To the editor:

Helicobacter pylori eradication as exclusive treatment for limited-stage gastric diffuse large B-cell lymphoma: results of a multicenter phase 2 trial

We read with great interest the article by Kuo et al on a retrospective study of *Helicobacter pylori* (*Hp*) eradication as exclusive treatment in Taiwanese patients with early-stage gastric diffuse large B-cell lymphoma (DLBCL).[1] Interestingly, a substantial

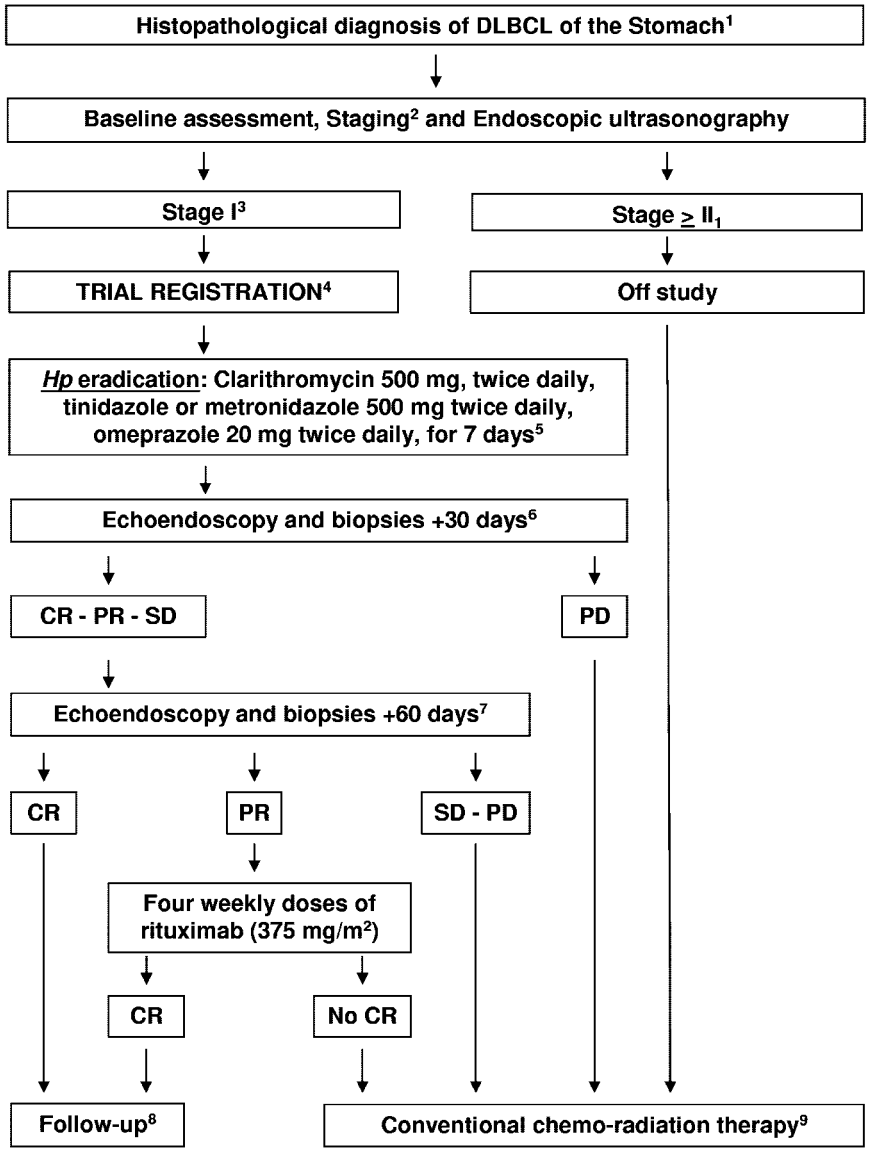

Figure 1. Study algorithm. [1]Diagnostic biopsies underwent centrally pathology review.[6] [2]Baseline and staging procedures: hemogram, biochemical profile, HIV, hepatitis B and C viruses' infection markers, contrasted thorax-abdomen CT scan, bone marrow biopsy, breath test, gastroscopy with at least 5 biopsies for each lesion and random sampling of residual normal mucosa, and echoendoscopy to evaluate gastric wall thickness and perigastric lymph nodes. The choice of areas suitable for biopsies was driven by echoendoscopy. *Hp* infection was confirmed by gastric biopsies ± breath test. [3]Perigastric lymphadenopathies of a diameter < 1.5 cm were admitted to avoid a potential selection bias related to specificity limits of echoendoscopy. This cut-off was in line with the cut-off value used by standardized lymphoma criteria to define lymph-node infiltration when assessed by non-functional exams.[7] [4]Sample size was not prospectively estimated in comparison with ORR reported with conventional chemo-radiotherapy (90%-100%) since it would request a non-inferiority design and hundreds of patients. Written informed consent was obtained from each registered patient; the trial conformed to the tenets of the Declaration of Helsinki and was approved by the IRB of participating centers. [5]Patients who failed eradication received a second-line antibiotic therapy following local guidelines. [6]The primary end point was overall response rate (ORR) after *Hp* eradication. Response was defined according to standardized criteria.[7] Residual macroscopic abnormalities at endoscopic examination or residual perigastric lymph nodes measuring < 1 cm in diameter or gastric wall alterations at ultrasonography were considered as CR if histopathologic examination did not show lymphomatous infiltration. Persistence of areas of MALT and/or DLBCL in histopathologic specimens in patients with normal/improved gastric aspect at endoscopy and ultrasonography were considered as PR. [7]Enhanced total-body CT scan was performed to exclude systemic dissemination. [8]Physical examination, hemogram and biochemical profile, gastroscopy, gastric echoendoscopy, and enhanced CT scan every 3 months for the first 2 years, every 6 months from the 3rd to the 5th year, and once a year from the 6th to the 10th year. [9]CHOP or CHOP-like regimens ± rituximab ± radiotherapy (physician's preference).

portion of these aggressive lymphomas is responsive to antibiotics, but the authors recommend their results should be taken as investigational until validated by prospective studies. Recently, we concluded the first multicenter prospective trial addressing this issue in Western countries, aiming to demonstrate that a proportion of these patients can achieve long-term remission with antibiotics alone, leaving intact the probabilities of cure for unresponsive patients.

Sixteen patients with stage-I *Hp*-related gastric DLBCL, with (n = 5) or without (de novo; n = 11) MALT areas, were registered (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Antibiotic therapy included clarithromycin, tinidazole or metronidazole, and omeprazole (Figure 1). *Hp* eradication and tumor response were assessed at +30 and +60 days after antibiotics: patients achieving complete remission (CR) were referred to follow-up; patients with partial response (PR) received rituximab; and patients with stable/progressive disease received chemo-radiotherapy.

Results were excellent, and similar to those reported by Taiwanese colleagues (supplemental Table 2). All patients achieved *Hp* eradication; 1 patient required a second-line antibiotic therapy. Lymphoma response after eradication was CR in 8 (50%) patients, and PR in 3 (overall response rate = 69%; 95% confidence interval [CI] = 47%-91%; supplemental Figure 1); 5 patients had progressive disease. Two of the 3 PRs achieved CR after rituximab (supplemental Table 3). Thus, 10 patients achieved CR after antibiotics ± rituximab (complete response rate = 63%; 95% CI = 39%-87%).

Lymphoma regression was documented in all investigated subgroups, divided according to histologic subtype (MALT-related vs de novo DLBCL), ontogenic stratification[2] ("germinal-center B cell–like" vs "nongerminal-center B cell–like" DLBCL), and presence of perigastric lymph nodes (yes vs no; supplemental Table 3). Regression of de novo DLBCL is an important achievement since a few responsive cases have been reported,[3] whereas patients with de novo DLBCL were not assessed prospectively in the Kuo et al's study.[1] Interpretation of these responses could be biased by the lack of recognition of MALT areas in scanty or undersized biopsies.[4] However, the extensive bioptic mapping used in our trial bona fide rules out this bias and confirms that a proportion of de novo DLBCL are *Hp*-dependent. Responses in patients with perigastric lymphadenopathies are a challenging finding. Noteworthy, lymphadenopathies lacked confirmation of tumor infiltration both in this trial and in occasionally reported cases,[5] whereas patients with stage II_1 disease included in the Taiwanese study were not analyzed separately.[1] Nevertheless, our results suggest that the presence of small perigastric lymphadenopathies is not a contraindication for exclusive treatment with antibiotics.

Two-thirds of patients achieved long-term remission without chemo-radiotherapy. At a median follow-up of 68 months (range 14-114), 9 of the 10 CRs remain relapse-free (median progression-free survival: 83+ months). Patients with unresponsive/relapsed lymphoma retained unaltered their probabilities of cure; all of them achieved CR after chemo-radiotherapy and remain relapse-free at 13-90 months (median 55+). No patient died of lymphoma; 14 patients are alive (5-year OS: 94%), and elderly patients died of cardiac failure and gallbladder cancer at 13 and 90 months, respectively.

Although encompassing small series and exhibiting some design differences, this trial and the Taiwanese study demonstrate that *Hp* eradication, keeping chemo-radiotherapy for unresponsive patients, is an affordable strategy for patients with limited-stage gastric DLBCL. An international trial aimed to extend these encouraging results and to distinguish the best candidates for this conservative strategy is warranted.

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To the editor:

Screening of novel genetic aberrations in pediatric acute myeloid leukemia: a report from the AIEOP AML-2002 study group

Acute myeloid leukemia (AML) is a heterogeneous disease with known specific recurrent genetic aberrations. The continuous and increasing identification of new genetic lesions has permitted the identification of new subgroups of patients with different prognosis.[1] In the present work, we evaluated the incidence of rare genetic abnormalities in pediatric AML such as del(4)(q12)FIP1L1-PDGFRA, t(16;21)(p11;q22)FUS/ERG, t(8;16)(p11;p13)MOZ/CBP, t(11;17)(q23;q12-21)MLL/AF17, t(4;11)(q35;q23)MLL/ArgB2, t(5;11)(q35;p15.5)NUP98/NSD1, t(3;5)(q25;q34)NPM1/MLF1, and MLLPTD in 306 children with newly diagnosed de novo AML other than acute promyelocytic leukemia enrolled in Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) centers from 2000 to 2009,[2] all negative for known recurrent genetic abnormalities involving *MLL*, *CBFB*, and *FLT3* genes (77 males and 77 females, median age at diagnosis 7.2 years, range 17 days to 17 years). RNA was extracted from fresh bone marrow at diagnosis, and multiplex RT-PCR was used. Sequencing by Sanger method was applied to all positive cases to characterize fusion breakpoints. We identified 1 patient each positive for t(16;21)(p11;q22)FUS/ERG, t(11;17)(q23;q12-21)MLL/AF17, and t(4;11)(q35;q23)MLL/ArgB2, respectively, suggesting that these rearrangements are extremely rare in pediatric AML. Two of the 306 patients had del(4)(q12)FIP1L1/PDGFRA, and 4 had t(8;16)(p11;p13)MOZ/CBP. Interestingly, 6 patients (2%) had t(3;5)(q25;q34)NPM1/MLF1, 6 (2%) had MLLPTD, and 6 (2%) were found to carry t(5;11)(q35;p15.5)NUP98/NSD1. In our pediatric cohort, the incidence of this last aberration is lower than that previously reported by Hollink et al.[3] Subsequently, because a strong association of t(5;11) fusion with FLT3ITD has been described (91%),[3] we extended the screening to 42 children with de novo AML harboring the FLT3ITD mutation, enrolled in the AIEOP-LAM 2002 protocol. We found that 6 of 42 (14%) had the NUP98-NSD1 fusion. So, 6 of 12 NUP98/NSD1-positive patients (50%) were FLT3ITD positive, showing a lower association in our pediatric cohort for these 2 aberrancies than that reported by Hollink et al.[3] Then, we looked at the event-free survival (EFS) of patients with t(5;11)NUP98-NDS1 (n = 12) and found that it was worse, compared with patients negative for known molecular lesions and enrolled into the LAM 2002-AIEOP protocol (30.1% vs 57.1% at 3 years, $P < .05$).[4] Furthermore, we did not find any difference in either clinical or biologic features between patients with isolated t(5;11) and those with t(5;11) + FLT3ITD (Figure 1). The 8-year EFS of FLT3ITD+ children who did or did not carry t(5,11) was 33.3% and 42.7% ($P = .2$), respectively. This finding suggested that NUP98/NSD1 fusion protein identifies a previously unrecognized subgroup of FLT3ITD patients with an even worse prognosis.

To test whether MLLPTD might also play a role in the occurrence of childhood AML relapse, we analyzed samples from 40 AML patients at relapse, never finding this abnormality. By contrast, 4 patients harbored at relapse the same MLLPTD found at diagnosis, suggesting the stability of this mutation.

In summary, we confirm that t(5,11) is not exceptional in pediatric AML, being frequently associated with FLT3ITD, and identifying patients at high risk of treatment failure. We also suggest a negative role of this translocation in FLT3ITD positive patients to be further considered in the risk stratification of patients. The putative role of the remaining rare abnormalities[5,6] in AML remains to be confirmed in prospective studies with larger cohorts of patients.