

LETTERS TO THE EDITOR

Prognostic significance of Nottingham Prognostic Index in non-metastatic breast cancer

Dear Editor,

Nottingham Prognostic Index (NPI) has been created by evaluating important prognostic parameters in combination, such as tumor size, lymph node status and histological grade. According to calculated score, 3 prognostic groups are created: score <3.4: good prognostic group, score 3.4-5.4: moderate prognostic score, and > 5.4: poor prognostic score [1-3]. We tried to investigate whether NPI has prognostic significance or not and its effect on other prognostic factors, like clinical progression and overall and disease-free survival.

The study consisted of 7 male and 366 female breast cancer patients with an average age of 55.7 years. Sixty-two percent of the patients were aged between 40-60 years, 42% were premenopausal, 45% had stage II (AJCC) disease, 36.7% N1 had disease, 51.2% grade II tumors, 84% had received radiotherapy, 95.1% chemotherapy and 66.2% endocrine therapy. There were 148 (39.6%) cases with NPI scores less than 3.4, 168 (45%) between 3.41 and 5.4 and 57 (15.4%) with NPI greater than 5.41. Follow-up time ranged from 4.8 to 195 months. The median overall and progression-free survival were 125.6 and 89.8 months, respectively.

NPI scores were analyzed according to the clinicopathological patient features and significant difference was noticed between AJCC disease stage, lymph node status, histological grade and radiotherapy ($p < 0.001$). When the groups were evaluated according to NPI scores, although overall and disease-free survival rates were higher in the group with NPI < 3.4, the difference was not statistically significantly ($p = 0.150$ and $p = 0.386$, respectively). In univariate and multivariate analysis, factors that affected overall survival were AJCC stage ($p < 0.001$) and lymph node status ($p < 0.001$); factors that affected progression-free survival were estrogen receptors ($p = 0.028$) and hormone therapy ($p = 0.038$).

In this study, highest percent distribution of NPI scores was observed in the moderate prognostic group and the lowest in the poor prognostic group. The mean overall survival was 145.6, 101.2 and 86.6 months respectively and progression-free survival was 92.6, 88.2 and 86.2 months when evaluated according to NPI. Five-year overall sur-

vival was 87, 73 and 67%; 5-year progression-free survival was 72, 58.5 and 58%. Hearne et al. also reported higher moderate prognostic group distribution [2]. In the work of Galea et al., the authors worked with operated breast cancer patients and they found 29% of the patients in the good, 54% in the moderate and 17% in the poor prognostic group. In these groups, 15-year overall survival rate was 80, 42 and 13%. In another report, 10-year overall survival was 96, 81 and 50% according to NPI index [3].

As a result, although not statistically significant, overall survival and disease-free survival of patients in the poor prognostic group were shorter compared with other groups. Thus, the number of patients with poor prognostic score in the randomly selected cases was lower than in the moderate and good prognostic score. This situation may have affected the statistical analysis. Efforts with larger series can shed more light on this matter in terms of statistical significance.

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Decitabine+ CAG +DLI in relapsed acute myeloid leukemia after allogeneic stem cell transplantation

Dear Editor,

Disease recurrence is one of the major causes of treatment failure in acute myeloid leukemia (AML) patients who undergo allogeneic stem cell transplantation. Relapsed patients always have an extremely poor prognosis and the therapeutic options are limited to conventional salvage chemotherapy, donor lymphocyte infusion (DLI) or a second transplantation. However, DLI alone has a response rate between 0% and 25% and when combined with chemotherapy it can increase up to 40% [1].

In recent years, there was evidence that DNA-methylation inhibitor 5-azacytidine can induce remissions in patients with AML who relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [2,3]. Decitabine is also a hypomethylating agent that was used in high-risk myelodysplastic syndrome and AML patients. However, its role in patients with relapsed AML after allo-HSCT is not well studied up to now.

Here we retrospectively identified one AML patient who relapsed after allo-HSCT and was treated with DCAG (Decitabine 10mg/m² d1-5, Aclarubicin 20mg d1, 3 and 5, Cytarabine 10mg/m² q12h d1-5, G-CSF 300µg/day) with DLI on the 7th day. Relapse of AML after allo-HSCT was defined as decrease (<80%) or loss of donor chimerism with morphologically increased blasts (≥5 %) [4].

Table 1 shows the clinical characteristics of the patient. The time to relapse after allo-HSCT was 44 months, with 70.4% bone marrow blasts and 80.8% donor chimerism. MA (mitoxantrone 5mg/m² d1-3, cytarabine 100mg/m² d1-7) regimen was given 4 days after relapse and the patient didn't get complete remission all the time and about 5 months after MA regimen the donor chimerism was only 9.8%.

Then, DCAG+DLI (matched sibling donor lymphocyte infusion of 0.573×10⁸/kg) was administered 154 days after relapse. According to the grading criteria of Seattle BTM Center, he developed signs and symptoms of grade II acute graft-versus-host disease (aGVHD) 7 days after DCAG+DLI. About 80% of the skin of the limbs and back showed scattered red dots with a slight diarrhea. Methylprednisolone 80 mg was administered for the first 3 days, the red dots increased and then methylprednisolone was increased to 100 mg. One day after treatment, the red dots decreased quickly and methylprednisolone was reduced to 120 mg for 2 days and 110 mg for another 4 days, after which the symptoms disappeared and the drug was withdrawn. Three weeks after DLI the peripheral blood cell count returned to normal levels and no peripheral blasts could be detected; bone marrow examination showed complete remission and donor chimerism increased to 99.6%. Up to day (10 months after DCAG+DLI) the patient is in good condition with normal peripheral blood cell count and 98.8% donor chimerism, and minimal residual disease

(MRD) continues to be negative.

Recent studies had shown that hypomethylating agents can augment the graft versus leukemia (GVL) effect without increasing GVHD after transplantation, which may suggest a new treatment strategy [5]. Likewise, this patient had only mild GVHD of skin and the symptom turned better soon after glucocorticoids therapy. Moreover, the patient had a history of myelodysplastic syndrome (MDS), in which aberrant DNA hypermethylation participates in the pathogenesis and progression of this disease, and hypomethylating agents have shown effectiveness for this disease by their ability to inhibit DNA methyltransferase. Additionally, studies had identified that decitabine was effective in relapsed patients with low blast percentage (<15%) [4]. In our study, after administering MA regimen, the patient's tumor burden decreased a lot, which may be another reason of effectiveness.

In conclusion, our data shows that DCAG+DLI is a safe and effective regimen and consequently can be a choice for AML patients relapsed after allo-HSCT without high burden, at least for those who had a previous history of MDS. Further prospective studies are warranted in the future to identify the role of decitabine in relapsed AML after allo-HSCT.

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Table 1. The clinical characteristics of the patient in this study

Age /sex	Diagnosis	Date of HSCT	Transplant type	Preparatory regimen	Date of relapse	Date of MA	Date of DCAG	Patient status
27/ M	AML-M2	July 14,2010	MSD PBSCT	DA+CY+ TBI	May 19,2014	May 27,2014	October 24,2014	Complete remission
Date	WBC ($\times 10^9/L$)	Hgb (g/L)	PLT ($\times 10^9/L$)	BM blasts	FCM blasts	Donor chimerism		
May 19,2014	3.62	3.62	89	15	70.4%	88.45%	80.8%	
July 1, 2014	0.23	0.23	87	33	BM hypoplasia	12.53%	Not done	
September 4, 2014	3.58	3.58	102	63	BM hypoplasia	7.33%	Not done	
October 21, 2014	2.46	2.46	77	45	BM hypoplasia	Not done	9.8%	
November 18,2014	4.86	4.86	94	136	Undetected	Undetected	99.6%	
April 07,2015	5.24	5.24	130	228	Undetected	Undetected	98.8%	
August 27,2015	5.32	5.32	121	234	Undetected	Undetected	Not done	

MSD: matched sibling donor, PBSCT: peripheral blood stem cell transplant, DA: daunorubicin and cytarabine, CY: cytarabine, TBI: total body irradiation, DLI: donor lymphocyte infusion, DCAG: decitabine aclarubicin cytarabine and G-CSF, WBC: white blood cell, Hgb: hemoglobin, PLT: platelet, BM: bone marrow, FCM: flow cytometry, M: male

The role of tyrosine kinase inhibitors in the treatment of renal cell carcinoma with brain metastases

Dear Editor,

Before the discovery of angiogenesis inhibitors, cytokine-based therapies including interferon and interleukin-2 were the main components of the treatments of metastatic renal cell carcinoma (RCC) despite their limited clinical activity and significant toxicity. With newly developed angiogenesis inhibitors (VEGF-TKI=Vascular Endothelial Growth Factor Receptor- Tyrosine Kinase Inhibitor), the mean survival has increased up to 28 months. The incidence of brain metastases in RCC was reported as 6-10% and the mean survival was 5 months in patients in whom whole-brain-irradiation was performed [1]. In animal studies, sunitinib [2] and pazopanib [3] have been shown to penetrate the blood-brain barrier.

In a study carried out in 2013, 216 metastatic brain lesions of 81 patients with RCC were examined. As a result, while improvement in survival was obtained with the TKI treatment in patients with brain metastases, improvement in local control was not significant and it is mentioned that the treatment can be effective in patients who have not previously received TKI [4]. In RCC patients with small supratentorial brain metastases, response to the initial su-

nitinib treatment without local treatment was reported in a case series .

In a case report where pazopanib was used, approximately 23 months of survival has been reported in a patient with type 2 papillary RCC with more than 20 brain metastases [5].

In our clinic, interferon was initiated to a patient who underwent surgery for clear cell renal cancer with bone and lung metastases during follow-up. After 1 year under the treatment, a mass was observed in the brain with no progression in non-brain-organs (peripheral), and the patient was operated. Pathology was consistent with metastatic RCC. After whole brain radiotherapy, treatment with pazopanib was started. A recurrent mass was observed in the operation area after 5 months. The patient underwent gamma knife therapy and because the disease in the periphery was under control, treatment with pazopanib was and still is continued.

As a result, the clinical significance of these findings remains controversial. There are insufficient data regarding the optimal treatment selection in RCC patients with brain metastases. Whole brain irradiation, surgical or radiosurgical procedures can be applied in symptomatic

patients. However, morbidity and mortality of these methods are very high and it is difficult to reapply them when a recurrence or progression occurs. TKIs are not expected to affect symptoms related to the brain metastases in the short-term. Furthermore, there is conflicting evidence about their activity. In symptomatic patients with brain metastases, we suggest an initial local therapy followed by an anti-angiogenic therapy. And for asymptomatic patients, TKIs can be started immediately. Nonetheless, our knowledge in this regard is inadequate and further research is required.

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Can diffusion-weighted whole-body magnetic resonance imaging with body signal suppression play a role in the management of lymphoma patients?

Dear Editor,

¹⁸F-fluorodeoxyglucose positron emission tomography with non-enhanced computed tomography (¹⁸F-FDG-PET/CT) has become the cornerstone in the management of the majority of lymphoma patients. It has become essential in disease staging, monitoring response to treatment, detecting recurrence, characterizing tumor biology and predicting prognosis.

As a new no-radiation whole body imaging technology, diffusion-weighted whole-body magnetic resonance imaging with body signal suppression (WB-MR/DWIBS) is showing great possibility for clinical application, representing a potential competitor for ¹⁸F-FDG-PET/CT. By recording microstructural and cellular density alterations, which translates to elevated signal intensity resulting in images that remarkably resemble ¹⁸F-FDG-PET/CT studies, it has also an emerging role in staging and response assessment of lymphomas, showing complementary information to ¹⁸F-FDG-PET/CT [1-3].

We present a case in which WB-MR/DWIBS proved superior to ¹⁸F-FDG-PET/CT in the detection of a peculiar and rare renal involvement of diffuse large B-cell lymphoma (DLBCL), strengthening the relevance of this new technique.

A 52-year-old man presented with normocytic anemia, hepatomegaly, splenomegaly, weight loss and hyperpyrexia. The bone marrow biopsy was conclusive for DLBCL (CD20+ CD10- BCL6+ BCL2+ MIB-1 60%). ¹⁸F-FDG-PET/CT and WB-MR/DWIBS were performed before and after treatment which consisted of 8 courses of R-CHOP every 14 days. He also received intrathecal prophylaxis (4 doses of methotrexate and dexamethasone) because of the elevated risk of central nervous system involvement due to the bone marrow and renal infiltration. WB-MR/DWIBS was performed on a 1.5 Tesla MR scanner (ACHIEVA, Philips Healthcare) using a rolling table platform, for complete anatomical coverage (acquisition time of about 25 min).

Staging ¹⁸F-FDG-PET/CT documented mediastinal and abdominal nodal involvement (SUV max 12.1), focal and diffuse uptake of the spleen (SUV max 9.0) and bone marrow involvement (SUV max 13.3). WB-MR/DWIBS confirmed the described sites adding a focal, well defined lesion (1.5 cm) localized at the left renal cortex. The lesion was hypointense in T1-weighted and iso-hypointense in T2-weighted sequences, with elevated signal intensity in DWIBS that confirmed the hypercellular nature of the nodular kidney lesion. A subsequent contrast-enhanced CT confirmed the renal involvement. Flow cytometry of cere-

brospinal fluid was negative. The patient was treated with R-CHOP14 and intrathecal prophylaxis with methotrexate. After first-line treatment, imaging evaluation showed disappearance of all sites of disease, including the renal lesion. He then received R-DHAP and ASCT and is still in complete remission (21 months follow-up).

At diagnosis, kidney may be involved by DLBCL in about 2% of the patients. Renal infiltration is clinically associated to widespread disease, increased risk of central nervous system involvement and poor prognosis [4]. The identification of renal involvement during staging is therefore essential for the optimal therapeutic choice.

^{18}F -FDG-PET/CT remains the reference standard imaging modality for patients affected by Hodgkin's lymphoma or aggressive non Hodgkin's lymphoma. However this case demonstrates that WB-MRI/DWIBS can be of additional value for ^{18}F -FDG-PET/CT for the detection of "critical" organs, such as kidneys, ureters and bladder, in which neoplastic lesions may be obscured. It represents a whole body, fast-scanning and radiation-free method that could be used in these patients in association with or as an alternative to ^{18}F -FDG-PET/CT, when not available.

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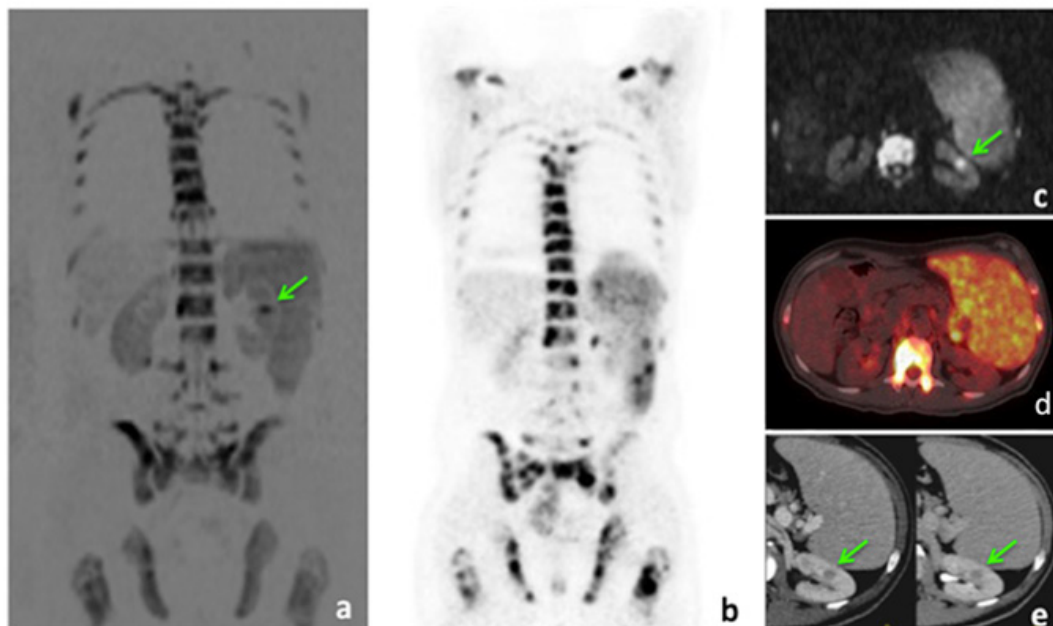


Figure 1. (a) Coronal WB-MRI/DWIBS; (b) Coronal ^{18}F -FDG-PET; Axial DWIBS image; (c) Axial DWIBS image; (d) Axial fused ^{18}F -FDG-PET/CT image; (e) Contrast-enhanced CT. WB-MR/DWIBS shows a focal area (arrows) of elevated signal intensity in the left kidney (a, c), confirmed by contrast-enhanced CT (e) but not evident in ^{18}F -FDG-PET/CT images (b, d).