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Background

Adrenocortical carcinoma (ACC) is a rare and highly aggressive endocrine malignancy. For patients with advanced disease, the largest study conducted to date (FIRM-ACT) has shown a progression-free survival (PFS) benefit with a combination of etoposide, doxorubicin, cisplatin and mitotane (EDP-M) versus mitotane and streptozocin as front-line therapy¹. For patients failing EDP-M, other cytotoxic and molecular therapies have demonstrated disappointing results as salvage regimens in mostly small-scale trials²⁻⁴. In recent years the groundbreaking progress in elucidating the signalling pathways involved in ACC carcinogenesis has led to the development of molecularly targeted agents and has progressively increased the number of ACC patients referred for consideration of Phase I therapies⁴. However, the outcome of these patients have not yet been systematically evaluated. This study aims to describe the experience of refractory ACC patients treated on Phase I clinical trials at the RMH.

Methods

We retrospectively reviewed the records of advanced ACC patients refractory to conventional therapies treated in our Drug Development Unit between January-2003 and December-2014. Data concerning patient demographics, treatment outcome, prognostic factors and tolerability are reported. The RMH prognostic model was developed based on the following three variables associated with poor overall survival (OS): LDH normal (0) versus > upper limit of normal (+1), albumin ≥ 3.5 g/dL (0) versus <3.5 g/dL (+1) and number of metastatic sites ≤ 2 (0) versus >2 (+1). Patients were subcategorized based on the prognostic score derived from the sum of these three components into good (RMH score 0-1) and poor-prognostic groups (RMH score 2-3)⁵. Median PFS and OS were determined with the Kaplan-Meier method and log-rank test was used to compare survival curves among subgroups.

Results

Sixteen patients were treated on 24 Phase I clinical encounters: 18 (75%) targeted therapy (55.5% insulin-like growth factor pathway inhibitors), 3 (12.5%) chemotherapy and 3 (12.5%) chemotherapy combined with targeted agents (Figure 1). Baseline characteristics of patients are shown in Table 1. Overall response rate was 8.4% and clinical benefit rates at 4 and 6 months were 37.5% and 8.4%, respectively. Median PFS and OS were 3.1 months (95% CI, 1.7-4.4) and 7.2 months (95% CI, 4.2-20.8), respectively. ECOG PS 1 versus 0 ($p=0.009$), >2 metastatic sites ($p<0.001$), peritoneal metastases ($p=0.016$), high platelet count ($\geq 410 \times 10^9/L$) ($p=0.014$), albumin <35 g/dL ($p=0.026$) and elevated LDH ($p=0.019$) were significantly associated with shorter OS (Table 2). Patients with RMH score 0-1 (good prognosis) had superior median OS (14.1 months, 95% CI, 7.8-24.8) than those with a score 2-3 (bad prognosis) (5 months; 95% CI, 3.5-6.6) ($p=0.001$) (Figure 2). Three (18.8%) patients experienced drug-related grade 3-4 adverse events (AE). Any grade and grade 3-4 toxicities deemed possibly or likely related to study drugs are summarized in Table 3. There were no toxicity-related treatment discontinuations or deaths.

TABLE 1: Baseline patients characteristics; n=16

VARIABLE	N (%)
Median age (range)	45 (23-62)
Gender Male/ Female	7(43.8)/9(56.3)
ECOG PS 0/1	7(43.8)/9(56.3)
Hormone-producing tumour No/Yes	7(43.8)/9(56.3)
Stage at diagnosis	
II	5 (31.3)
III	9 (56.3)
IV	2 (12.5)
Local recurrence	10 (62.5)
N° metastatic sites	
0-2	7 (43.8)
>2	9 (56.3)
Metastatic sites	
Liver	10 (62.5)
Non-regional lymph nodes	10 (62.5)
Lung	9 (56.3)
Peritoneum	7 (43.8)
Bone	3 (18.8)
Albumin (g/dl)	
<35	7 (43.8)
≥ 35	9 (56.3)
LDH (IU/L)	
≤ 192	5 (31.3)
>192	11 (68.8)
N°previous lines of systemic therapies	
≤ 192	9 (56.3)
>192	7 (43.8)
RMH prognostic score	
0-1	6 (37.5)
2	4 (25)
3	6 (37.5)

FIGURE 1: Therapies used in 24 Phase I encounters

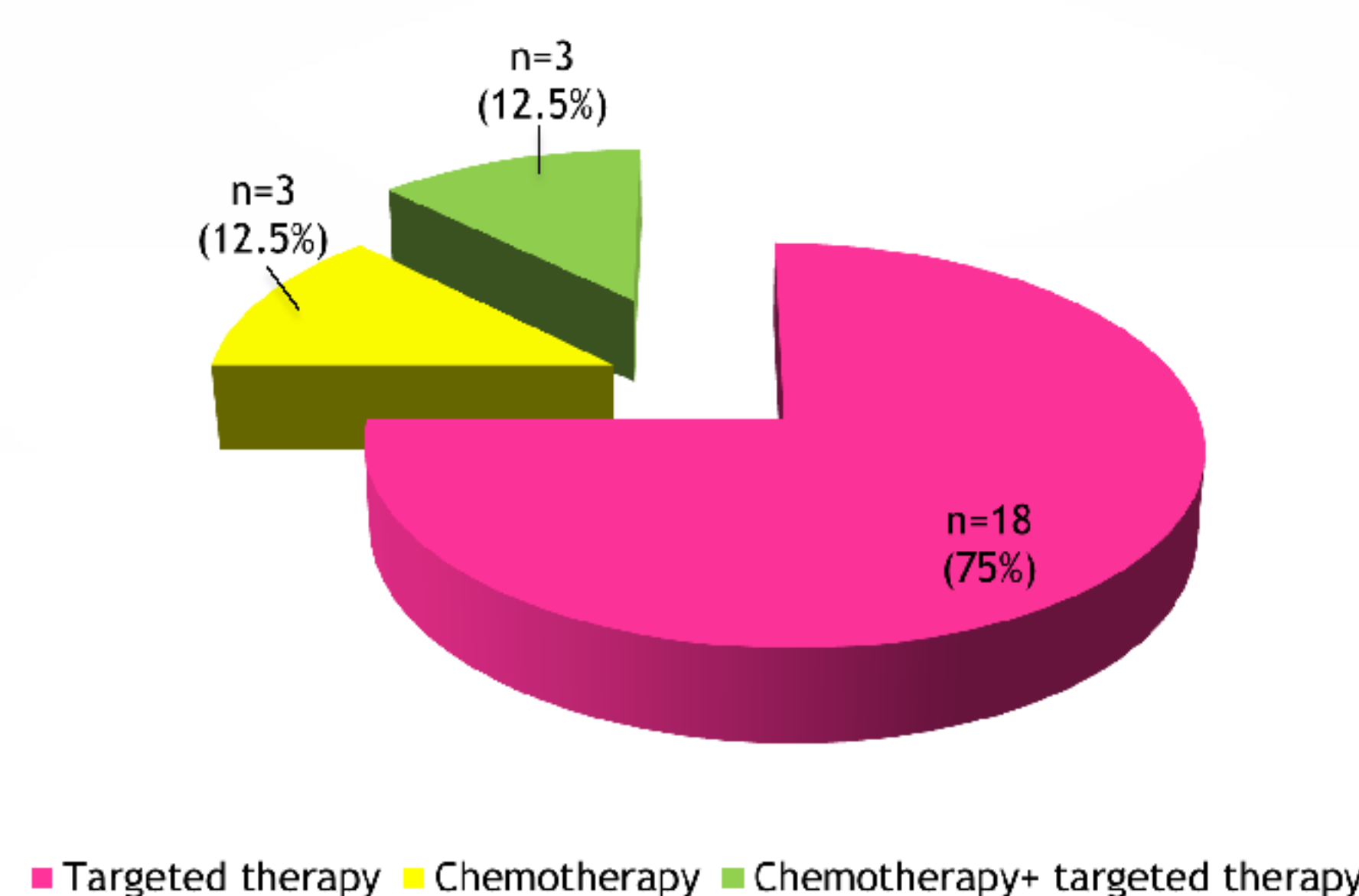


TABLE 2: Prognostic factors for OS

VARIABLE	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)
ECOG PS 0 1	8.36 (1.68-41.53) $p=0.009$	NS
N° metastatic sites 0-2 >2	10.71 (2.13-53.7) $p<0.001$	4.95 (1.12-18.27) $p=0.037$
Peritoneal metastasis No Yes	7.35 (1.45-37.39) $p=0.016$	NS
Platelet count, $\times 10^9/L$ <410 ≥ 410	9.98 (1.57-63.13) $p=0.014$	NS
Albumin, g/dL ≥ 35 <35	4.17 (1.19-14.49) $p=0.026$	NS
LDH, IU/L ≤ 192 >192	1.94 (1.06-2.56) $p=0.019$	NS

FIGURE 2: OS according to the RMH prognostic score

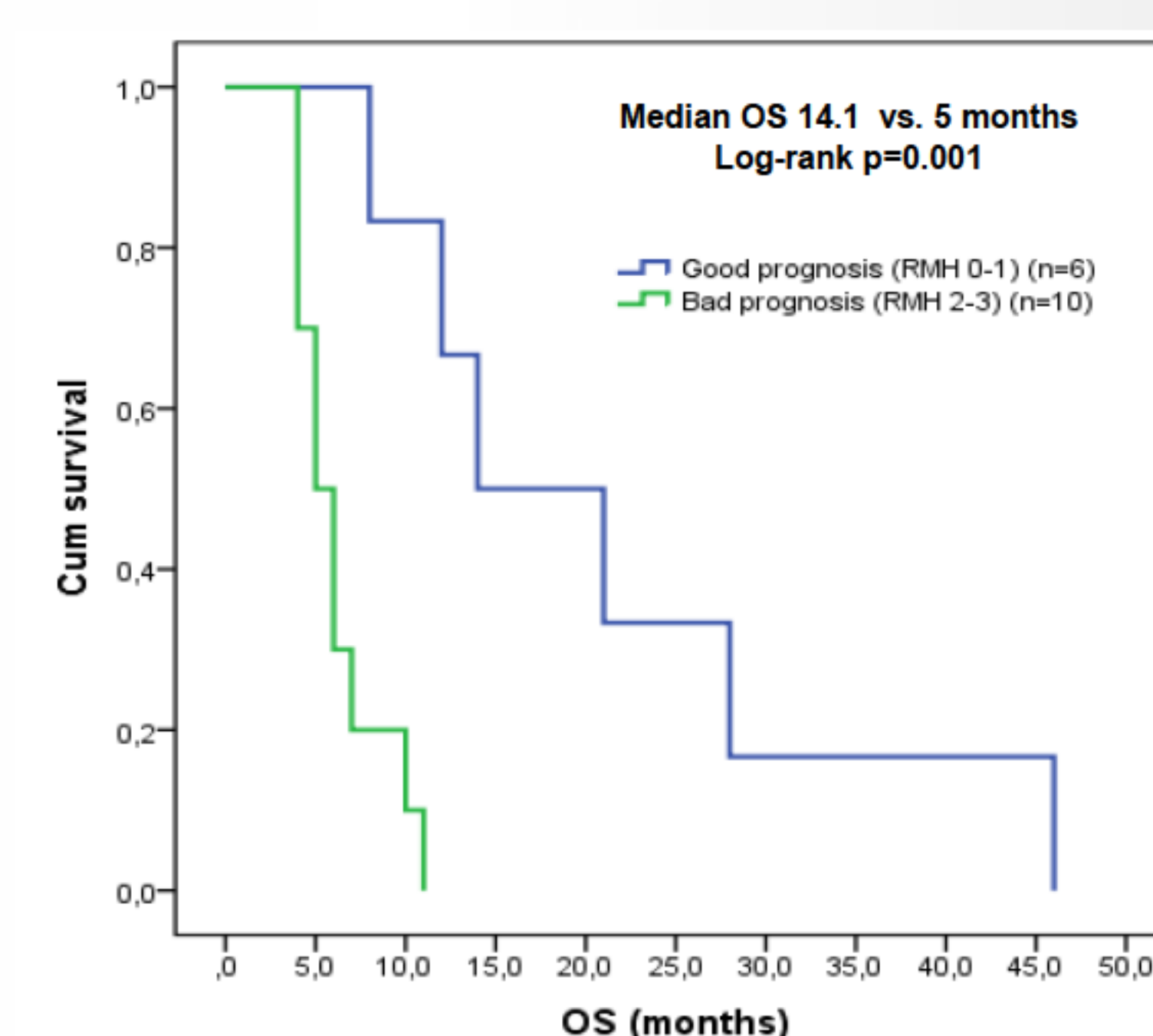


TABLE 3: Possible or likely treatment-related AEs in study patients (n, %)

Adverse events	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	9 (56.3)	8 (50)	1 (6.3)	-	-
Rash	4 (25)	3 (18.8)	1 (6.3)	-	-
Emesis	8 (50)	7 (43.8)	1 (6.3)	-	-
Diarrhea	4 (25)	2 (12.5)	1 (6.3)	1 (6.3)	-
Anemia	7 (43.8)	6 (37.5)	1 (6.3)	-	-
Neutropenia	7 (43.8)	4 (18.8)	1 (6.3)	1 (6.3)	1 (6.3)
Thrombocytopenia	2 (12.5)	1 (6.3)	1 (6.3)	-	-
Hyperglycemia	7 (43.8)	5 (31.3)	2 (12.5)	-	-
Rise in hepatic transaminases	4 (25)	3 (18.8)	-	1 (6.5)	-

Conclusions

Phase I clinical trials can be considered a reasonable therapeutic approach for ACC patients who failed conventional treatments due to low risk of toxicity and the potential for clinical benefit. The RMH prognostic score can help to identify patients most likely to benefit from these investigational agents.

References

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