Published in final edited form as:

Leuk Res. 2009 November ; 33(11): 1485–1489. doi:10.1016/j.leukres.2009.01.020.

Phase II study of interleukin-12 for treatment of plateau phase multiple myeloma (E1A96): A trial of the Eastern Cooperative Oncology Group[☆]

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Abstract

The Eastern Cooperative Oncology Group (ECOG) conducted a phase II trial of interleukin-12 (IL-12) for plateau phase multiple myeloma. Patients were initially treated with IL-12 250 ng/kg I.V. daily for 5 days every 3 weeks. The trial was modified due to toxicity after the first 16 patients. IL-12 was given 300 ng/kg subcutaneously twice weekly for 24 weeks. Of 48 eligible patients, there were 4 objective responses (8.3%), all CR. The median survival and progression-free survival were 42.8 and 11.4 months. Unacceptable grade 3 or 4 non-hematologic toxicity (31% with IL-12 subcutaneously and 63% with IL-12 intravenously) was observed.

Keywords

Multiple myeloma; Interleukin-12; Immunomodulatory therapy

1. Introduction

Multiple myeloma (MM) patients who have achieved the so-called plateau phase have stable disease with no need for chemotherapy until relapse. This population with measurable residual disease after completion of chemotherapy may be the most likely to benefit from immunologically targeted therapy. This is based on the premise that the malignant clone is responsive to host immune mediated suppression. Some studies have shown prolongation of

[☆]This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, M.D.) and supported in part by Public Health Service Grants CA23318, CA66636, CA21115, CA13650 and from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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Contributions. Dr Lacy: served as Principal Investigator; wrote the trial, analyzed data, and wrote the manuscript, Dr. Jacobus: statistician, did data analysis and edited manuscript, Emily Blood: statistician, did data analysis and edited manuscript, Dr. Kay: helped with trial design, conducted and analyzed the laboratory correlates, edited the manuscript, Dr. Rajkumar: helped with data analysis and edited the manuscript and Dr. Greipp: helped with trial design, data analysis and edited the manuscript.

5. Conflict of interest

None of the authors have any conflicts of interest.

remission with use of alpha interferon but the benefit is modest [1–7]. More recent trials have suggested a benefit using thalidomide [8], an effect that may be in part due to the immunomodulatory effects of thalidomide. New immunoregulatory agents are needed for treatment of plateau phase myeloma.

To determine the efficacy and toxicity of interleukin-12 (IL-12), the Eastern Oncology Cooperative Group (ECOG) conducted a randomized phase II trial of this agent in previously treated patients with plateau phase multiple myeloma. We hypothesized that treatment with IL-12 may help to restore a full repertoire of lymphocytes and may augment vaccine responses. In order to assess this hypothesis, we used a randomized phase II design in which half the patients received IL-12 in conjunction with vaccines against *Haemophilus influenza* and *Streptococcus pneumoniae* and half received IL-12 a month following their vaccines. Here we report the clinical results of this trial.

2. Methods

To be eligible for this study, patients must have met ECOG criteria for multiple myeloma (MM). Patients must have been in stable plateau as defined by ECOG which requires objective response, no evidence of continuing improvement by any criteria, and <20% variation in M protein over at least 4 weeks prior to registration. Patients must have been off chemotherapy for at least 60 days prior to registration. Patients must have had measurable or evaluable M protein and must have been taken within 14 days prior to registration. Measurable disease was considered to be a serum M protein ≥ 1.0 g/dL or urine M protein > 200 mg per 24 h. Patients with M proteins less than these values were considered evaluable rather than measurable. (Serum > 0 and < 1 g/dL, urine > 0 and < 200 mg/24 h). Non-secretory patients were ineligible. Patients must have had ECOG performance status 0–2 and have had adequate organ and marrow function. All patients provided written informed consent. The study was approved by the Institutional Review Board of each participating institution in accordance with federal regulations and the Declaration of Helsinki.

At study entry, patients were randomized to arm A or arm B. Patients were initially treated with a test dose of IL-12 given intravenously followed by IL-12 250 ng/kg I.V. daily for 5 days every 3 weeks for 6–12 cycles. After unexpectedly high toxicity was observed an amendment was activated which changed the administration of IL-12 from I.V. to SC as following:

Arm A. Vaccines against *H. influenza* and *S. pneumoniae* (Hib TITER and Pnu-Immune-23) were given on day 1 of cycle 1. IL-12 100 ng/kg SC was given twice a week for 2 weeks. The dose was then increased to 300 ng/kg SC twice a week for 12 weeks or up to 26 weeks.

Arm B. Vaccines against *H. influenza* and *S. pneumoniae* (Hib TITER and Pnu-Immune-23) were given on day 1 of cycle 1. Patients were then observed for 4 weeks prior to IL-12 treatment. They then received IL-12 100 ng/kg SC twice a week for 2 weeks. The dose was then increased to 300 ng/kg SC twice a week for 12 weeks or up to 26 weeks. For both arms, after the 300 ng/kg SC IL-12 administration, patients who did not progress after 12 weeks of

treatment were offered an additional 12 weeks. Liver function tests were checked weekly in all patients.

Response was evaluated using the following ECOG Myeloma Response Criteria [9], which had been modified to exclude references to non-secretory myeloma and to include evaluable disease. For patients with evaluable disease only, a response is defined by the CR criteria.

2.1. Statistical methods

The primary endpoints for this study were best overall response and non-hematologic toxicity. Anti-tumor activity was further assessed with time to event endpoints: overall survival (OS) and progression-free survival (PFS). This study was designed with one-stage although an evaluation of toxicity was planned for the first 15 enrolled patients. After unexpectedly high toxicity was observed in this cohort, the study was amended with the administration of IL-12 changed from intravenous to subcutaneous. The accrual goal was modified to reflect patients treated only on SC administration of IL-12 and chosen such that a 90% confidence interval for the true response rate would be $<30\%$. Treatment arms were combined for the primary analyses because a difference was not anticipated in the effect of the timing of IL-12 administration. However, these analyses were done within patient subgroups reflecting treatment received: either I.V. or SC only. Response was evaluated using the ECOG Myeloma Response Criteria [9], which had been modified to exclude references to non-secretory myeloma and to include evaluable disease. For patients with evaluable disease only, a response is defined by the CR criteria. OS and PFS were measured from the start of IL-12 therapy. Patients who did not die or experience progression were censored at the date of their last disease evaluation.

Descriptive statistics were used to characterize the eligible population in the two study groups. Exact binomial confidence intervals were used to describe response rate. The method of Kaplan and Meier [10] was used to characterize overall survival and progression-free survival.

2.2. T cell subset analyses

T cell data (cell counts per cubic millimeter) was collected from patients at 3 time-points during the study including: time 1: baseline (prior to therapy), time 2: 4 weeks after study registration (arm A: after 4 weeks of IL-12 treatment; arm B: after 4 weeks of observation, before start of IL-12 treatment), and time 3: At the end of therapy. All blood T cell subset analysis was performed on purified blood lymphocytes after ficol-hypaque centrifugation by flow cytometry as previously described. The following blood T cells were quantified by two color flow cytometry; total CD4+, CD4+/CD4 5RA+ (naïve) and CD4+/CD45RO+ (activated) and used in both absolute levels as well as for calculating the naïve/activated ratios.

3. Results

Fifty-six patients were entered from 14 institutions. Of these 56 patients, 48 eligible patients were included in the analysis. Eight patients were ineligible, one of whom never started the assigned therapy. Reasons for ineligibility included: not at plateau at study entry (5 patients),

no evaluable M protein (3 patients). Ineligible patients were excluded from analysis regarding efficacy but included in the toxicity analysis. At study entry, patients were randomized to two arms. Since the two arms received the same treatments and the only difference was the timing of IL-12 administration the main analyses were done with the arms combined. Relevant descriptive results are reported by treatment arm. This study was initially opened using intravenous (I.V.) administration of IL-12. After unexpectedly high toxicity was observed, the administration of IL-12 was changed to be subcutaneous (SC). Among the 48 eligible patients, 36 patients received all of IL-12 through SC administration only. Given the unacceptable toxicity in the patients with I.V. administration of IL-12, analyses were done primarily for the 36 patients who received IL-12 SC only with analyses for the overall 48 eligible patients of secondary interest. Patient characteristics are described in Tables 1a and 1b.

3.1. Toxicity

Toxicity data were available on the 55 treated patients. Given the change in administration of IL-12 from I.V. to SC due to unacceptable toxicity using I.V. route, toxicity was analyzed separately for the 39 patients who received IL-12 through SC only, the 16 patients who received IL-12 through I.V., and for the overall 55 treated patients. Ten patients among the 16 patients who received IL-12 through I.V. (63%, 95% CI: [35%, 85%]) experienced a worst degree non-hematologic toxicity grade 3 or higher and 4 patients (25%, 95% CI: [7%, 52%]) had grade 4 non-hematologic toxicities. Twelve of the 39 patients who received IL-12 through SC only (31%, 95% CI: [17%, 48%]) experienced a worst degree non-hematologic toxicity grade 3 or higher and 2 patients (5%, 95% CI: [1%, 17%]) had grade 4 non-hematologic toxicities. Of the overall 55 treated patients, 22 patients (40%, 95% CI: [27%, 54%]) had a worst degree non-hematologic toxicity grade 3 or higher and 6 patients (11%, 95% CI: [4%, 22%]) had grade 4 non-hematologic toxicities. No lethal toxicities were observed. Toxicities are described in Tables 2a and 2b.

3.2. Response to therapy

Table 3 summarizes the best overall response among all 48 eligible patients in this study. There were 4 objective responses, all of which were complete responses (8.3%, 95% CI: [2.3%, 20.0%]) Among these 4 the median time to response was 6 months (range 3–6.6 months) and the median duration was 29 months (range 4–56 months). Twenty-nine patients (60.4%) remained stable and fifteen (31%) had progressive disease.

3.3. Survival

Median follow-up time for survivors from the start of IL-12 was 57 months in the I.V. group and 34 months in the SC group. Among the 48 eligible patients, 21 (43.8%) had died. The median survival from the start of IL-12 therapy was 42.8 months. The 1, 2, and 3 year estimates of survival are 75% (95% CI: 41%, 91%), 50% (95% CI: 21%, 74%) and 25% (95% CI: 6%, 50%), respectively in the I.V. group and 92% (95% CI: 76%, 97%) 80% (95% CI: 63%, 90%), and 69% (95% CI: 49%, 82%) in the SC group (Table 4). Fig. 1 shows the overall survival for the I.V. patients and for SC only patients.

3.4. Progression-free survival

Progression-free survival from the start of IL-12 therapy was computed as time from start of IL-12 to death or progression, whichever occurred first. For patient who were still alive and progression free, progression-free survival was censored at the date of last disease assessment. The 1, 2, and 3 year estimates of progression-free survival are 25% (95% CI: 6%, 50%), 17% (95% CI: 3%, 42%), 17% (95% CI: 3%, 42%) respectively in the I.V. group and 58% (95% CI: 40%, 72%), 42% (95% CI: 25%, 58%), 24% (95% CI: 9%, 42%) in the SC group (Table 5). Fig. 2 shows the progression-free survival for the I.V. patients and for SC only patients.

3.5. T cell subset analyses

To take into account the fact that at time 2 arm A already had 4 weeks of IL-12 therapy and arm B only had 4 weeks of observation before IL-12 therapy, when combining arms we analyzed time 3–time 1 for arm A and time 3–time 2 for arm B as this represents the start of IL-12 therapy (i.e. baseline) and the end of IL-12 therapy for both arms. Boxplots of CD4 data at 3 time-points were shown in Fig. 4 (naive/activated CD4 ratio).

3.5.1. Difference of CD4 counts between time-points—Within each arm, pair-wise comparisons between different time-points (time 2–time 1, time 3–time 2 and time 3–time 1) were done for each cell type as well as the ratio of naive CD4/activated CD4. For arms combined, when looking at the change regardless of the time difference there was a significant increase from baseline to the end of IL-12 therapy in naive CD4 counts (p -value = 0.02, mean change = 17.2) and naive/activated ratio (p -value < 0.0001, mean change = 0.28) and a significant decrease of absolute CD4 counts (p -value = 0.02, mean change = –85.72) and activated CD4 counts (p -value = 0.01, mean change = –68.92).

In arm A, there was a significant decrease between time 1 and time 3 in activated CD4 counts with and without taking into account the time difference (p -value 0.01 with mean change –91.77 and p -value 0.02 with mean change/day –0.68, respectively) and a significant increase in naive/activated ratio between time 1 and time 3 (p -values: 0.0005 with mean change = 0.30 and mean change/day = 0.002).

In arm B, there was a significant increase between time 2 and time 3 in naive CD4 counts with and without taking into account the time difference (p -value 0.04 with mean change 29.83 and p -value 0.02 with mean change/day of 0.22) and naive/activated ratio (p -values: 0.001 with mean change = 0.26 and mean change/day = 0.002). There was a significant difference in total CD4 levels between time 2 and time 3 (p -value = 0.03, mean change = –83.83) and this decrease became marginal when taking into account the time difference (p -value = 0.05) with a mean change of –1.07 per day and is equivalent to a 7.48 mean decrease in total CD4 counts per week.

4. Discussion

IL-12 has been used in clinical trials for B cell malignancies. Studies have shown that IL-12 given in conjunction with rituximab for low-grade non-Hodgkin lymphoma is well tolerated and may be associated with longer response duration than previous trials using rituximab

alone [11,12]. IL-12 has also been studied after autologous stem cell transplant for hematological malignancies resulting in the expansion of T, B, and NK cells *in vivo* [13]. Interleukin-12 alone or with GM-CSF has been used to enhance anti-idiotypic vaccines in patients with multiple myeloma [14].

Overall for the 48 patients there were 4 complete responses (8.3%, 95% CI: [2.3%, 20.0%]). The median survival and median time to progression from the start of IL-12 were 42.8 months and 11.8 months respectively. Since this treatment was maintenance/consolidation therapy in patients who have already responded and achieved a stable plateau, the low percent of responders is not surprising. The duration of response and stability is impressive given that all patients were previously treated and were approximately 2 years out from the original myeloma diagnosis. The change in the overall number of blood CD4 cells as well as the naive/activated ratio during therapy was modest, but may have played a role in the prolonged stability noted in the patients enrolled.

This phase II study in plateau phase MM patients shows that both intravenous and subcutaneous administration of IL-12 appeared to have unacceptable toxicity for this patient population. Changing the route of administration from intravenous to sub-cutaneous improved the rate of grade 3 and 4 non-hematologic toxicity from 63% to 31%, a rate that is unacceptable in a population of patients who would otherwise be observed or offered thalidomide.

IL-12 is not currently available for clinical use. The stability of our patients suggests utility for immunomodulatory agents. This is further supported by emerging data supporting a role for thalidomide for maintenance therapy. Future studies should be directed at understanding the role of an intact immune system in the treatment of MM and finding less toxic agents or combination regimens that enhance immune control over myeloma cells.

Acknowledgments

Dr. Lacy: Grant/Research Support: Celgene Corporation, Millennium, The Takeda Oncology Company, and Genzyme.

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Fig. 1.
Overall survival: (a) I.V. only (median f/up 57 months) and (b) SC only (median f/up 34 months).

Fig. 2.
Progression-free survival: (a) I.V. only and (b) SC only.

Table 1

Patient characteristics: by treatment group.

	Treatment group					
	I.V. only			SC only		
	N	Median	Range	N	Median	Range
Interval from diagnosis to registration (years)	12	2.1	0.7–7.1	36	1.8	0.7–13.5
Age (years)	12	58	40–74	36	59	47–85
Serum M-component electrophoresis (g/100 ml)	6	1.4	0.6–2.8	26	1.2	0.3–2.3
Urine light chain excretion	2	0.09	0.08–0.09	7	0.07	0.02–0.55
Total urine protein excretion	6	0.08	0.03–0.24	18	0.05	0.01–0.69
IgG(mg/100ml)	12	638	278–3080	35	1085	186–2710
IgA (mg/100 ml)	12	39	8–658	35	56	10–1900
IgM (mg/100ml)	12	32	13–213	35	38	10–170
Serum creatinine (mg/100ml)	12	1.1	0.5–1.7	36	1.0	0.5–1.9
Serum calcium (mg/100ml)	9	9.3	8.3–9.8	36	9.4	8.5–10.1
Serum albumin (mg/100ml)	12	3.8	3.2–4.2	31	3.9	0.4–4.7
Bilirubin (mg/100ml)	12	0.7	0.2–1.3	36	0.5	0.2–1.1
Number of cycles	12	5	1–12	36	15	1–26

	Treatment group			
	I.V. only		SC only	
	N	%	N	%
Sex				
Male	8	67	21	58
Female	4	33	15	42
NCI race				
White	11	92	34	94
Black	1	8	2	6
Stage				
1	1	12	7	23
2	4	44	11	35
3	4	44	13	42
Unknown	3		5	
Previous systemic treatment				
Yes	12	100	36	100
Previous BMT				
No	8	67	16	44
Yes	4	33	20	56
ECOG performance status				
0	8	67	24	67
1	3	25	12	33
2	1	8	0	0

Table 2

Toxicity: I.V. only.

Toxicity type	Total (n =16)		
	Grade		
	1,2 (n)	3(n)	4(n)
Leukopenia	5	3	1
Granulocytopenia	5	4	–
Thrombocytopenia	4	–	–
Anemia	13	–	–
Infection	3	–	–
Fever (no infection)	13	–	–
GU	5	–	–
Nausea/vomiting	7	1	–
Vomiting	6	–	–
Diarrhea	1	–	–
Stomatitis	2	–	–
Liver	6	5	1
Pulmonary	4	–	–
Cardiac	1	–	–
Hypotension	6	–	–
Skin	1	–	–
Allergy	1	–	–
Local (no phlebitis)	1	–	–
Alopecia	1	–	–
Weight loss	3	–	–
Neuro-sensory	2	–	–
Neuro-motor	3	–	–
Neuro-psych	1	–	–
Neuro-clinical	3	2	–
Metabolic	1	–	–
Rhinitis, rhinorrhea	1	–	–
Anorexia	4	–	–
Epigastric distress	1	–	–
Edema	2	–	–
Arthralgia	–	1	–
Myalgia	4	1	2
Dizziness	1	–	–
Fatigue	6	–	1
Sweats	1	–	–
Flu-like symptoms	2	–	–
Chills	6	1	–
Dehydration	–	2	–

Toxicity type	Total (n =16)		
	Grade		
	1,2 (n)	3(n)	4(n)
Pain, other	1	–	–
All other toxicities	5	–	–
Worst degree	6	6	4

Toxicity type	Total (n = 39)		
	Grade		
	1,2 (n)	3(n)	4(n)
Leukopenia	24	12	–
Granulocytopenia	23	10	–
Thrombocytopenia	27	–	1
Anemia	32	2	–
Hemorrhage	1	–	1
Infection	13	1	–
Fever (no infection)	14	–	–
GU	6	–	–
Nausea/vomiting	12	1	–
Vomiting	4	1	–
Diarrhea	7	2	–
Stomatitis	5	–	–
Liver	14	3	–
Pulmonary	8	–	–
Cardiac	2	–	–
Hypertension	2	–	–
Hypotension	22	–	–
Skin	3	–	–
Local (no phlebitis)	6	–	–
Alopecia	2	–	–
Weight loss	3	–	–
Neurosensory	6	–	–
Neuro-motor	4	1	–
Neuro-psych	8	–	–
Neuro-clinical	11	1	1
Metabolic	4	–	–
Abdominal cramps	1	1	–
Anorexia	5	1	–
Vaginal bleeding	1	–	–
Insomnia	2	–	–
Edema	1	–	–
Hotflashes	1	–	–
Eye irritation	–	1	–

Toxicity type	Total (n = 39)		
	Grade		
	1,2 (n)	3(n)	4(n)
Arthralgia	7	2	–
Fatigue	23	1	–
Sweats	1	–	–
Bone pain	2	1	–
Flu-like symptoms	2	–	–
Chills	10	–	–
Dehydration	–	1	–
Pain, other	3	–	–
All other toxicities	5	1	–
Worst degree	27	10	2

Table 3

Best overall response: all patients.

Response	Total	
	<i>N</i>	%
CR	4	8.3
NCR	0	0
PR	0	0
NC	29	60.4
PD	15	31.3
Total	48	

Table 4

Overall survival: by treatment group.

	Treatment group	
	I.V. only	SC only
	Survival (95% CI)	Survival (95% CI)
1 year	75% (41%, 91%)	92% (76%, 97%)
2 year	50% (21%, 74%)	80% (63%, 90%)
3 year	25% (6%, 50%)	69% (49%, 82%)

Table 5

Progression-free survival: by treatment group.

	Treatment group	
	I.V. only	SC only
	Survival (95% CI)	Survival (95% CI)
1 year	25% (6%, 50%)	58% (40%, 72%)
2 year	17% (3%, 42%)	42% (25%, 58%)
3 year	17% (3%, 42%)	24% (9%, 42%)