

Response in Acute Myeloid Leukemia

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Abstract: For many years, response to induction therapy in acute myeloid leukemia was classified as “complete response” (CR) or “no CR.” The emphasis on CR reflected the proven ability of CR to extend survival, the outcome of primary interest to patients. Beginning with the adoption of complete response with incomplete platelet recovery (CRp), recent years have seen the acceptance of responses less than CR as beneficial. Although these responses denote that a drug is active, relatively little attention has been paid to the effect of such responses on survival. This article explores the effect of such responses on survival.

Categories of Response in AML

In a 2003 report, an International Working Group (IWG) proposed several categories of response to treatment in acute myeloid leukemia (AML).¹ Foremost among these was complete remission (CR). In its report, the IWG lowered its neutrophil requirement for CR from less than 1,500/ μ L cited previously to less than 1,000/ μ L.² This change reflected observations that relapse-free survival is similar regardless of whether the neutrophil count at CR is 1,000–1,500/ μ L or over 1,500/ μ L.³ Similarly, because the presence of up to 5% circulating blasts at CR seems not to affect relapse-free survival,⁴ the IWG noted that such a finding might still be consistent with CR. Further modifying its 1990 report, the IWG noted that physicians often wish to re-treat once CR has been observed and eliminated the requirement that the requisite blood counts and marrow findings be maintained for at least 4 weeks before CR is declared.

The distinction accorded CR reflects its ability to prolong survival. At first glance, the longer survival seen in patients entering CR might appear to result merely from an inherently superior prognosis in such patients—that is, these patients would have lived longer than patients who did not achieve CR even if both groups had remained untreated. However, Freireich and colleagues’ finding that the difference in survival time between the two groups was entirely the result of the time spent in CR made this possibility quite unlikely.⁵ The fact that disease recurs in the majority of patients who achieve CR prompted the IWG to discuss—though not formally propose—two other requirements for CR:

Keywords

Acute myeloid leukemia, complete response, CRc, CRm, CRp

Table 1. Effect of Response on Probability of Long-term Survival

Database	Age	Response	Patients, n	Alive at 3 Years	Alive at 5 Years
ECOG	≥60	CR	228	22%	13%
MDACC	≥60	CR	381	19%	12%
ECOG	≥60	<CR	190	2%	2%
MDACC	≥60	<CR	211	1%	0%
ECOG	<60	CR	1199	39%	34%
MDACC	<60	CR	644	38%	31%
ECOG	<60	<CR	517	8%	8%
MDACC	<60	<CR	144	6%	4%

CR=complete remission; ECOG=Eastern Cooperative Oncology Group; MDACC=The University of Texas M. D. Anderson Cancer Center.

normal cytogenetics (CRc) and absence of molecular or immunologic evidence of AML (CRm) in patients who presented with such abnormalities.⁶

On the other side of the spectrum from CRc and CRm are categories of response with less stringent criteria than those for CR. Perhaps the first of these was partial remission (PR), defined as CR but with 5–25% marrow blasts. In its 1990 publication, the IWG noted that although PR is a reasonable endpoint for phase I or II studies, whose primary concern is discovery of “activity,” it is not a valid endpoint for phase III studies, whose fundamental concern, at least in AML, is prolongation of survival.² Beginning with the introduction of “CR with incomplete platelet recovery” (CRp; ie, platelet count 30,000–100,000/ μ L) as a category of response in patients treated with gemtuzumab ozogamicin (Mylotarg, Wyeth), several other response categories have come into vogue and are commonly cited in reports of clinical trials.⁷ Included are “CR with incomplete blood count recovery” (CRI; generalizing CRp to include neutrophils), “hematologic improvement” (HI; corresponding to the IWG’s criteria for myelodysplastic syndromes [MDS]),⁸ and “marrow CR” (<5% marrow blasts regardless of blood counts). As with PR, the criteria for each of these new response categories are less stringent than those for CR.

As recognized by the IWG in its discussion of PR, identification of response in clinical trials in AML is important because it indicates that a drug is active.² However, from a patient’s perspective, response is principally important because it may lengthen survival or improve quality of life. In particular, patients might well be less impressed than investigators were a drug to be active but without effect on survival. Thus, the principal purpose of this article is to examine the relation between survival and response categories other than CR, CRc, or CRm;

I collectively refer to these categories as “less than CR.” As a response may be associated with an improvement in survival but not in an improvement in the likelihood of a potential cure, I discuss these two types of improvement separately.

Ability of Responses Less Than CR to Lead to Potential Cure

I define potential cure as a CR of at least 3 years’ duration.⁹ To consider AML cured, the risk of relapse from a response such as CR must be the same as the risk of AML in the general population. Although it is unlikely that AML can be cured in this sense, once 3 years have elapsed from the CR date, the risk of relapse or death in CR becomes less than 10%, suggesting 3 years as a reasonable criterion for potential cure. (Specifically, the hazard ratios for relapse or death in CR are 74%, 51%, 23%, and 9% for the 1st, 2nd, 3rd, and 4th years, respectively, after CR.) The University of Texas M. D. Anderson Cancer Center (MDACC) and Eastern Cooperative Oncology Group (ECOG) investigators thus examined the probability of being alive at 3 years according to whether patients achieved CR.¹⁰ A total of 4,108 patients treated on various ECOG (n=2,413) and MDACC (n=1,695) protocols over the 20 years from 1979–1999 formed the database for the analysis. Each patient’s induction therapy contained cytarabine (ara-C). Because such therapy typically requires 4 weeks to produce CR, the 13% of patients who died in the 4 weeks after beginning treatment were excluded. The investigators found that among patients 60 years or older who did not achieve CR with initial treatment there was essentially no chance of surviving 3 or 5 years after treatment began; the probability was only somewhat higher (<10%) in patients younger than

Table 2. Frequency of CRp and CR in Different Prognostic Groups

Group	Patients, n	CRp	Number CRp/Number CR
CBF AML	64	5%	1 per 20
Normal karyotype AML	416	4%	1 per 12.9
-5/-7 AML	245	4%	1 per 7.3
De novo AML	483	3%	1 per 19.1
Secondary AML	515	6%	1 per 6.6

AML=acute myeloid leukemia; CBF=core binding factor; CR=complete remission; CRp=complete remission with incomplete platelet recovery.

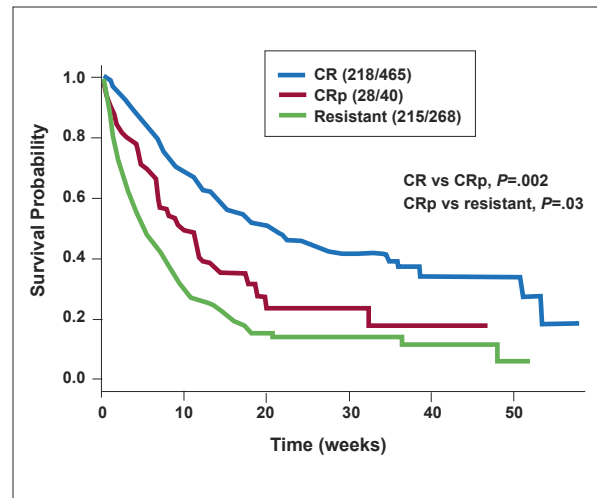
60 years (Table 1). Eleven of the 12 MDACC patients who lived at least 3 years despite not achieving CR with initial therapy did so with subsequent therapy (data not readily available for ECOG).

It remains plausible that responses less than CR will convey the possibility of cure in patients given therapies that do not contain ara-C; in particular, some clinicians have hypothesized that such responses may convert AML to a chronic disease. To test this hypothesis, I examined survival in the 105 MDACC patients with AML given therapies without ara-C from 2000 to 2003. The most commonly employed therapies were gemtuzumab ozogamicin (n=61) and midostaurin (formerly PKC412; n=17). The CR rate was only 15%, as might have been predicted given that these patients were judged to be unlikely to benefit from ara-C. Each of the 5 patients who survived at least 3 years achieved CR: 3 with initial treatment and 2 with subsequent treatment.

The link between CR and long-term survival in the absence of ara-C suggests that the ability of a treatment to produce CR, rather than the specific treatment, is what is relevant for long-term survival. At the very least, the data presented above seem to put the burden of proof on those who contend that non-ara-C-containing therapies may affect cure by converting AML to a chronic disease. Such therapies will have to contribute more than responses less than CR—they will have to change the fundamental biology of the disease—if they are to improve long-term survival in AML.

Abilities of Responses Less Than CR to Lengthen Survival: CRp

Although a response may not lead to potential cure or long-term survival, it still may lengthen survival and

**Figure 1.** Survival by eventual response among alive at 60 days.

CR=complete remission; CRp=complete remission with incomplete platelet recovery.

thus be beneficial. My colleagues and I first investigated this possibility by comparing survival times in patients in whom initial therapy produced CR, CRp, or neither (“resistant”).¹¹ Our database was composed of 1,040 patients with AML or high-risk MDS (10–19% blasts) who received therapy containing ara-C. In all, 35% of patients entered CR and 4% entered CRp; 35% lived 30 days or more without entering CR or CRp, whereas 12% were dead by day 30 of initial treatment. The relative frequency of CRp to CR increased as prognosis worsened (Table 2). For example, there was 1 CRp for every 20 CRs in patients with inv(16) or t(8;21) (collectively, core binding factor AML) but 1 CRp for every 7.3 CR in patients with abnormalities of chromosomes 5 and/or 7, usually in a complex pattern. Time to CR was shorter than time to CRp (median: 32 vs 47 days, respectively; 75% of CRs seen by day 39 vs day 61 for CRp). After excluding patients who died before day 30, the median time before patients who achieved neither CR nor CRp were considered resistant was 41 days; 75% were considered resistant by day 61. Including only patients who lived at least 60 days (by which time 90% of patients had entered CR and 75% CRp), survival was longer in the CR group than in the CRp group, whereas survival was longer in the CRp group than in the resistant group (Figure 1). The same was true considering only patients alive on day 30 or only patients alive on day 90.

This investigation appears to have been the first demonstration of the value of CRp in patients with AML. However, it could be argued that the differences

Table 3. Multivariate Cox Model for Survival in Patients Alive on Day 60

Covariate	Relative Risk of Death	P Value
CBF AML vs normal karyotype	0.52	.02
-5/-7 AML vs normal karyotype	2.49	<.001
Age	1.01	<.001
CRp vs CR	1.61	.02
CRp vs resistant	0.72	.11

AML=acute myeloid leukemia; CBF=core binding factor; CR=complete remission; CRp=complete remission with incomplete platelet recovery.

Table 4. Multivariate Cox Model for Relapse-free Survival

Covariate	Relative Risk of Relapse or Death in CR	P Value
CBF AML vs normal karyotype	0.65	.005
-5/-7 AML vs normal karyotype	2.34	<.001
Age	1.01	<.001
CR vs CRp	0.65	.02

AML=acute myeloid leukemia; CBF=core binding factor; CR=complete remission; CRp=complete remission with incomplete platelet recovery.

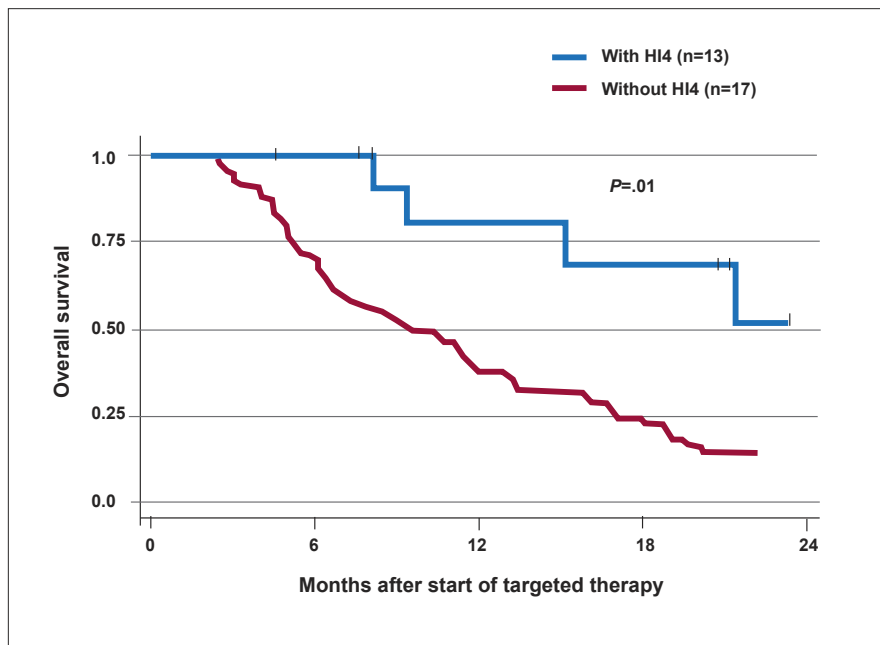


Figure 2. Survival in patients with or without HI4.

HI4=hematologic improvement lasting at least 4 weeks.

in survival time between patients in the three groups could have resulted from better inherent prognoses in the CR patients, who were more likely to have more favorable cytogenetics than CRp patients (Table 2), or from differences in treatment given after relapse was observed. We addressed the first criticism by performing a multivariate analysis in which CR versus CRp versus resistant patients were tested together with other covariates for independent association with survival in patients alive on day 60. The results indicated that after

accounting for age and cytogenetics, the relative risk (RR) of death was 1.61 ($P=.02$) with CRp as compared to CR (Table 3). In contrast, the RR was 0.72 in patients who achieved CRp versus resistant patients, although the P value was nonsignificant ($P=.11$). The possibility that the survival advantage conferred by CR rather than CRp reflected different postrelapse therapy seems lessened by the observation that the risk of relapse in the CR group was only 65% of that in the CRp group, again after accounting for age and cytogenetics (Table 4).

Ability of Responses Less Than CR to Lengthen Survival: HI

Further support for the possible ability of responses less than CR to prolong survival comes from an analysis of HI in MDACC patients given various targeted therapies (ie, lower-intensity therapies not containing ara-C) for AML or high-risk MDS (10–19% blasts).¹² Specifically, 180 patients were thus treated from 2000 to 2006, generally because they were over 60 years old. Ninety-nine (55%) of these patients were judged resistant (no CR) to therapy, most commonly decitabine (Dacogen, MGI Pharma). Of these 99 patients, 32 achieved HI using IWG blood count criteria for MDS.⁸ HI lasted at least 8 weeks (HI8), in 13 of the 32, thus meeting an IWG criterion for HI, and lasted at least 4 weeks (HI4) in 14 patients. Because results were similar for HI4 and HI8 patients, we focused on the former, comparing their survival with that in resistant patients in whom HI4 was not observed. Again it was necessary to account for the time necessary to achieve HI4; we thus limited our initial analysis to patients who lived at least 68 days, the median time to achieve HI4. The results suggest that HI4 is of value in prolonging survival (Figure 2). Similar results were obtained when considering only patients alive on day 138 (by which time 75% of the patients who achieved HI4 had done so) and only patients treated with decitabine.

Conclusions

The data presented above suggest that CR is of unique value in the therapy of AML. Only patients achieving CR appear to be potentially cured, and CR provides a survival advantage over CRp, even after accounting for other covariates. This advantage does not appear to reflect differences in therapy given once initial therapy has failed. However, patients who achieve CRp or HI appear to live longer than patients who do not achieve even these responses, although the difference between CR and CRp

appears larger than the difference between CRp and resistant cases. Whether the same will be true with targeted therapy remains to be seen. At the least, I hope this article prompts physicians to examine the effects on survival of responses less than CR rather than uncritically accept the continued addition of these categories of response.

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