

Early Results of Total Therapy II in Multiple Myeloma: Implications of Cytogenetics and FISH

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Abstract

Long-term follow-up on Total Therapy I revealed, with a median follow-up of about 10 years, median durations of event-free survival (EFS) and overall survival (OS) of 37 and 80 mos in the 88% of patients lacking cytogenetic abnormalities (CA) of chromosome 13 compared to only 28 and 34 mos in those with CA 13. Total Therapy II (TT II) was developed to test whether more intensive remission induction and post-tandem transplant consolidation chemotherapy prior to interferon maintenance could further improve clinical outcome. All patients were also randomized to \pm thalidomide at a starting dose of 400 mg. Results obtained in the first 231 patients enrolled in TT II are presented for the two study arms combined (data for effect of thalidomide still blinded). Three-year projection of EFS and OS are 71% and 77%. On an intent-to-treat basis, 66% achieved complete remission (CR) or near-CR. Major independent adverse features associated with shortened survival included CA and chromosome 13 deletion using interphase FISH. CA identified 29 among 102 patients with FISH 13 deletion who had a very grave prognosis (3 yr EFS, 32%; OS 49%) compared to all remaining patients who enjoyed 3 yr EFS of 79% and OS of 83%. Thus, both cytogenetics and FISH are recommended in the initial evaluation of patients with MM.

1. Introduction

Total Therapy I (TT I) was the first dose-intensive program for newly diagnosed patients with multiple myeloma (MM) that made cure an objective [1]. As a result of a series of non-cross resistant induction regimens followed by tandem autotransplants with melphalan 200 mg/m² (MEL 200) and interferon maintenance, complete responses (CR) were achieved in more than 40% and, with a median follow-up now of almost 10 years, the median durations of event-free survival (EFS) and overall survival (OS) have been extended to 34 mos and 70 mos, respectively. In the absence of cytogenetic abnormalities involving chromosome 13 (CA 13), present in 12% of all 231 TT I patients at baseline, median EFS and OS were 37 and 80 mos compared to 28 and 34 mos, respectively, in those with CA 13.

Total Therapy II (TT II) was initiated in late 1998 and built on TT I by further intensifying remission induction and incorporating post-transplant consolidation chemotherapy [2]. The remarkable activity of thalido-

mid in end-stage MM [3,4] justified its evaluation in the management of newly diagnosed disease in a randomized trial design (Figure 1). These changes in protocol design were motivated by the high relapse rate and poor salvage rate of MM patients with CA 13, hypothesizing that strategies effective in high risk disease would even more markedly benefit patients presenting with more favorable features.

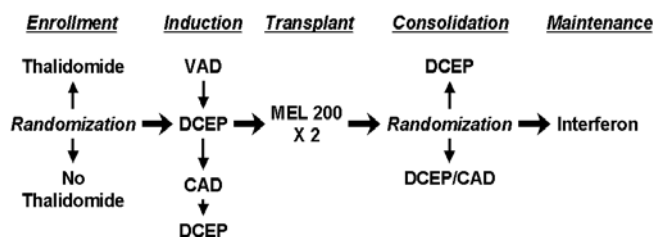


Figure 1. Schema.

Table 1.
Patient Characteristics.

Parameter	< 65 Yr* (N = 184)	65 Yr * (N = 47)
Cytogenetic abnormalities	24	37
CA 13	13	14
Other CA	11	23
FISH 13	50	56
PCLI ≥ 0.4%	55	64
CRP ≥ 4.0 mg/L	53	65
β2M ≥ 4.0 mg/L	24	45
Creatinine ≥ 2.0 mg/dL	6	21
Hemoglobin < 10 g/dL	18	36
Albumin < 3.5 g/dL	18	9
Completed HDT-1	86	66
Completed HDT-2	76	62
Cumulative TRM	4	9
Post-HDT2 CR+n-CR	70	53
Median Follow-up	29 mo	24 mo

*in percent; $P < .05$ for percentages listed in italic

This report summarizes the early experience with TT II in the first 231 patients of currently 450, enrolled with an accrual goal of ultimately 660 patients. As data are still blinded with regard to outcome by thalidomide arm, results are presented for both study arms combined. The median follow-up of TT II patients is 27 mos.

2. Results

2.1. Patient Characteristics

There was no difference in prognostically relevant features between the 2 treatment arms (data not shown). The 47 patients over age 65 had a higher incidence of CA other than CA 13, more often elevations of beta-2-microglobulin ($B2M \geq 4.0$ mg/L) and renal insufficiency (creatinine ≥ 2.0 mg/dL) (Table 1). So far, 81% have completed one and 68% two cycles of MEL 200. More patients under age 65 completed (first and second transplant ($P < .05$), reflecting more insurance denials, toxicities and patient preferences in the older age group. Cumulative treatment-related mortality (TRM) from the entire induction and both transplant phases was 4% among younger and 9% among older patients ($P < .05$).

2.2. Clinical Outcome

Rates of CR and near-CR (only immunofixation positive) increased from 30% at the end of induction to 52% after the first and 66% after the second HDT cycle (intent-to-treat). Because more of the younger patients completed two cycles of high dose therapy, they achieved CR or near-CR more frequently than the older age group (70% vs. 53% ($P = .001$)). Three-year estimates

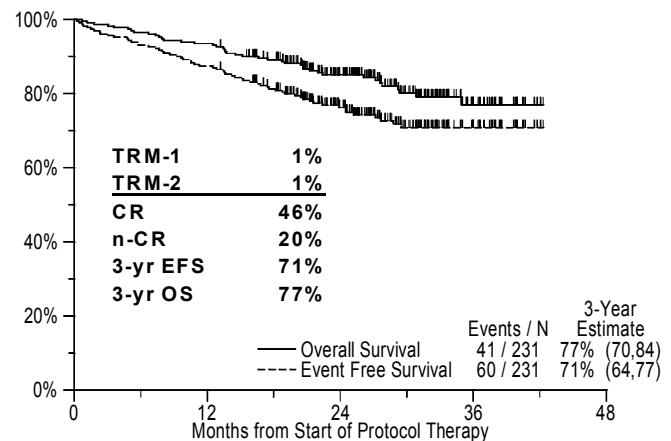


Figure 2. Event-free and overall survival.

of EFS and OS are 71% ($\pm 6\%$) and 77% ($\pm 7\%$) (Figure 2). Examination of potentially relevant prognostic factors revealed, on multivariate examination, a dominant adverse impact of CA 13 for both EFS and OS. In addition, other CA and interphase FISH-defined deletion 13 (present in 52% of patients) were additional adverse variables for OS whereas EFS was inferior in the presence of hypoalbuminemia < 3.5 g/dL and age ≥ 65 years. When the combined impact of both FISH 13 and CA were examined, the presence of CA identified a high-risk group among patients with FISH 13-positive (Figure 3). Indeed the 29 patients with CA among the 102 with FISH 13 deletion had 3 year EFS/OS of only 30% and 49% respectively. The remaining 84% had comparably favorable outcomes (79% and 83%; $P < .0001$, $P < .0001$).

3. Discussion

This is the first study to report on the prognostic implications of both CA and FISH in MM in the context of standard laboratory parameters. We confirm previously published frequencies of CA 13 and FISH 13 deletion in 13% and 51% of patients, respectively, accounting for the presence of FISH 13 in 49% of patients with normal diploid karyotype, probably representing normal hematopoietic cells) [5,6]. Independent prognostic implications of CA and FISH 13 for OS were not suspected. The high risk imposed by the presence of CA in FISH 13 deletion MM underscores the clinical importance of the in vitro mitotic activity of MM cells harboring this abnormality (autocrine growth?). As presented elsewhere, the MM cell-labeling index combined with FISH could not substitute for CA137. The truly dismal prognosis of patients with CA justifies the routine application of cytogenetics in the work-up of patients with MM along with FISH 13. Identification of patients at high risk of early treatment failure and death is critical to the introduction of novel and potentially more hazardous therapeutic interventions such as mini-

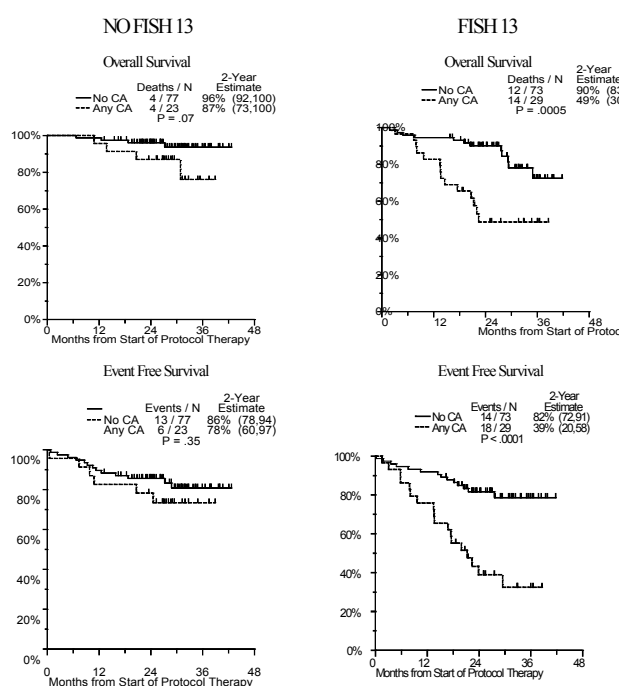


Figure 3.

allogeneic transplants, which have been demonstrated to exert a powerful graft-vs.-MM effect in the presence of CA [8,9].

Toward the identification of critical molecular abnormalities associated with the poor prognosis of specific CA and FISH 13, gene expression profiling studies are now being performed routinely in the work-up of all patients with MM referred to the Myeloma Institute for Research and Therapy (MIRT) [10]. We have recently discovered several genes that differentiate MM with FISH 13 deletion as to whether or not they exhibit also CA13 (J. Shaughnessy, unpublished observations.) We anticipate that the concomitant application of interphase FISH, conventional cytogenetics and microarray analyses will generate a robust molecular classification permitting a more accurate prognostication of patients' clinical course.

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