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Treatment patterns and clinical outcomes in patients with renal cell carcinoma in the UK: insights from the RECCORD registry

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Background: The aim of the RECCORD registry was to gather real-world UK data on the use of targeted therapies in renal cell carcinoma (RCC) and assess clinical outcomes. Here, demographic and outcome data are presented with the treatment patterns and demographic profile of patients on the registry.

Patients and methods: Patients were retrospectively identified at seven UK hospitals with large cancer centres in England (5), Scotland (1) and Wales (1). Anonymised data were collected through an online registry covering demographics, treatments and outcomes. Five hundred and fourteen UK adult patients with metastatic RCC were included in the study for analysis. Patients were included if they were treated for metastatic RCC at one of the seven centres, and started systemic anti-cancer treatment from March 2009 to November 2012 inclusive. In addition to demographic factors, the principal outcome measures were overall survival (OS), time to disease progression and toxicity.

Results: The majority of first-line treatment was with sunitinib; first-line use of pazopanib increased as the study progressed. 15.8% of patients received second-line treatment, half of whom were prescribed everolimus. Median OS (from initiation of first-line treatment) was 23.9 months (95% confidence interval [CI] 18.6–29.1 months), similar to that reported for clinical trials of targeted RCC therapies [Ljungberg B, Campbell SC, Choi HY et al. The epidemiology of renal cell carcinoma. Eur Urol 2011; 60: 615–621; Abe H, Kamai T. Recent advances in the treatment of metastatic renal cell carcinoma. Int J Urol 2013; 20: 944–955; Motzer RJ, Hutson TE, Tomczak P et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 3584–3590]. OS was significantly longer for those who received second-line treatment after disease progression (33.0 months; 95% CI 30.8–35.2 months) than those who did not (20.9 months; 95% CI 16.4–25.3 months; $P = 0.008$).

Conclusions: RECCORD is a large 'real-world' database assessing metastatic RCC treatment patterns and outcomes. Treatment patterns changed over time as targeted therapies were approved and became widely available; survival data in RECCORD are consistent with those reported for systemic treatments in clinical trials. Kaplan–Meier analysis of results demonstrated that receiving second-line therapy was a major prognostic factor for longer OS.

Key words: renal cell carcinoma, systemic therapy, overall survival, adverse events, health policy

introduction

Renal cell carcinoma (RCC) is a malignancy that accounts for over 90% of kidney cancers [1]. Clear cell RCC is the most common (70%–85%) [2]. Approximately 30% of all RCC patients have metastatic disease at presentation, and until recently, treatment options were limited as these cancers are relatively resistant to cytotoxic chemotherapy [2]. However, the introduction of targeted therapy has significantly improved the prognosis and treatment outcome for these patients [3–5]. These therapies target the vascular endothelial growth factor (VEGF) pathway and the

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mammalian target of rapamycin (mTOR) pathway, both of which are related to the pathogenesis of clear cell metastatic RCC [6]. Despite this progress, there are still a number of treatment challenges, including identifying and optimising the most appropriate sequences or combinations of agents and managing associated side-effects. Health-related quality of life has also become an important medical outcome among this patient population, particularly since there is evidence that tumour response and delay in disease progression can affect it [7, 8].

Clinical guidelines for the treatment of metastatic RCC reflect clinical trial evidence for targeted therapy [9–11]. Trial populations may not represent real-life patient populations and have better outcomes than patients ineligible for studies [12, 13]. Optimisation of disease management must therefore be based on clinical trials and real-world experience [14]. Worldwide, registries provide insights into treatment patterns and outcomes for patients with RCC in the real world [15–17]. Their results suggest that survival has improved in the era of targeted therapies compared with the era of cytokine therapy [15, 16]. While the sunitinib expanded access programme included patients from the UK [18], real-life data for RCC management in UK clinical practice are limited. These data could provide important information on disease progression, as well as facilitating optimisation of treatment.

The aim of the Renal Cell Carcinoma Outcomes Research Dataset (RECCORD) registry was to collect real-world demographic, treatment, histological and outcome data from RCC patients in the UK. Here, we report on the demographics of RECCORD, the current use of systemic therapy and the clinical outcome associated with different therapeutic approaches.

methods

patients

A retrospective, non-interventional study was conducted using data from the medical records of eligible patients. To be eligible, patients were required to meet the following inclusion criteria: (i) have histologically confirmed clear cell locally advanced or metastatic RCC, (ii) started systemic therapy [tyrosine kinase inhibitors, mTOR inhibitors, anti-VEGF agents, and cytokine therapy, including interferon-alpha or interleukin-2 (IL-2), or other] between 1 March 2009 and 31 October 2012 and (iii) aged ≥18 years at the time of diagnosis of RCC.

Patients treated as part of clinical research trials were included.

data source

RECCORD is a web-based registry system that comprises data from seven UK centres specialising in RCC (Bristol, Birmingham, Manchester, London, Leeds, Swansea and Glasgow). Medical records of eligible patients were retrospectively abstracted and the data held on the centre's local database, then transferred to a central server where they were combined and analysed. Data collection was from March 2009 to October 2012. Patients were identified by a unique RECCORD sequence number, but no other patient identifiers were collected to ensure anonymity. The registry was regulated by the RECCORD Steering Committee, comprised of recognised experts in the management of RCC. RECCORD was conducted according to the Declaration of Helsinki. The study protocol was approved by the NHS Research Ethics Committee, local ethics committees and the principal investigators at each centre.

outcome variables

The outcomes of interest included survival, disease progression, treatment patterns (systemic therapies used and dose changes or discontinuation of therapy) and treatment toxicity. Disease progression was assessed using radiology, symptomatology, clinical investigation and therapy change as markers, and included death. Patterns of switching from first- to second- and third-line treatment were also examined. Switch to second-line treatment was defined as a switch due to disease progression only; changes in treatment due to reasons of toxicity were considered as an extension of first-line treatment. Some patient records did not include data for all parameters; available data from these patients were used where appropriate.

statistical analysis

Descriptive statistics were used to describe baseline characteristics, treatment patterns and adverse events. Changes in treatment patterns were considered for three 12-month cohorts (March 2009–February 2010; March 2010–February 2011 and March 2011–February 2012). Overall survival (OS), disease progression and treatment toxicity data were analysed from the onset of first systemic therapy using Kaplan–Meier survival curves. Relationships between outcomes, demographic factors and treatment patterns were assessed using Kaplan–Meier analyses and log-rank comparisons. All statistical analyses were carried out using SPSS for Windows 15.0 (SPSS, Inc., Chicago, IL, USA).

results

patient characteristics

In total, 514 patients were eligible for inclusion and retrospectively analysed (Table 1). All patients had metastatic disease, and 56.3% had stage IV disease at diagnosis; however, the sites of metastases were not routinely captured within RECCORD. Mean age at diagnosis was 61.6 years [standard deviation (SD): 10.9], and 66% of patients were male. Patients were enrolled from England (66.7%), Wales (10.3%), and Scotland (23.0%). 56.8% of patients enrolled in Scotland joined the study in 2009 (reflecting a national delay in access to treatment).

Table 1. Baseline characteristics of patients in RECCORD ($n = 514$)

Male, *n* (%)[a]	341 (66.3)
Mean age at diagnosis; years (SD)[b]	61.6 (10.9)
Mean time from diagnosis to enrolment; years (SD)[c]	2.1 (3.6)
Patients with nephrectomy, *n* (%)	257 (50.0)
Total nephrectomy, *n* (%)	164 (63.8% of all nephrectomies)
With curative intent, *n* (%)	87 (53.0%)
Without curative intent, *n* (%)	37 (22.6%)
Unknown intent, *n* (%)	40 (24.4%)
Partial nephrectomy, *n* (%)	11 (4.3% of all nephrectomies)
With curative intent, *n* (%)	5 (45.5%)
Without curative intent, *n* (%)	2 (18.2%)
Unknown intent, *n* (%)	4 (36.4%)
Nephrectomy with unknown extent, *n* (%)	82 (31.9% of all nephrectomies)

[a]The gender of two patients was not recorded.
[b]Thirty patients excluded due to missing data.
[c]Twenty-four patients excluded due to missing data.

treatment patterns

first-line therapies. The first-line therapies for the RECCORD population are detailed in Table 2. Sunitinib was the first-line treatment in 78.6% of cases, followed by pazopanib (11.7%) and everolimus (6.4%); 35 patients (6.8%) changed first-line therapy due to toxicity. A decline in the number of different first-line treatments was observed; seven different treatments were used in the 2009–2010 cohort, compared with four in 2011–2012 (sunitinib, pazopanib, everolimus and sorafenib). First-line treatment with pazopanib increased from 0.9% in 2009–2010 to 27.1% in 2011–2012, following European marketing approval [19]. Everolimus was used as part of a first-line clinical trial in 32 patients (6.2%).

second-line and third-line therapies. Second-line treatment was received by 15.8% of patients, with a substantial regional variation in its use (Scotland: 8.5%; Wales: 7.5%; England: 19.5%). Everolimus (53.1%), sunitinib (14.8%) and pazopanib (9.9%) were the most commonly used second-line treatments (Table 2).

The use of second-line treatment increased between the first (2009–2010) and second (2010–2011) cohorts (17.3% and 20.4%, respectively); a smaller proportion of the third cohort (2011–2012) switched to second-line treatment (13.9%) due to the shorter study period. The mean length of time before second-line switch decreased from 17.4 ± 11.8 months (2009–2010 cohort) to 12.3 ± 7.1 months (2010–2011 cohort). Time to second-line switch was lower again in the 2011–2012 cohort (6.3 ± 3.7 months), reflecting the shorter follow-up for these patients.

Similar to first-line treatment, more different treatments were used second-line in 2009–2010 (8) than in 2011–2012 (5).

Sixteen (3.1%) of the RECCORD cohort received third-line treatment (Table 2). Everolimus was the dominant third-line treatment of patients enrolled in 2009–2010 (seven of nine patients), and this decreased over time while the use of axitinib increased. Patients who received third-line treatment were all enrolled in England.

At the end of the study, 95 of 514 (18.5%) patients were still on first-line treatment; 10 had switched first-line treatment due to toxicity. Twenty-one of 81 (25.9%) patients were still on second-line treatment.

Table 2. Systemic treatment patterns among patients with advanced RCC in RECCORD

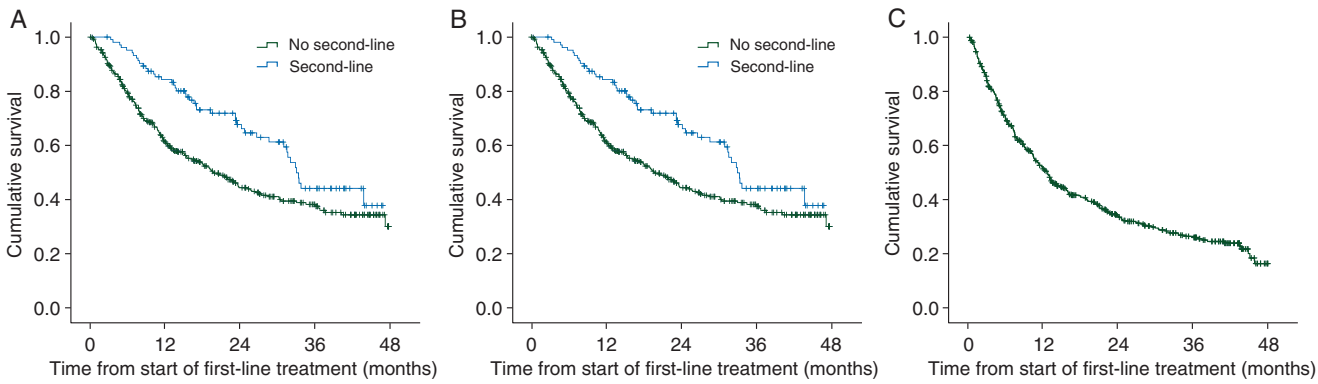
Agent	First-line ($n = 514$) n (%)	Second-line ($n = 81$) n (%)	Third-line ($n = 16$) n (%)
Sunitinib	404 (78.6)	12 (14.8)	–
Pazopanib	60 (11.7)	8 (9.9)	–
Everolimus	33 (6.4)	43 (53.1)	8 (50.0)
Sorafenib	6 (1.2)	3 (3.7)	1 (6.3)
Temsirolimus	4 (0.8)	1 (1.2)	–
Axitinib	–	4 (4.9)	5 (31.3)
IL-2	3 (0.6)	2 (2.5)	–
Interferon-alpha	2 (0.4)	–	1 (6.3)
Other	2 (0.4)	8 (9.9)	1 (5.9)

Thirty-five patients also switched to a different first-line treatment due to toxicity (see text).

overall survival

Almost half of patients (49.8%) died during the study period. Median OS from the start of treatment was 23.9 months (Figure 1A).

The relationship between OS and individual demographic factors and treatment patterns was assessed. A number of factors were associated with increased survival (Table 3). Median OS of patients who received second-line treatment (33.0 months) was significantly longer ($P = 0.008$; Figure 1B) than that of patients who only received first-line treatment (20.9 months). A similar



	K-M estimate of median survival; months (95% CI)
RECCORD cohort	23.9 (18.6–29.1)

	K-M estimate of median survival; months (95% CI)
No second-line	20.9 (16.4–25.3)
Second line	33.0 (30.8–35.2)

	K-M estimate of median survival; months (95% CI)
No third-line	23.4 (19.3–27.6)
Third line	33.9 (25.2–42.6)

Figure 1. Kaplan–Meier survival plots of mortality in RECCORD. Kaplan–Meier analysis of: (**A**) overall survival of the RECCORD cohort; (**B**) survival with and without second-line treatment; (**C**) survival with and without third-line treatment. Crosses represent censored cases. Kaplan–Meier estimates of median survival with 95% confidence intervals (CI) are presented below.

Table 3. Demographic factors and treatment patterns associated with survival of RCC patients

Variable (n)		Kaplan–Meier estimate of median survival time; months (95% CI)
Second-line treatment ($X^2(1) = 7.031$; $P = 0.008$)	No second-line (431)	20.9 (16.4–25.3)
	Received second-line (81)	33.0 (30.8–35.2)
Third-line treatment	No third-line (496)	23.4 (19.3–27.6)
($X^2(1) = 2.619$; $P = 0.106$)	Received third-line (16)	33.9 (25.2–42.6)
Time from diagnosis to systemic treatment split by band in days[a]	0–100 (185)	13.6 (9.7–17.4)
($X^2(5) = 28.713$; $P < 0.001$)	100–200 ($n = 59$)	19.3 (7.1–31.6)
	200–300 ($n = 29$)	32.2 (–)
	300–400 ($n = 29$)	23.4 (8.7–38.2)
	400–600 ($n = 33$)	25.4 (12.9–37.9)
	>600 (155)	36.9 (31.9–41.9)
Time from diagnosis to systemic treatment using a 365-day split[a]	0–365 (290)	16.5 (10.8–22.2)
($X^2(1) = 19.174$; $P < 0.001$)	>365 (200)	33.6 (27.5–39.7)
Time to progression split by band in days ($X^2(1) = 138.828$; $P < 0.001$)	0–100 (95)	5 (2.9–7.1)
	100–200 ($n = 72$)	8.5 (7.1–9.9)
	200–300 ($n = 55$)	16.8 (11.1–22.4)
	300–400 ($n = 44$)	23.4 (11–35.7)
	>400 (75)	47.3 (–)[b]
Gender[c]	Male (339)	28.8 (22.1–35.4)
($X^2(1) = 2.774$, $P = 0.096$)	Female (171)	21.9 (16.6–27.1)
Dose decreases	No dose decrease (355)	19.8 (14.7–24.9)
($X^2(1) = 9.434$; $P = 0.002$)	Received decrease (157)	30.6 (25–36.3)

[a]Date of diagnosis was not recorded for 22 patients.
[b]95% CI was not calculable.
[c]Gender of two patients was not recorded. All survival estimates are from the start of systemic treatment in RECCORD. Time to systemic treatment is from diagnosis, and time to progression is from the start of systemic treatment. Two records were excluded from analysis due to irregularities with recorded date of death.

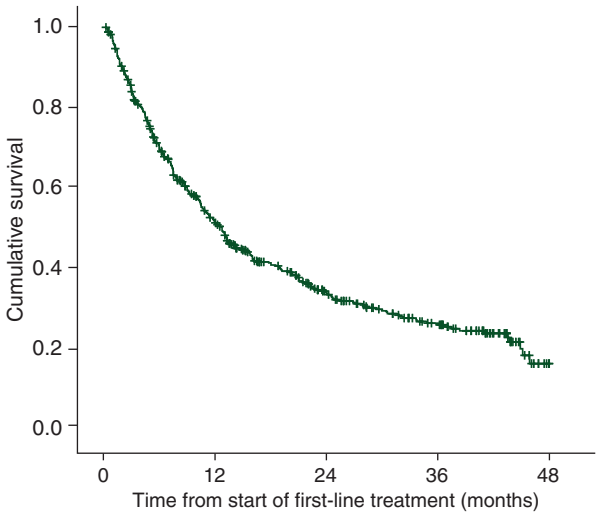


Figure 2. Kaplan–Meier survival plot of time to disease progression on first-line treatment.

pattern was seen when considering the switch to third-line treatment (Figure 1C), although it did not attain statistical significance, most likely due to the limited number of patients in this group.

The length of time between diagnosis and systemic treatment was significantly associated with OS ($P < 0.001$); OS from the start of systemic treatment was lower for patients treated within 100 days of diagnosis than for those who did not receive treatment until 600 days or more after diagnosis.

There was also a significant association between toxicity-induced dose decreases and OS ($P = 0.002$). The median survival time for patients with first-line treatment dose decreases was 30.6 months; for other patients, it was 19.8 months.

disease progression

At the time of analysis, disease progression had been experienced by the majority (66.1%) of patients on first-line therapy (median duration of follow-up: 13.1 months, 95% CI 12.0–14.1 months). Median time to disease progression was 8.8 months (95% CI 7.7–9.9 months; Figure 2). There was a significant association between the time from RCC diagnosis to first-line treatment and disease progression ($X^2(5) = 13.521$, $P = 0.019$). Estimated time to progression was shortest for patients who had started first-line treatment within 100 days of diagnosis (16.8 months [95% CI 14.1–19.5 months]).

treatment toxicity

Dose decreases and discontinuations of systemic therapy due to toxicity are summarised in Table 4. In total, 30.5% patients had their first-line treatment dose decreased due to toxicity, and

Table 4. Dose decreases and discontinuations of systemic therapy due to toxicity

	First-line ($n = 514$) n (%)	Second-line ($n = 81$) n (%)	Third-line ($n = 16$) n (%)
Patients decreasing dose due to toxicity	157 (30.5)	9 (11.1)	2 (7.4)
Patients with >1 toxicity-induced dose decrease	28 (17.8)[a]	0 (0.0)	0 (0.0)
Patients decreasing dose due to 'other' reason	16 (3.1)	0 (0.0)	0 (0.0)
Patients discontinuing due to toxicity	97 (18.9)[b]	12 (14.8)	2 (12.5)
Patients discontinuing due to toxicity after toxicity-induced dose reduction	27 (17.1)[a]	0 (0.0)	0 (0.0)

Absolute patient numbers are given with percentage values in brackets.
[a]As a percentage of patients who already experienced one dose decrease.
[b]Includes $n = 35$ patients who changed to a different first-line treatment due to toxicity.

17.8% of these had a further dose decrease due to toxicity. First-line therapy was switched for 35 patients (6.8%) due to toxicity (32 to pazopanib and 3 to sorafenib). The median time to first reported toxic event on first-line therapy was 3.1 months (95% CI 2.0–4.2 months). The median time to discontinuation of a first-line drug was 4.0 months (95% CI 0.2–5.8 months). Kaplan–Meier analyses did not identify any factors that had a statistically significant association with toxicity.

discussion

RECCORD is the first UK-specific registry to provide information on real-world treatment patterns and outcomes of RCC patients treated with a range of systemic therapies. We found systemic RCC treatments to be used in accordance with clinical guidelines; fewer treatment options were used as the study progressed. Additionally, patients receiving second-line treatment survived longer than those who did not. The treatment of advanced RCC has changed in the past 5 years with new treatment options significantly improving outcomes. The licensing of targeted therapies before and during RECCORD are reflected in the changing patterns of treatment [20–22]. Sunitinib and pazopanib were the predominant first-line treatments, with the shift from sunitinib to pazopanib driven by the expectation of improved patient quality of life with the latter [23, 24].

15.8% of RECCORD patients received second-line therapy, with over half treated with everolimus. This low proportion receiving second-line treatment may reflect the limited access to these therapies in the UK; there was a pattern of increased use of second-line therapy over time but with regional variability in access. In England, money to increase access to treatments not routinely funded by the NHS is available through a cancer drugs fund [25]. There is no cancer drug fund in Wales or Scotland, leading to markedly lower rates of second-line treatment. Median OS from the start of systemic treatment in RECCORD was estimated at 22.3 months. This is consistent with clinical trials of systemic therapies including pazopanib (22.9 months) [4], sunitinib (26.4 months) [3] and bevacizumab (23.3 months) [26]. Several factors assessed in RECCORD were found to be associated with OS. Most notably, the OS of patients who switched to second-line therapy was significantly longer than those who did not switch. This may be due to selection bias (good prognosis patients are more likely to receive further therapy), an artefact of the relatively short follow-up period in the study, or because post first-line therapy is causing prolongation of survival. Clinical trials have shown that second-line therapies, e.g. everolimus and axitinib, improve quality of life and extend progression-free survival, but have failed to conclude prolongation of survival [27, 28]. Clearly, there is a need to improve general access to these beneficial agents and equalise such access across the UK.

A length of time between diagnosis and systemic treatment of <365 days is established as a marker for poor prognosis and survival [29, 30]. In this study, there was a significantly longer OS for patients with longer than 365 days between diagnosis and treatment than those with a shorter interval ($P > 0.001$). However, further analysis showed that it was the extreme intervals (<100 days or over 600 days) that underlie this association with survival. Between 100 and 600 days, there was a gradual increase in survival associated with increasing delay from diagnosis to treatment. This analysis suggests the potential for improved accuracy of prognosis thorough more precise recording of the time from diagnosis to treatment.

There was also an apparent association between first-line treatment toxicity-induced dose decreases with increased survival. The widespread use and investigation of sunitinib has led to reports linking increased survival to toxicity-induced dose reductions [31] or to incidence of side-effects, such as hypertension [32] and hypothyroidism [33]. As these links are not commonly investigated in trials, no such reports have been found for other treatments utilised within RECCORD. Many factors may contribute to this link, such as clinicians being more at ease with dose reductions in patients performing well, that these patients received a higher exposure to the drug (causing toxicity) resulting in greater efficacy, or because patients with poor prognoses are not on therapy long enough to experience dose reductions.

Our study had several strengths and provides important insights into treatment patterns and outcomes of patients with advanced RCC in a 'real-life' setting. The data provided by the registry will enable clinicians to better understand the utilisation and outcomes associated with systemic treatment. RECCORD is a secure, web-based registry system that allows data to be uploaded from the local clinical centres to a central database. Further analysis of outcomes and prognostic factors not reported in this initial study will allow greater understanding of the effect of disease stage and laboratory markers of disease activity on clinical outcomes in the UK. Limitations to our study included the risk of bias inherent in retrospective studies, the

relatively modest numbers enrolled from Wales and Scotland, and follow-up periods that varied substantially. Additionally, databases are prone to incomplete or late entries of clinical data, or data input errors. A small number of the RECCORD patients were taking part in clinical trials (32 patients on first-line everolimus), and so their inclusion would only have had a small overall effect.

In conclusion, registries are becoming important tools to help make more informed treatment decisions since data are representative of a real-world setting. Our results provide valuable information on the outcomes and systemic treatment of patients with metastatic RCC, which remains a major therapeutic challenge. This study shows that as RECCORD progressed, there was a simplification of clinical decision-making as systemic treatments became routinely available. Additionally, there was a significant association between increased survival and treatment beyond first-line therapy. This is important because access to second-line treatments is not equitable across the UK, risking differences in the quality of RCC care and outcomes across the UK arising.

These data are useful for devising future sequencing studies in advanced RCC, as well as adding valuable 'real-life' evidence to previous clinical trial data. Data from RECCORD therefore have a central role in improving care and outcomes for people with RCC.

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disclosure

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Comprehensive serum cytokine analysis identifies IL-1RA and soluble IL-2Rα as predictors of event-free survival in T-cell lymphoma

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Background: T-cell malignancies are heterogeneous in their clinical presentation and pathology, and have a poor prognosis. New biomarkers are needed to predict prognosis and to provide insights into signal pathways used by these cells. The goal of this study was to evaluate pretreatment serum cytokines in patients with newly diagnosed T-cell neoplasms and correlate with clinical outcome.

Patients and methods: We evaluated 30 cytokines in pretreatment serum from 68 untreated patients and 14 normal controls. Significantly elevated cytokines were correlated with patterns of abnormalities, event-free survival (EFS) and overall survival (OS).

Results: Our data demonstrated significantly elevated levels (versus controls) of seven cytokines—epidermal growth factor (EGF), IL-6, IL-12, interferon gamma-induced protein (IP)-10, soluble interleukin (sIL)-2Rα, monokine induced by gamma interferon (MIG), and IL-1RA—in all T-cell neoplasms ($P < 0.05$). In the angioimmunoblastic subset, all seven cytokines except IP-10 and in the peripheral T-cell lymphoma (TCL)-not otherwise specified subset, only IP-10, sIL-2Rα, MIG, and IL-8 were statistically elevated compared with control. Of these, elevated cytokines all but EGF were predictive of an inferior EFS; IL-1RA, sIL-2Rα, and MIG predicted an inferior OS. In a multivariate analysis, sIL-2Rα [hazard ratio (HR) = 3.95; 95% confidence interval (CI) 1.61–8.38] and IL-1RA (HR = 3.28; 95% CI 1.47–7.29) levels remained independent predictors of inferior EFS. TCL cell lines secreted high levels of sIL-2Rα and expressed the IL-2Rα surface receptor.

Conclusions: This report describes the cytokines relevant to prognosis in patients with untreated TCL and provides the rationale to include serum IL-1RA and sIL-2Rα as biomarkers in future trials. Inhibition of these cytokines may also be of therapeutic benefit.

Key words: T-cell lymphoma, cytokines, IL-1RA, sIL-2Rα, PTCL-NOS, AITL

introduction

T-cell lymphoma (TCL) comprises ~10% of all non-Hodgkin lymphoma (NHL) in the United States and up to 20% of cases in Asia [1]. TCL are currently classified by WHO criteria [2, 3], with the most common subtypes being peripheral TCL-not otherwise specified (PTCL-NOS), angioimmunoblastic TCL (AITL), anaplastic large cell (ALCL), and the predominant subsets of cutaneous TCL (CTCL), Sézary syndrome (SS) and mycosis fungoides (MF). The long-term outcome of the non-CTCL groups remains poor with ~30% of patients being cured [4]. Induction therapy is typically with cyclophosphamide,

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