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A comparison of patients with acute myeloid leukemia and high-risk myelodysplastic syndrome treated on versus off study

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ABSTRACT

Patients with newly diagnosed (ND) and relapsed/refractory (RR) acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS, $\geq$10% blasts) often receive intensive chemotherapy at diagnosis and relapse. We retrospectively identified 365 patients and categorized the reasons for receiving treatment off study (medical, logistical, or unclear). The pretreatment characteristics of the on and off study groups were similar. Rates of the complete remission (CR) without measurable residual disease were significantly higher for ND patients treated on versus off study (61% versus 35%), but CR rates and survival were low for all RR patients regardless of study assignment. The subset of ND patients treated off study for medical reasons had significantly decreased overall survival and relapse-free survival. Standard, stringent study eligibility criteria may delineate a population of ND, but not RR, patients with improved outcomes with intensive induction chemotherapy.

Introduction

Fit, younger individuals with acute myeloid leukemia (AML) typically undergo intensive induction chemotherapy at diagnosis and relapse [1]. Despite National Comprehensive Cancer Network recommendations [2], only 5 to 10% of the adults with AML in the United States are treated on a clinical trial [3]. There are many reasons for low enrollment, including a decentralized healthcare system leading to travel burdens [4], financial concerns [5], stringent inclusion/exclusion criteria, logistical problems, and physician and patient preferences. These factors lead to selection bias, limiting broad applicability of conclusions from clinical trials. In one analysis, patients excluded from participation in phase 3 trials but treated in a similar fashion had similar survival [6]. Other studies, however, have shown that patients not enrolled on trials were less fit and had worse outcomes following similar treatment [7,8]. These studies are from European centers with higher trial enrollment (close to 50% in all three studies) than is common in the U.S.

Drugs not routinely employed in AML, although approved by the Food and Drug Administration (FDA), are sometimes administered via investigator-initiated studies independent of pharmaceutical company participation. These trials can test novel combinations of approved drugs. They generally provide more latitude for treating patients "off study" and formed the basis for the following effort to compare characteristics, response, and survival in patients with AML treated on study versus off study.

Methods

Patients treated for AML or high-risk MDS ($\geq$10% blasts) at the University of Washington/Fred Hutchinson Cancer Research Center between 1 January 2008 and 15 November 2015 were identified through our institutional database. This retrospective analysis was approved by the Fred Hutchinson/Cancer Consortium Institutional Review Board and conducted in accordance with the principles of the Declaration of

Helsinki. Protocols for newly diagnosed (ND) and relapsed/refractory (RR) patients were included if >15 patients were each treated on and off study. The ND protocols were: (1) G-CSF, cladribine, cytarabine, and dose-escalated mitoxantrone (ND G-CLAM) [9], and (2) idarubicin, cytarabine, and pravastatin (ND IAP) [10]. The RR protocols were: (1) RR G-CLAM, (2) decitabine followed by mitoxantrone, etoposide, cytarabine (RR D-MEC) [11], and (3) G-CSF, clofarabine, cytarabine (RR G-CLAC) [12]. Responses were evaluated based on European LeukemiaNet guidelines [13] and included (1) the more stringent complete remission (CR) without measurable residual disease (MRD) as <5% morphologic blasts with peripheral blood neutrophils ≥1000/μL, platelets ≥100,000/μL, and no MRD by flow cytometry, conventional metaphase cytogenetics, or fluorescence in situ hybridization, and (2) the broader CR/CRi, which included CR without MRD, CR with MRD, and CRi (neutropenia and/or thrombocytopenia). We identified 401 induction attempts. Four patients treated off-protocol did not have a marrow performed to assess response, and were excluded from further analysis, leaving a total of 397 induction attempts in a total of 365 patients. Two-hundred and eight of these attempts (52%) were given on study with the remaining 48% given off study for medical, logistical, or unclear reasons, as detailed below.

Because it was at times difficult to retrospectively identify the reason for off study treatment our primary comparison was between attempts given on versus off study. We also analyzed outcomes [response, relapse-free survival (RFS) and survival] in those treated off study. We classified the reasons patients received off study treatment as medical, logistical, or unclear in our retrospective analysis. Medical reasons leading to off study treatment includied high Treatment-Related Mortality (TRM) score [14], treatment urgency (i.e. hyperleukocytosis or leukostasis), low ejection fraction, abnormal laboratory values, and concurrent life-limiting diagnosis; logistical reasons for off study treatment included patient or physician preference, protocol not open, financial constraints, blast count too low. Relapse was defined as morphologic increase in blasts to ≥5%. TRM score approximates the probability of death of ND patients within 28 days of beginning intensive induction treatment. A "high" score generally corresponded to a >10–15% probability of TRM and is similarly applicable to people with ND or relapsed/refractory AML.

Logistic regression was used to evaluate the association between baseline factors and best response after up to two induction cycles while the Cox model did the same for overall survival (OS) and relapse-free survival (RFS). For ND patients, covariates evaluated were age (as a continuous variable), cytogenetics (adverse versus not using Medical Research Council criteria) [15], de novo versus secondary disease, regimen, number of cycles to best response, and TRM score. For RR patients, additional covariates included prior allogeneic HCT, duration of first CR (refractory versus ≤6 versus >6 months), and number of prior regimens. Generalized estimating equation (GEE) methods with unstructured correlation structures were used to account for patients ($n = 32$) with data on more than one trial as needed. All authors had access to the primary data. Statistical analysis was performed by M.O.

Results

Analyses included 397 induction attempts (in 365 separate patients), including 160 for ND and 237 for RR AML with median follow-up for censored patients of 16 months (range 3–84) (Table 1). No significant differences in baseline characteristics were noted between patients treated on versus off study, except for a higher TRM score in patients treated off study (ND 2.9 versus 4.3, $p = .006$; RR: 3.0 versus 5.2, $p < .001$. Compared to patients treated on study, the subset treated off study for medical reasons had higher TRM scores (ND: 2.9 versus 4.7, $p = .006$; RR: 3.0 versus 13.0, $p < .001$). Patients treated off study for logistical reasons were similar to those treated on study in all measured respects except that they were more likely to have undergone HCT if they were RR ($p = .002$). Reasons for treatment off study are summarized in Table 2.

Among ND patients, remission rates were significantly higher for patients treated on versus off study [CR without MRD: 61% (51/83) versus 35% (26/74), $p = .001$, CR/CRi: 86% (72/83) versus 64% (48/75), $p = .002$)], and were particularly low for patients treated off study for medical reasons [CR without MRD: 30% (8/28), CR/CRi 61% (17/28)]. Among the other covariates examined only adverse cytogenetics was associated with lower rates of CR without MRD and of CR/CRi while secondary AML was similarly associated with lower CR/CRi rates (Table 3). However after accounting for these variables, odds of CR without MRD and CR/CRi were approximately 4-fold and 2.5-fold higher respectively if treatment was given on study versus off study for medical reasons (Table 3). In contrast, remission rates among RR patients were not significantly higher for those treated on versus off study (CR without MRD: 26% versus 22%, $p = .41$; CR/

Table 1. Baseline patient characteristics.

Characteristic	Newly Diagnosed Patients					Relapsed / Refractory Patients				
	On study (n = 84)	Off study, all (n = 76)	Off study, medical (n = 28)	Off study, logistical (n = 42)	Off study, unclear (n = 6)	On study (n = 124)	Off study, all (n = 115)	Off study, medical (n = 20)	Off study, logistical (n = 57)	Off study, unclear (n = 36)
Age (median, range)	57 [21–80]	55 [21–84]	63 [24–84]	53 [21–71]	43 [24–75]	55 [19–73]	52 [19–91]	63 [42–73]	49 [20–75]	55 [19–91]
Adverse cytogenetics[a] (n, %)	24 (29%)	29 (40%)	11 (42%)	15 (37%)	3 (50%)	49 (40%)	51 (46%)	9 (45%)	23 (42%)	20 (56%)
Secondary leukemia (n, %)	36 (43%)	36 (47%)	14 (50%)	20 (48%)	2 (33%)	36 (30%)	40 (37%)	9 (45%)	18 (33%)	13 (38%)
TRM score (median, range)	2.9 [0.2–18]	4.3 [0.1–61]	4.7 [0.2–61]	4.2 [0.1–35]	2.4 [1.2–8.1]	3.0 [0.1–21]	5.2 [0.3–42]	13 [1.0–42]	4.2 [0.1–36]	3.5 [0.3–24]
Prior allogeneic HCT (n, %)						25 (20%)	33 (30%)	2 (10%)	24 (43%)	7 (19%)
Duration of first remission (median, range) in months						3 [0–128]	4 [0–92]	0 [0–33]	6 [0–85]	2 [0–92]
Prior regimens (median, range)						1 [1–6]	2 [1–5]	2 [1–3]	2 [1–5]	1 [1–4]
Treatment type (n, %)										
ND G-CLAM	60 (71%)	37 (49%)	20 (71%)	11 (26%)	6 (100%)					
ND IAP	24 (29%)	39 (51%)	8 (29%)	32 (74%)	0 (0%)					
RR G-CLAM						34 (27%)	63 (56%)	0 (0%)	29 (51%)	18 (50%)
RR D-MEC						43 (35%)	24 (21%)	4 (20%)	12 (21%)	9 (25%)
RR G-CLAC						47 (38%)	25 (22%)	16 (80%)	16 (28%)	9 (25%)

[a]Cytogenetics assessed by Medical Research Council criteria [15].
Abbreviations: TRM: treatment-related mortality; HCT: hematopoietic cell transplantation; ND: newly diagnosed; RR: relapsed/refractory.

Table 2. Breakdown of reasons for off study treatment for newly diagnosed and relapsed/refractory patients.

Reason Off Study	Newly diagnosed (n = 76)	Relapsed / Refractory (n = 113)
Medical reason	20 (18%)	28 (36%)
High TRM score	9 (12%)	15 (13%)
Abnormal labs or cardiac function	8 (11%)	5 (4%)
Urgency to starting treatment	11 (14%)	0 (0%)
Logistical reason	42 (55%)	57 (50%)
Patient or physician preference	6 (8%)	24 (24)
Protocol not open	31 (41%)	28 (25%)
Financial constraints	5 (7%)	2 (2%)
Blast count too low	0 (0%)	3 (3%)
Unclear reason	6 (8%)	36 (32%)

Percentages do not sum to 100% due to rounding.

Table 3. Multivariable analysis for odds of remission for ND and RR patients treated on study versus off study.

Characteristic[a]	Newly Diagnosed Patients		Relapsed/Refractory Patients	
	CR without MRD Odds Ratio (p-value)	CR/CRi Odds Ratio (p-value)	CR without MRD Odds Ratio (p-value)	CR/CRi Odds Ratio (p-value)
Off study for medical reasons (versus on study)	0.27 (.03)	0.39 (.11)	0.63 (.59)	1.41 (.63)
Off study for logistical reasons (versus on study)	0.60 (.31)	0.34 (.06)	1.26 (.64)	1.27 (.56)
Off study for unclear reasons (versus on study)	0.759 (.60)	0.57 (.60)	0.92 (.86)	0.75 (.53)
Age (years)	0.99 (.62)	0.98 (.09)	1.00 (.96)	1.00 (.92)
Adverse cytogenetics	0.17 (.003)	0.42 (.05)	0.27 (.002)	0.31 (<.001)
Secondary leukemia	0.60 (.22)	0.37 (.03)	0.69 (.41)	1.42 (.31)
TRM score	0.99 (.98)	0.97 (.36)	0.96 (.46)	0.92 (.03)
>1 cycle to best response	0.41 (.29)	–	1.64 (.39)	–
Prior allogeneic HCT			2.05 (.20)	0.74 (.51)
CR1 ≤ 6 months (versus refractory)			0.38 (.06)	0.78 (.53)
CR1 > 6 months (versus refractory)			1.71 (.28)	1.34 (.49)
Number of prior regimens			0.31 (<.001)	0.54 (.001)

Odds ratio >1 indicates that a patient in that group was more likely to achieve remission than in the comparison group. Patients who achieved CR without MRD are a subset of the patients who achieved CR/CRi.
[a]Model also adjusted for treatment regimen. Odds ratios for specific regimens are not listed in this table as results from some protocols have yet to be published.
Abbreviations: CR: complete remission; MRD: measurable residual disease; CRi: complete remission with incomplete count recovery; TRM: treatment-related mortality; HCT: hematopoietic cell transplant; CR1 = first complete remission; ND: newly diagnosed; RR: relapsed/refractory.
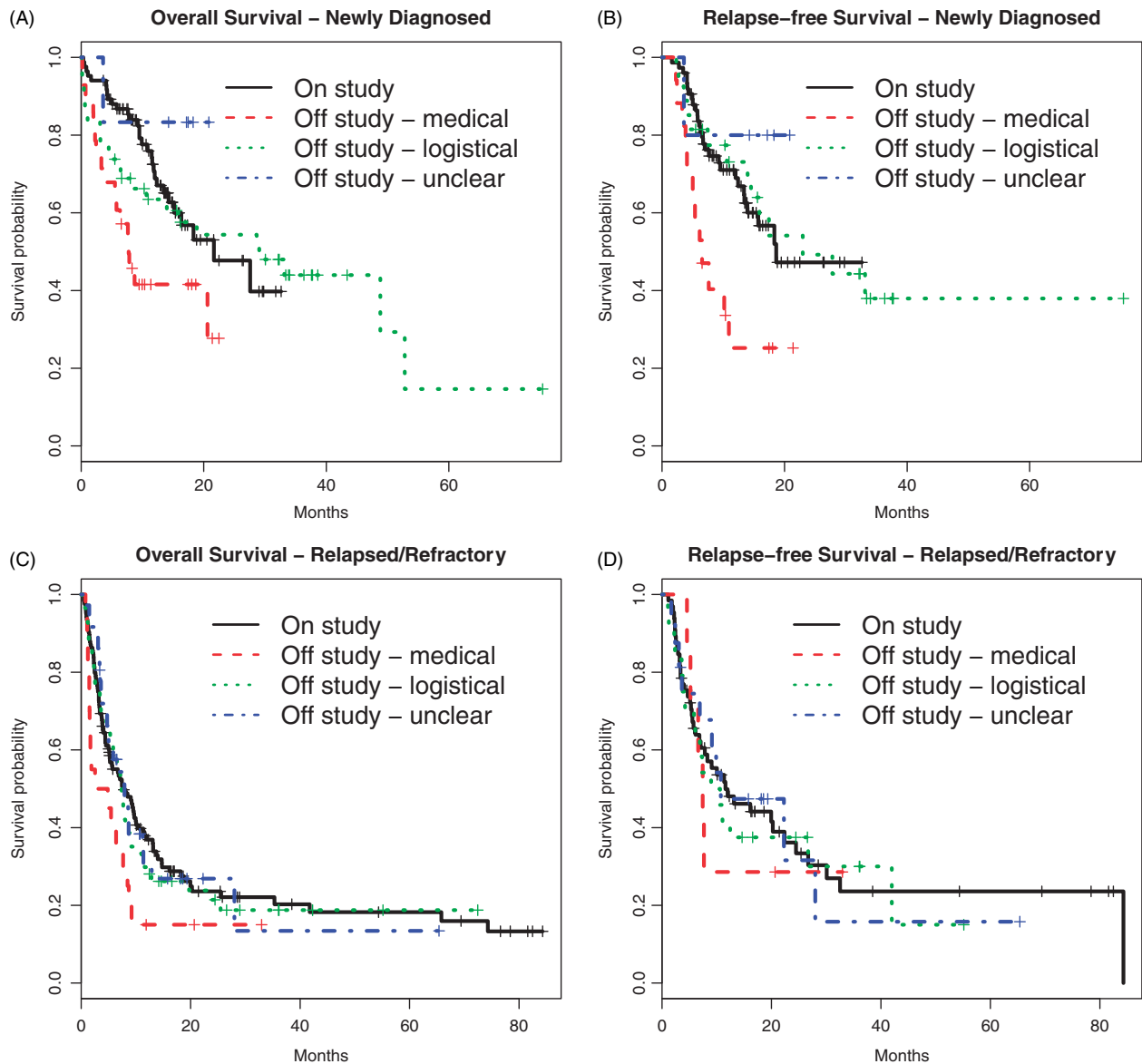
Figure 1. Survival curves for patients treated on and off study among ND patients (a, b) and RR patients (c, d).

CRi: 50% versus 44%, $p = .42$). Although remission rates for patients treated off study for medical reasons were particularly low (CR without MRD: 11%; CR/CRi: 39%), multivariable analysis did not find this variable affected remission rates (odds ratio 0.63 for CR w/o MRD, 1.41 for CR/CRi, p-values .59, .63) certainly at least to the same extent as was observed in ND patients (Table 3).

Time-to-event outcomes among ND patients treated on versus off study indicated survival and RFS were similar comparing on study vs off study for any reason patients (median OS: 22 versus 21 months, $p = .17$ and RFS: 19 versus 16 months, $p = .32$). However, those treated off study for medical reasons had significantly poorer OS (median 8 months) and RFS (median 7 months) (Figure 1 and Supplemental Figure). Survival outcomes for those treated off study

for logistical reasons as well were most similar to those treated on study (Figure 1). Multivariable analysis confirmed these results: ND patients treated on versus off study had similar OS and RFS, though those treated off study for medical reasons had approximately 2 to 3-fold higher risk of death (OS) or RFS than patients treated on study (Table 4). On and off study RR patients had similar OS (median 8 versus 7 months, $p = .46$) and RFS (median 12 versus 10 months, $p = .79$), and those treated off study for medical reasons fared slightly worse though not significantly so (Figure 1), including after multivariable adjustment (Table 4).

We examined whether other effects could account for the findings we observed. In case patients who were treated off study only because the protocol was not available had better outcomes, we performed

Table 4. Multivariate analysis for overall and relapse-free survival for ND and RR patients treated on study versus off study.

	Newly Diagnosed Patients		Relapsed/Refractory Patients	
	OS	RFS	OS	RFS
Characteristic[a]	Hazard Ratio (p-value)	Hazard Ratio (p-value)	Hazard Ratio (p-value)	Hazard Ratio (p-value)
Off study for medical reasons (versus on study)	2.37 (.009)	3.11 (.001)	1.46 (.32)	0.70 (.67)
Off study for logistical reasons (versus on study)	0.65 (.27)	0.61 (0.22)	0.82 (.35)	1.09 (.84)
Off study for unclear reasons (versus on study)	0.72 (.76)	0.67 (.73)	1.22 (.40)	0.98 (.96)
Age (years)	1.03 (0.03)	1.01 (.40)	1.00 (.92)	1.00 (.72)
Adverse cytogenetics	1.95 (0.01)	2.08 (.02)	1.19 (.30)	1.17 (.59)
Secondary leukemia	0.98 (.95)	0.92 (.78)	0.56 (.01)	0.37 (.01)
TRM score	.99 (.79)	1.02 (.07)	1.03 (.24)	1.07 (.22)
>1 cycle to best response	0.31 (.07)	0.33 (.11)	0.65 (.02)	1.72 (.14)
Prior allogeneic HCT			1.24 (.43)	1.19 (.71)
CR1 ≤ 6 months (versus refractory)			1.61 (.04)	3.36 (.003)
CR1 > 6 months (versus refractory)			0.64 (.09)	1.09 (.83)
Number of prior regimens			1.58 (<.001)	1.24 (.25)

Hazard ratio <1 indicates that patients in that group had longer average survival than in the comparison group.
[a]Model also adjusted for treatment regimen. Hazard ratios for specific regimens are not listed in this table as results from some protocols have yet to be published.
Abbreviations: OS: overall survival; RFS: relapse-free survival; HCT, hematopoietic cell transplantation; CR1, first complete remission; ref: reference regimen.

another multivariable analysis of the data excluding these 59 patients, and results remained unchanged and non-significant (data not shown). We also examined rates of transplant in patients on and off study; a cause-specific Cox regression model accounting for censoring and competing risks demonstrated no significant differences, with a HR for ND patients of 0.99 (95% CI 0.56–1.74; $p = .96$) and a HR for R/R patients of 0.72 (95% CI 0.42–1.25, $p = .25$).

We wondered if the poorer survival outcomes in off study ND patients could be explained by treatment-related mortality or by higher rates of relapse. Four-week TRM rates for patients with ND AML were 4% for on study patients and 12% for off study patients ($p = .07$); broken down by reason off study, the rates were 11% for medical reasons, 14% for logistical reasons, and 0% for unclear reasons. At 8 weeks, the corresponding TRM rates were 6% for on study and 13% for off study ($p = .17$); broken down by reason off study, the rates were 11% for medical reasons, 17% for off for logistical reasons, and 0% for off for unclear reasons. Analysis of the competing risks of relapse and TRM without relapse showed that in neither ND nor RR patients were these risks affected by treatment on vs off study, or by treatment on study versus off study for medical reasons. We also fit multivariable logistic regression models in the subset of patients alive at day 28. In all the models we fit, the CR rate was significantly higher among patients who received therapy on study. In models that controlled for cytogenetic risk, secondary AML, and TRM score, the odds ratio (OR) for morphologic CR was 2.92 ($p = .026$) and the OR for CR without MRD was 2.48 ($p = .021$). The poorer survival outcomes in off study ND patients were not clearly explained by treatment-related

mortality or rates of relapse, and the CR rate remained higher in on study patients when limited to patients who survived to day 28.

Discussion

Our data suggest little difference in survival between on and off study patients given intensive induction therapies. However, the off study group is heterogeneous, and perhaps a more interesting comparison is with the subset of patients treated off study for medical reasons. Our study is limited because reasons for off study treatment were assessed retrospectively and were susceptible to misclassification.

Nonetheless, our data suggest that ND patients excluded for medical ineligibility fare particularly poorly. While this finding may seem intuitive it remained true even after accounting for potential differences in pretreatment medical characteristics between these patients and those treated on study. This finding may simply reflect failure to account for other quantifiable medical characteristics. Many comorbidity indices exist, but no one methodology has been adopted widely for optimal risk stratification, particularly for older patients [16–18]; our study did not capture many of the factors captured in these indices, and one or more of those factors may be predictive of outcome. Additionally, the overall survival diverges early between the off-study medical group and others (Figure 1(A)), suggesting that the poor outcomes in this subset may reflect higher early treatment-related mortality that could not be fully demonstrated in our small sample size. However, our finding that medically ineligible patients fare poorly may also reflect the ability of treating physicians to

subjectively, but accurately, assess which ND patients will do particularly poorly and therefore exclude them from studies, or to subconsciously be more attentive to patients treated on study. The absence of differences between medically excluded and other RR patients may reflect the poor outcomes for all patients with RR AML.

Our results suggest that current study eligibility criteria help delineate an ND, but not demonstrably an RR population, with better treatment responses. The desirability of maintaining these criteria is less clear and assumes that patients who are currently medically ineligible and thus excluded from many clinical trials would do worse if treated on these putatively promising studies than if given alternative (or no) treatment. Perhaps allowance could be made for inclusion of such patients when evaluating new treatments. Indeed, the recently published 2017 European LeukemiaNet AML guidelines encourage movement away from arbitrary age and organ function eligibility cutoffs when deciding whether older patients should receive intensive induction therapy [13]. Additionally, the American Society of Clinical Oncology now recommends liberalizing enrollment criteria for patients in oncology clinical trials, because of high rates of organ dysfunction, comorbidity, or prior malignancy in otherwise eligible patients with solid tumors [19,20]. The generalizability of results is also limited if obtained in highly select clinical trial cohort. We suggest that RR studies should include more liberal eligibility criteria, especially since a recent brief report indicated that the response rate for phase 1 oncology studies may be higher than previously suggested [21].

Determining the proper balance of treatment intensity for medically less fit patients has been challenging at our center. We performed a trial with reduced doses of CPX-351 for patients with a high TRM score ($\geq$13.1, which corresponds roughly to a 13% chance of dying in the first 28 days after induction), which showed minimal efficacy without adequate improvement in toxicity [22]. An ongoing study at our center randomizes patients with a similarly high TRM score to full-dose G-CLAM or reduced-dose G-CLAM (NCT03012672). Additionally, a recent provocative study from MD Anderson Cancer Center specifically enrolled patients who did not meet eligibility criteria for other trials, demonstrating that treatment of such "ineligible" patients was feasible [23]. Only prospective studies with less rigid eligibility criteria can assess whether patients with co-morbidities currently precluding enrollment in most clinical trials would benefit from enrollment on such trials relative to the often unsatisfactory alternatives.

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