Retrospective analysis of the safety and efficacy high-dose interleukin-2 after prior tyrosine kinase inhibitor therapy in patients with advanced renal cell carcinoma

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Abstract

Although tyrosine kinase inhibitors (TKI) are the most common first-line therapy for metastatic renal cell carcinoma (mRCC), high-dose interleukin-2 (HD-IL2) remains the only agent that

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provides durable complete responses. The optimal sequence of these agents remains uncertain. This retrospective multi-institutional study examined the safety and efficacy of HD-IL2 following TKI therapy. After IRB approval at 7 HD-IL2 centers, data relating to patient, disease, and treatment characteristics among 40 consecutive patients with mRCC who were treated with HD-IL2 after at least one prior TKI therapy were retrospectively collected. The most common cardiac adverse events (AEs) were grade 3 hypotension and vascular leak syndrome. Six patients (15%) experienced other grade 3 cardiac AEs. There were two treatment-related deaths due to congestive heart failure, occurring in one patient with short TKI to HD-IL2 interval and another patient with an abnormal baseline cardiac stress test. Best responses included two CRs (5%, duration 40+ and 62+ months), 3 PRs (8%, duration 6, 11, and 24 months), 13 SD (32%, median duration 12 months), 20 PD (50%), and 2 not evaluable patients. Median overall survival was 22 months. Administration of HD-IL2 could be safe and effective after TKI therapy; however, careful selection of patients is critical. We recommend baseline cardiac risk factor assessment, screening with both cardiac stress test and echocardiogram, and allowing a TKI to HD-IL2 interval of at least 2 months.

Keywords

High-dose interleukin-2; tyrosine kinase inhibitor (TKI); renal cell carcinoma; sunitinib; sorafenib

Introduction

Renal cell carcinoma (RCC) accounted for nearly 64,000 new cases and over 13,000 deaths in the United States in 2014.[1] One-third of patients present with primary metastatic disease and 20–40% of patients have recurrent metastatic disease after primary nephrectomy with curative intent.[2] Therefore, approximately 50% of all patients diagnosed with RCC will require systemic therapy during the course of their disease. Interleukin-2 [(IL-2) Proleukin®, Prometheus Laboratories, Inc., San Diego, CA)] was approved in 1992 for the treatment of relapsed mRCC based on an objective response rate (ORR) of 14% and, more importantly, a durable complete response (CR) rate of 5%.[3,4] However, high dose IL-2 (HD-IL2) is associated with moderate to severe acute toxicity and requires intensive inpatient supportive management, limiting its use to major centers. While most IL-2-related toxicities reverse rapidly after therapy is completed, the cardiovascular treatment-related mortality has been reported to be as high as 4% in the early phase II studies of HD-IL2.[3] In more recent series, the HD-IL2 treatment-related mortality rate was around 1–2% in patients who were carefully screened and did not have coronary artery disease (CAD), and the CR, PR, and ORR rates were 5–9%, 12–23%, and 21–28%, respectively.[5,6] In one retrospective analysis of 259 patients treated with HD-IL2 at the National Cancer Institute (NCI), in which patients > 50 years old underwent cardiac stress testing and those with ischemic heart disease, significant arrhythmias, or significant comorbidities were specifically excluded, only two treatment-related deaths were observed.[5] In the Cytokine Working Group (CWG) Select trial, there were two deaths in approximately 120 HD-IL2 treated patients in which CAD was an exclusion.[6]

Multi-targeted tyrosine kinase inhibitors (TKIs) such as sunitinib, sorafenib, pazopanib, and axitinib have demonstrated improved ORR and/or survival compared with interferon therapy and/or supportive care.[7–12] Because of oral administration, higher response rates, and more favorable toxicity profiles, TKIs have largely replaced cytokine therapies in the first-line treatment of mRCC. Nevertheless, HD-IL2 remains the only available treatment option that produces durable complete responses.

The safety and efficacy of TKIs after prior cytokine therapy have been previously demonstrated in large prospective trials of these agents in the second-line setting.[7–10,13,14] However, whether HD-IL2 can be given safely and effectively after prior TKI therapy has not been investigated prospectively. In a retrospective analysis of 23 patients who received salvage HD-IL2 therapy after prior VEGF-targeted therapy, there were no responses, and the incidence of severe cardiovascular toxicity was high, including one sudden cardiac death during HD-IL2 therapy.[15] The authors suggested that better patient selection with rigorous cardiovascular screening and increasing the time interval between TKI and HD-IL2 therapy may allow safer administration of HD-IL2.[15]

Reports of toxicity and futility for HD-IL2 therapy post TKIs potentially impact the delivery of beneficial, possibly curative, therapy to mRCC patients. Thus this collaborative effort was mounted to evaluate the safety and efficacy of HD-IL2 therapy in an expanded cohort of such patients, and to explore the potential patient-, disease-, and drug-related factors that may predict safety and efficacy.

The therapeutic sequence of a TKI followed by high dose IL-2 may occur in a number of settings. A patient may have a recent diagnosis of metastatic renal cell cancer and be anxious to initiate any therapy. Once on medical therapy, the disease may stabilize. Then, as the patient learns more about their disease they may realize the potential for durable response with high dose IL-2 therapy. Alternatively, the patient at diagnosis may not want to accept the potential toxicity associated with high dose IL-2, but later discover the treatment is more tolerable than anticipated. Finally the patient may have rapidly progressive disease that is stabilized by a TKI and later becomes a good candidate for high dose IL-2.

Patients and Methods

IRB approval or exemption was obtained at all of the participating institutions. We retrospectively collected information regarding patient-related, disease-related, and treatment-related variables among patients with mRCC who were treated with HD-IL2 [600,000 IU/kg intravenously every 8 hours for up to 14 doses (in 36 patients) or 720,000 IU/kg every 8 hours for up to 12 doses per treatment week (in 4 patients)] between January 2005 and December 2010 after at least one prior TKI therapy (sunitinib, sorafenib, or both). Patient-related variables included age, gender, performance status, cardiac risk factors, personal history of CAD, and baseline cardiac evaluation if available. Cardiac risk factors were chosen based on the Framingham/Adult Treatment Panel III and the American Heart Association guidelines on assessment and management of cardiovascular risk and included age >55 for men or >65 for women, current or former tobacco use, diabetes, hypertension, dyslipidemia, and family history of CAD.[16–20] For the majority of patients, primary lipid

data was not available and dyslipidemia status was inferred based on statin use. Disease-related variables included histology, number and sites of metastatic disease, Memorial Sloan Kettering Cancer Center (MSKCC) prognostic stratification[21,22], and prior treatments. Primary data was too sparse to stratify by the Heng criteria.[23] HD-IL2 treatment-related variables collected included time from initial diagnosis to start of HD-IL2 therapy, interval from discontinuation of TKI to start of HD-IL2, duration and amount of HD-IL2 therapy received, grade 3–5 cardiac and non-cardiac adverse events. Outcome variables included best response (RECIST v1.0)[24], duration of response, time from end of HD-IL2 therapy to start of subsequent therapy, progression-free survival (PFS) and overall survival (OS). For OS and PFS, we evaluated the time from start of HD-IL2 to time of death or data cutoff in December 2010.

In this retrospective analysis, we used descriptive statistics including estimates of proportions, as well as, means, medians, and interquartile range, and range. We estimated the proportion of patients with significant cardiac toxicity and the proportion with any or 2 cardiac risk factors. Relationships between two factors were explored using Fisher's exact test. Quantitative outcomes such as the number of cardiac risk factors were explored, especially in relation to incidence of severe cardiac toxicity, and analyzed using Wilcoxon rank sum tests. However, given the sample size limitations, any formal comparisons were truly exploratory and hypothesis-generating. A Kaplan-Meier survival curve was used to display the OS function. Cox proportional hazards regression models were used to estimate the hazard ratios of potential prognostic factors.

Results

Forty patients treated consecutively at seven HD-IL2 centers [Roswell Park Cancer Institute (9 patients), University of Colorado (8 patients), University of Utah Huntsman Cancer Institute (7 patients), University of Michigan (6 patients), Feinberg School of Medicine of Northwestern University (6 patients), Indiana University Melvin and Bren Simon Cancer Center (3 patients), and The Ohio State University Wexner Medical Center (1 patient)] met criteria for analysis.

Baseline patient and disease characteristics are described in Table 1. Twenty-eight men and 12 women were treated. The median age was 53.5 years (range 40–72). Thirty-nine patients (98%) had prior nephrectomy. All but one patient had clear cell histology (subclassification data not available). Twenty-two patients had primary metastatic disease, and 18 patients had recurrent metastatic disease. Thirty-one patients had multiple sites of metastases, most commonly involving lymph node, lung, bone, and liver. Three, 25, and 2 patients had MSKCC good-risk, intermediate-risk, and poor-risk disease, respectively. Data was not available to categorize 10 patients using this model. Best response to prior TKI therapy was stable disease (SD) in 50% of patients and partial response (PR) in 20% of patients. The median interval between TKI and HD-IL2 therapies was 6 weeks (range 10 days to 52 weeks).

Baseline cardiac risk factors and baseline cardiac evaluations are listed in Table 2. Two patients had personal history of CAD. Thirty-four patients (85%) had at least one cardiac

risk factor. Twenty-seven patients (68%) had 2 cardiac risk factors and 13 patients had 3 risk factors. Thirty-three patients (83%) underwent baseline cardiac evaluation with one or more modalities (7 with transthoracic echocardiogram or MUGA alone, 26 with nuclear medicine stress test or stress echocardiogram), including all 13 patients with 3 cardiac risk factors. Median ejection fraction (EF) was 65% (range 50–79%). Left ventricular hypertrophy and valvular abnormalities were seen in 2 patients each. Wall motion abnormality and ischemic changes were seen in one patient.

The most common cardiac adverse events (AEs) while on HD-IL2 therapy were grade 3 hypotension and vascular leak syndrome. Six patients (15%) experienced other grade 3 cardiac AEs, as noted in Table 3. Grade 1 creatine kinase or troponin elevations were reported in 3 patients. Two patients had reversible non-cardiac respiratory failure. Two patients died within one month of receiving HD-IL2 therapy. The first patient (age 58 years, 2 cardiac risk factors, baseline EF 55–70%, no wall motion abnormalities, and a 4-week TKI to HD-IL2 interval) died one month after week 1 of cycle 2 of HD-IL2 due to new onset atrial fibrillation and congestive heart failure (CHF). The second patient (age 72 years, positive history of CAD, EF 50–65%, apical hypokinesis and small area of reversible ischemia in distribution of a stented mid- left anterior descending coronary artery on pre-HD-IL2 nuclear stress test, and a 10-day TKI to HD-IL2 interval) died one week after week 1 cycle 1 of HD-IL2 with severe CHF. Although the numbers are small, in our analysis, the median time from TKI to HD-IL2 was 8 weeks in patients who did not experience grade 3–5 AEs, and 4.5 weeks in patients who experienced grade 3–5 AEs (p=0.1 by Wilcoxon Rank Sum test). The association between number of doses received and cardiac toxicity did not reach statistical significance, with p=0.064 for all-grade cardiac toxicity, and p=0.076 for grades 3 cardiac toxicity.

Twenty-seven, 12, and 1 patient(s) received 1, 2, and 3 courses of HD-IL2, respectively. The median number of doses of HD-IL2 received was 17 (range 2–49). The clinical benefit rate was 45% [CR in 2 patients (5%), PR in 3 patients (8%), and SD in 13 patients (32%)]. Twenty patients had disease progression (PD) and 2 patients were not evaluable. The median duration of SD was 12 months (range 1.5 to 41). The duration of response was 6, 11, and 24 months for the three patients with PR. The two patients (5%) who achieved CR had 40+ and 62+ month duration of response. There was a trend noted between dose intensity and response (Table 4). The median OS from time of starting HD-IL2 therapy was 22 months (95% CI, 9, 36), as shown in Fig 1.

There was a skewed distribution of the MSKCC prognostic category among the patients, with only 2 patients each having good and poor prognoses, and the majority of patients (25 patients, 86%) having intermediate prognosis. Thus, the association of MSKCC prognostic category on survival, either from the time of HD-IL2 or from time of metastatic disease, cannot be adequately estimated.

Discussion

To our knowledge, this study is the largest series of patients treated with HD-IL2 after prior TKI therapy. Most importantly, we found that prior TKI did not preclude these patients from

benefitting from HD-IL-2 therapy. Two patients (5%) achieved CR with continuing response at 40+ and 62+ months at the time of data cutoff. The clinical benefit rate was 45%, with a median duration of SD or better of 18 months (range 1.5 to >62). Although patient numbers were small and it is difficult to compare findings of small studies years apart, our observed median OS was 22 months, compared to 15.8 months in the original studies of HD-IL2.[25] There were no sudden cardiac deaths due to arrhythmias. There were two deaths due to CHF thought to be treatment-related. In comparison, the previously discussed Cho report noted severe cardiac events in 6/15 patients (40%), no responses, and 3 patients (13%) with SD with median duration of 9 months.[15] The differences in toxicity outcomes may reflect a more stringent patient selection process that has already been implemented at the major HD-IL2 institutions in this study. Our severe cardiac toxicity rate of 15% is higher than the previously reported rate 8.5% in mRCC patients receiving HD-IL2 therapy.[26] In addition, the treatment-related mortality (5%) in our series is higher compared to the contemporary trials of HD-IL2 therapy.[5,6] However, one death occurred in a patient with known CAD and findings of reversible ischemia on pre-HD-IL2 cardiac testing. This patient may well not have been eligible for treatment in the CWG or NCI trials. This highlights the importance of excluding CAD with cardiac testing prior to initiating HD-IL2.

This retrospective study design has several limitations. First, we did not examine outcomes for any patients who received HD-IL2 prior to TKI for comparison. Second, the reliance on chart review may underestimate cardiac-related AEs if they were not noted formally as in prospective therapeutic trials. However, we believe that this would mostly affect reporting of lower grade events, and that all clinically significant, especially higher grade (grades 3–5) cardiac events, would have been documented in the clinical chart and would have been captured in our data collection.

In our study, the ORR of HD-IL2 after prior TKI was 13%, which is similar to historical ORR of 14% in the pre-TKI era[3]; therefore, prior TKI therapy did not appear to compromise response from HD-IL2. Nevertheless, the response rate was less than that reported in several contemporary trials of HD-IL2 given prior to TKI. In the Select study, the ORR was 28%, mostly due to a PR rate of 23%.[6] In another study evaluating first-line HD-IL2 therapy of mRCC patients, Shablak and colleagues found an ORR of 49%, including CR of 25%.[27]

Other small studies in the post TKI setting have now been reported. In a abstract of 16 mRCC patients receiving HD-IL2 after prior TKI (8 after TKI failure and 8 for consolidation after TKI), Hawkins and colleagues reported 9 objective responses (56%), including 6 CRs (38%), with toxicity profile indistinguishable from those without prior TKI treatment.[28]

To our knowledge, our study is the first series to examine potential associations between number of cardiac risk factors and incidence of severe cardiac toxicities. Multiple traditional cardiovascular risk factors are used for risk assessment for CAD.[16–19,29,30] However, whether these same factors can be used to predict the risk of cardiovascular toxicity from HD-IL2 has not been evaluated. In this study, we found that patients with 3 cardiac risk factors seemed to have higher incidence of grade 3–5 cardiac AEs, compared to patients with 2 risk factors, although this was not statistically significant due to the low incidence

of severe cardiac toxicity overall. Based on our findings, and the assumption that the low overall incidence of cardiac toxicity is the result of a careful patient selection process already in place at major HD-IL2 institutions, we recommend risk-adapted cardiac evaluation prior to HD-IL2 therapy, similar to standard preoperative cardiac risk evaluation.[19] For all patients with any known cardiac risk factors, we would recommend cardiac stress testing to rule out ischemic heart disease and echocardiogram to rule out cardiomyopathy prior to initiating HD-IL2.

The optimal interval between TKI and HD-IL2 therapy requires further investigation. The half-life of sunitinib is 2.5 days. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary active metabolite accumulates 7- to 10-fold, with a metabolite half-life of 96 hours.[31] In this study, the two patients with treatment-related deaths had TKI to HD-IL2 intervals of 10 days and 4 weeks. All observed grade 3 cardiac toxicities occurred in patients whose TKI to HD-IL2 interval was 6 weeks, although there was no statistical correlation due to the small number of patients and cardiac events overall.

The cardiotoxicity, in particular CHF, associated with sunitinib and sorafenib, has been previously reported.[32–35] Sunitinib-induced pericyte depletion and coronary microvascular dysfunction has also been reported.[36] In the majority of patients who develop left ventricular (LV) dysfunction, symptoms improve after dose interruption, dose modification, and/or initiation of heart failure therapy. The reported time to improvement of LV ejection fraction was between 1 and 9.6 weeks.[32] While CHF is not a common toxicity reported for HD-IL2, myocardial dysfunction as a result of myocarditis is a known event.[37] Some institutions incorporate cardiac enzyme testing as a standard during and around HD-IL2 therapy.

Cho and colleagues suggested that patients should be off TKIs at least 1–2 months before initiation of HD-IL2.[15] Based on the pharmacologic half-lives of sunitinib and its active metabolites, complete clearance of the drug may require at least 3–4 weeks off therapy. However, the time to complete resolution of other clinical drug effects is not known. Based on these considerations, we would recommend an interval of at least 2 months between completion of a TKI and initiation of HD-IL2.

Sorafenib and sunitinib were the dominant TKIs in use during the time period encompassed by this study. With the approval of pazopanib and axitinib, we now have TKIs that are associated with a lower incidence of cardiomyopathy overall. Their impact on subsequent salvage IL-2 therapy is unknown and requires further investigation. In the meantime, it would be prudent to exercise the same degree of caution in the selection of patients for HD-IL2 therapy after prior treatment with these agents.

Newer immunotherapies (nivolumab, ipilimumab, AGS-003, MPDL3280A, and others) are in development for mRCC.[38–41] Long-term benefit and toxicity of these newer therapies remain to be determined. For the foreseeable future, HD-IL2 therapy remains the only modality with reproducible long-lasting CRs. Although limited by its retrospective nature and limited patient numbers, the strength of this study is that it incorporates data from multiple experienced investigators and HD-IL2 centers and reflects a diverse cross section of this patient population. We conclude that administration of HD-IL2 could be safe and

effective after TKI therapy; however, careful selection of patients is critical. We recommend baseline cardiac risk factor assessment, screening with both cardiac stress test and echocardiogram, and allowing a TKI to HD-IL2 interval of at least 2 months.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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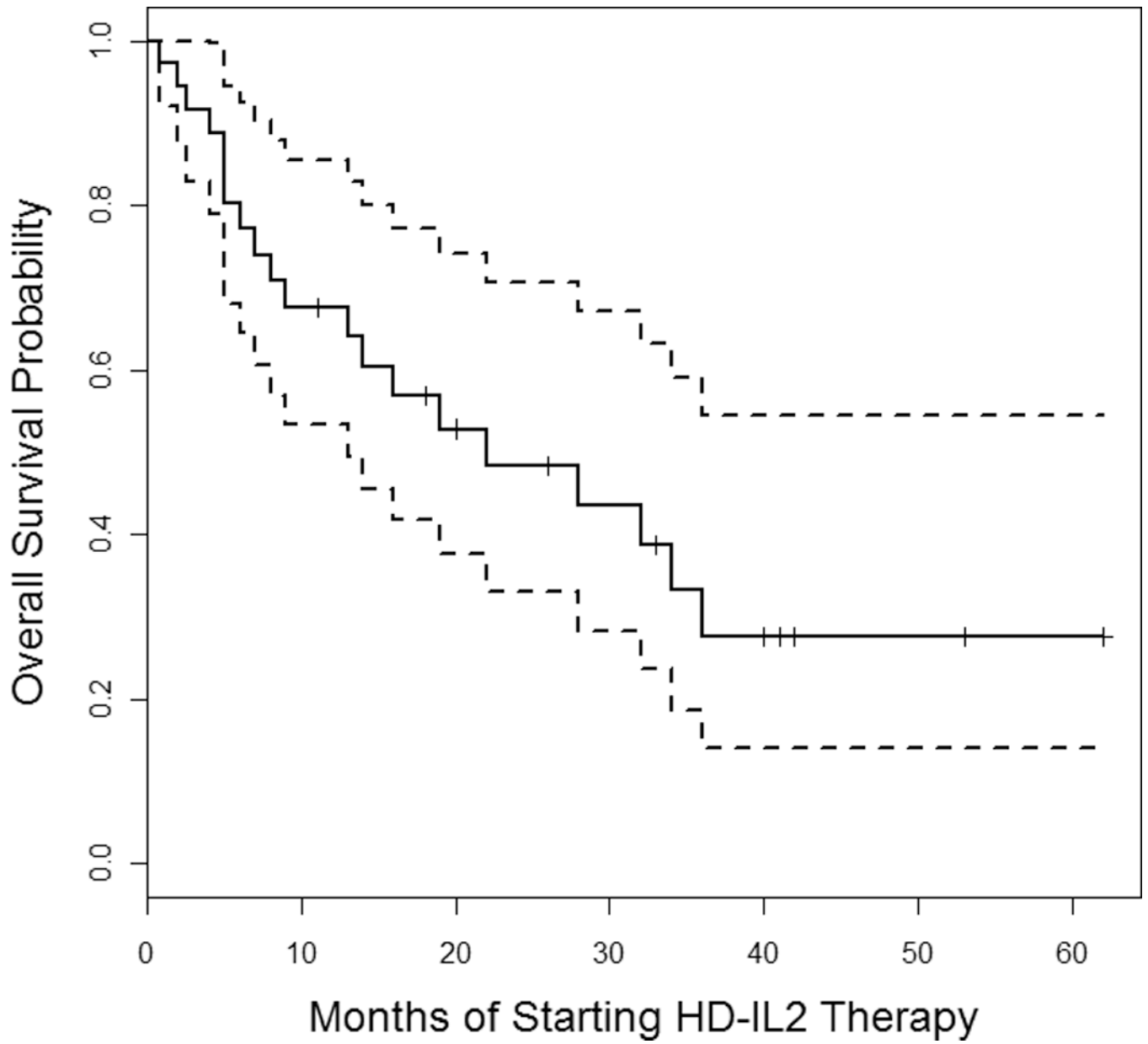
Figure 1. Overall Survival

Table 1

Patient Characteristics

	Number	Range
Age (median)		
At Diagnosis	52	34–68
At HD-IL2	53.5	40–72
No. of metastatic sites		
1	9	
2	15	
3	9	
>3	7	
Site of metastases		
Lymph node	21	
Lung	18	
Bone	13	
Liver	10	
Adrenal	5	
Abdomen	4	
Brain	0	
Other	3	
Prognostic factors at time of HD-IL2 treatment	40	
KPS 80%	40	
Normal Hemoglobin	22	
Normal Corrected Calcium	36	
Prior TKI therapy		
Sunitinib	20	
Sorafenib	12	
Both	8	
Best response to TKI		
PD	10	
SD	20	
PR	8	
Unknown or NE	2	
Duration of TKI therapy (median, weeks)	26	4–132
Time from TKI therapy to HD-IL2 therapy (median, weeks)	6	1.3–52
Time from onset of metastatic disease to HD-IL2 therapy (median, months)	11	1.5–95

Table 2

Cardiac Risk Factors

	Number	Range
Cardiac Risk Factors		
Smoking Status		
Current or former	24	
Never	16	
DM	4	
HTN	21	
Dyslipidemia[*]	7	
FH of CAD	6	
Personal h/o CAD	2	
No. of Cardiac Risk Factors		
0 cardiac RF	6	
1 cardiac RF	8	
2 cardiac RF	13	
3 cardiac RF	7	
4 cardiac RF	5	
5 cardiac RF	1	
Pre- HD-IL2 cardiac testing done?		
Yes	**33**	
0–2 cardiac RF	20	
3–5 cardiac RF	13	
Ejection fraction (median, %)	65	50–79
LV hypertrophy	2	
Wall motion abnormalities	1	
Valvular abnormalities	2	
Ischemic changes	1	
No	**7**	
0 cardiac RF	1	
1 cardiac RF	4	
2 cardiac RF	2	

[*] The lipid status was unknown for 5 patients.

Table 3

Patients with Severe (Grade 3–5) Cardiovascular Adverse Events

Patient	No. of Cardiac Risk Factors	TKI to HD-IL2 Interval (Weeks)	Cardiovascular Event
1	1	6	Supraventricular tachycardia
2	2	3	Nonsustained ventricular tachycardia
3	2	4	Atrial fibrillation and heart failure
4	3	6	Supraventricular tachycardia
5	4	5	Atrial fibrillation
6	4	1.3	Congestive heart failure

Table 4

Dose Intensity and Response

RECIST Response	Median no. of doses of HD-IL2
Complete Response	46
Partial Response	35
Stable Disease	22
Progression of Disease	13