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Commentary

Does hydroxycarbamide therapy really induce leukemic transformation in patients with essential thrombocythemia?

Hydroycarbamide (HC) has been used extensively to treat patients with myeloproliferative neoplasms (MPNs) for over 4 decades. Since HC is a chemotherapeutic agent there continues to be concern that use of this agent may increase the risk of patients developing a form of acute leukemia. The *BCR-ABL1*-negative MPNs including polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) are clonal hematopoietic stem cell disorders which have the potential to progress to acute myeloid leukemia, termed MPN-blast phase (BP). This secondary leukemia has a dismal prognosis being almost universally refractory to chemotherapy. After 10 years, 4% of PV patients, 1% of ET and 20% of MF patients will progress to MPN-BP [1]. Recently, a variety of factors have been reported to be associated with an increased risk of leukemic transformation (LT) including older age, leukocytosis, adverse cytogenetic and molecular abnormalities involving mutations in *TP53, ASXL1, SRSF2* and *IDH2*. While there is currently an absence of therapies to halt MPN disease progression, hematologists are especially concerned about the potential leukemogenic role of certain therapeutics. Several agents clearly accelerate LT rate of MPNs including alkylating agents, such as chlorambucil, busulfan and pipobroman and radioactive phosphorous.[2]

HC is a non-alkylating cytoreductive agent that halts DNA synthesis by inhibiting ribonucleotide reductase. As front-line therapy for high risk PV and ET, HC has been shown to reduce the risk of thrombohemorrhagic events. In the sickle cell population, the largest population treated with HC, an association has not been found between HC and increased risk of hematologic malignancy [3]. These findings, however, are questionably applicable to the MPN population. MPNs are clonal hematopoietic neoplasms and have potential for clonal evolution as part of the natural disease history, whereas sickle cell anemia is a non-malignant condition. The possible leukemogenic risk of HC in PV and ET was first brought to attention based on small prospective studies showing that a subset of patients receiving HC therapy acquired additional karyotypic abnormalities and progressed to acute leukemia [4,5]. Subsequent larger studies of HC in PV and ET have shown that HC monotherapy is not associated with an increase in risk of LT [2,6–8]. Sequencing HC with an alkylating agent has, however, been associated with an increase in risk of LT. Additionally, *ex-vivo* studies have validated that HC has low mutagenicity potential in cells from MPN patients [9].

A critical question which complicates this therapeutic decision is the absence of a defined target platelet count which would reduce the risk of additional thrombotic episodes. In high risk ET patients, many question if a relationship between platelet count and thrombotic risk in ET patients actually exists which challenges the need for such therapeutic interventions at all.

In this issue of *Leukemia Research*, Birgegard and colleagues use a post-marketing prospective trial comparing the rate of evolution to MPN-BP in 3460 high risk ET patients over a period of 5 years treated with either anagrelide or HC, making it the largest prospective study to date evaluating leukemic transformation in ET. Although the trial was sponsored by the maker of anagrelide, the investigators attest to their independence which provides certainty of the validity of the data. Overall, this study shows no statistically significant difference in the incidence of LT between the two groups. However, the authors report that MPN-BP was associated with the use of HC or HC in combination with anagrelide during the 5-year period of observation. It is notoriously difficult to obtain meaningful data from such post-marketing studies since the particular treatment strategies are chosen by practicing physicians well after the conception of the study. Potential co-founders contributing to this association must be appreciated. It is well recognized that acute leukemia is a disease of the elderly and the median age of patients receiving either HC or anagrelide in this study is quite disparate and, therefore, a likely confounder in association of LT risk with HC. The median age of the anagrelide group was 51 years while that of the HC group was 71 years. Of the patients 60–79.9 years of age, only 6% received anagrelide alone while 75% received HC and another 15% received anagrelide and HC therapy. Of the patients 80 years of age and older only 3% received anagrelide and 93% received HC alone or in combination. Additionally, as correctly stated by the authors, the finding of cases of LT in the HC treated group but not the anagrelide treated group could be confounded by the possibility that "higher risk" patients as assessed by the treating physician received HC and, therefore, the administration of HC is a surrogate marker for proliferative disease most at risk of developing AML.

While, the present study does suggest that anagrelide is not associated with LT, a conclusion of HC leukemogenicity would be unfounded based on the lack of statistical significance. Therefore, it would be incorrect to infer that anagrelide is the superior treatment choice solely based on leukemic risk. In fact, the ANAHYDRET trial comparing HC and anagrelide treatment in high risk ET also did not show a difference in myelofibrotic/leukemic transformation rate between the two arms but showed similar efficacy between the agents in reducing risk of thromboses and bleeding [10].

Current treatment guidelines put forth by National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN), recommend that HC therapy be used with caution in younger patients. HC use in young patients frequently committed to decades of treatment should be avoided if possible since it leads to sterility and due to its hypothetical but unfounded leukemogenic potential. As for elderly patients, anagrelide is often an impractical choice due to its potential to

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cause tachyarrhythmia, therefore, HC is often the favored option.

After years of controversy, the leukemogenic potential of HC in MPNs has not been clearly proven and the EXELS study does not in fact establish this risk, and would support the absence of an association. While debate is sure to ensue, it is critical to remain divorced from emotion and weigh the established benefits of HC against the purported risk of this agent on a case by case basis.

References

[1] F. Cervantes, D. Tassies, C. Salgado, M. Rovira, A. Pereira, C. Rozman, Acute transformation in nonleukemic chronic myeloproliferative disorders: actuarial probability and main characteristics in a series of 218 patients, Acta Haematol. 85 (3) (1991) 124–127.

[2] M. Bjorkholm, A.R. Derolf, M. Hultcrantz, et al., Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms, J. Clin. Oncol. 29 (17) (2011) 2410–2415.

[3] M.H. Steinberg, W.F. McCarthy, O. Castro, et al., The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: a 17.5 year follow-up, Am. J. Hematol. 85 (6) (2010) 403–408.

[4] A. Weinfeld, B. Swolin, J. Westin, Acute leukaemia after hydroxyurea therapy in polycythaemia vera and allied disorders: prospective study of efficacy and leukaemogenicity with therapeutic implications, Eur. J. Haematol. 52 (3) (1994) 134–139.

[5] E. Liozon, C. Brigaudeau, F. Trimoreau, et al., Is treatment with hydroxyurea leukemogenic in patients with essential thrombocythemia? An analysis of three new cases of leukaemic transformation and review of the literature, Hematol. Cell Ther. 39 (1) (1997) 11–18.

[6] G. Finazzi, V. Caruso, R. Marchioli, et al., Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study, Blood 105 (7) (2005) 2664–2670.

[7] J.J. Kiladjian, S. Chevret, C. Dosquet, C. Chomienne, J.D. Rain, Treatment of polycythemia vera with hydroxyurea and pipobroman: final results of a randomized trial initiated in 1980, J. Clin. Oncol. 29 (29) (2011) 3907–3913.

[8] A. Tefferi, E. Rumi, G. Finazzi, et al., Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study, Leukemia 27 (9) (2013) 1874–1881.

[9] V.N. Hanft, S.R. Fruchtman, C.V. Pickens, W.F. Rosse, T.A. Howard, R.E. Ware, Acquired DNA mutations associated with in vivo hydroxyurea exposure, Blood 95 (11) (2000) 3589–3593.

[10] H. Gisslinger, M. Gotic, J. Holowiecki, et al., Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial, Blood 121 (10) (2013) 1720–1728.

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