFN, laboratory abnormalities, gastrointestinal perforation and bleeding.
Conclusion: The costs of managing grade 3/4 adverse events are substantially lower for BEV + IFN than those for SUN in patients with mRCC in Spain.

7142 POSTER

Immune tuning in renal cell carcinoma patients

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Background: Immunosuppressive factors secreted by renal cell carcinoma (RCC) leads to the induction of regulatory T cells. The aim of the study was to determine the prognostic influence of interleukin (IL) 10 and transforming growth factor (TGF) β on mRNA and protein level and the frequency of Treg and IL10/TGFβ producing T cells of peripheral blood in a cohort of metastatic (m) RCC patients before receiving sorafenib treatment.
Material and Methods: Blood samples of 46 patients with histological proven mRCC were assessed before sorafenib treatment for their expression levels of TGFβ, IL10 and FoxP3 mRNA by quantitative RT-PCR. Serum levels of IL10 and active TGFβ were determined by ELISA. Frequency of different T cell subsets was analyzed by multicolour flow cytometry. Clinical features considered included ECOG performance status, hemoglobin, alkaline phosphatase, and calcium concentrations. Disease evaluation was performed every 8 weeks following RECIST criteria. Relationship between pre-treatment factors and survival were examined in univariate analyses and subsequently by multivariate analysis using a stepwise backward and forward Cox regression model.
Results: In contrast to FoxP3 the IL10 and TGFβ mRNA levels were significantly higher in RCC patients compared to healthy subjects ($p = 0.034$ and $p = 0.023$, respectively). CD4+CD25high/CD3+Treg cells were elevated in RCC patients compared to healthy subjects ($p = 0.008$) with a lower TGFβ positive fraction ($p = 0.002$). Serum levels of active TGFβ were reduced in RCC patients ($p < 0.001$), IL10 serum levels and IL10 production in T cells differed not significantly. Univariate analysis revealed a negative prognostic influence of IL10 on progression free survival (PFS) ($p = 0.04$) and overall survival (OS) ($p = 0.063$). Surprisingly, high TGFβ and FoxP3 expression level had a positive influence on PFS ($p < 0.001$ and $p = 0.047$, respectively) and OS ($p = 0.0002$ and $p = 0.031$, respectively). Frequency of Treg or IL10/TGFβ producing T cells or IL10/TGFβ serum levels had no prognostic influence. In the multivariate analysis including clinical features low ECOG and high TGFβ mRNA levels were independently associated with worse PFS ($p = 0.032$ and $p = 0.002$, respectively) and worse OS ($p < 0$ and $p = 0.01$, respectively).
Conclusion: RCC caused an immunosuppressive phenotype in peripheral blood characterized by increased mRNA, but not protein levels of IL10 and TGFβ. In contrast to IL10, high TGFβ mRNA levels were an independent good prognostic factor.

7143 POSTER

Safety and treatment (trx) patterns of angiogenesis inhibitors (AIs) in patients (pts) with metastatic renal cell carcinoma (mRCC): evidence from US community oncology clinics

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Background: Safety and trx patterns of sunitinib (SU) and sorafenib (SOR) in mRCC had been previously reported using a retrospective chart review of 119 pts in 2 US tertiary centers (ESMO, 2008). Trx patterns may vary between hospital and office-based settings. The present study evaluated safety and trx patterns in a US community oncology setting.
Methods: Medical records were retrospectively reviewed for 250 mRCC pts treated at 18 community oncology clinics. Eligible pts were ⩾18 yrs and received ⩾1 prescriptions for SU (n = 131) or SOR (n = 119) as first AI. Proportions of pts with adverse events (AEs), and trx discontinuations (d/c), dose reductions, and interruptions due to AEs were computed.
Results: Median trx duration was shorter in community practice than in tertiary centers (SU: 5.9 vs 10.5 months (m); SOR: 5.5 vs 8.1m). Pts in both groups had on average about 5 all-grade AEs; 29.8% (SU) and 27.7% (SOR) had ⩾1 grade 3/4 AE. Most common all-grade AEs were fatigue/asthenia (SU) and skin rash (SOR), followed by diarrhea, nausea, and pain (Table). 61.8% of SU and 63.9% of SOR pts had ⩾1 trx modification due to AEs. Compared to tertiary centers, in community practice AEs resulted in higher rates of d/c (SU: 24.4% vs 17.5%; SOR: 31.1% vs 17.7%), dose reductions (SU: 32.8% vs 29.8%; SOR: 42.0% vs 25.8%), and interruptions (SU: 33.6% vs 19.3%; SOR: 37.8% vs 32.3%) due to AEs.
Conclusions: AE rates in mRCC pts treated with SU or SOR in community practice tended to be lower than in tertiary centers and/or clinical trials, which may be due to considerably shorter trx duration or to under-reporting of AEs related to differences in practice patterns. Rates of d/c, dose reductions, and interruptions due to AEs tended to be higher. This study provides evidence in office-based setting of unmet need for agents that may provide improved tolerability in mRCC.

	SU (n = 131)			SOR (n = 119)		
AEs, n (%)	All Grades	Grade 3/4	⩾1 trx modification	All Grades	Grade 3/4	⩾1 trx modification
Fatigue/asthenia	55 (42.0)	7 (5.3)	28 (21.4)	41 (34.5)	2 (1.7)	15 (12.6)
Diarrhea	47 (35.9)	3 (2.3)	17 (13.0)	39 (32.8)	3 (2.5)	14 (11.8)
Nausea	36 (27.5)	2 (1.5)	18 (13.7)	31 (26.1)	2 (1.7)	12 (10.1)
Pain	31 (23.7)	5 (3.8)	5 (3.8)	29 (24.4)	4 (3.4)	6 (5.0)
Skin rash	13 (9.9)	1 (0.8)	4 (3.1)	42 (35.3)	7 (5.9)	27 (22.7)
Mucositis/stomatitis	27 (20.6)	2 (1.5)	12 (9.2)	19 (16.0)	4 (3.4)	11 (9.2)
Hand–foot syndrome	15 (11.5)	0 (0)	10 (7.6)	29 (24.4)	6 (5.0)	17 (14.3)
Vomiting	21 (16.0)	1 (0.8)	12 (9.2)	13 (10.9)	2 (1.7)	7 (5.9)

7144 POSTER

Predictive value and biologic significance of circulating tumor cells (CTC) in sporadic and von hippel lindau (VHL) renal cancer

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Background: Haematogenous spreading of tumor cells is a key step toward metastasis; the automated analysis of CTC by Cellsearch platform