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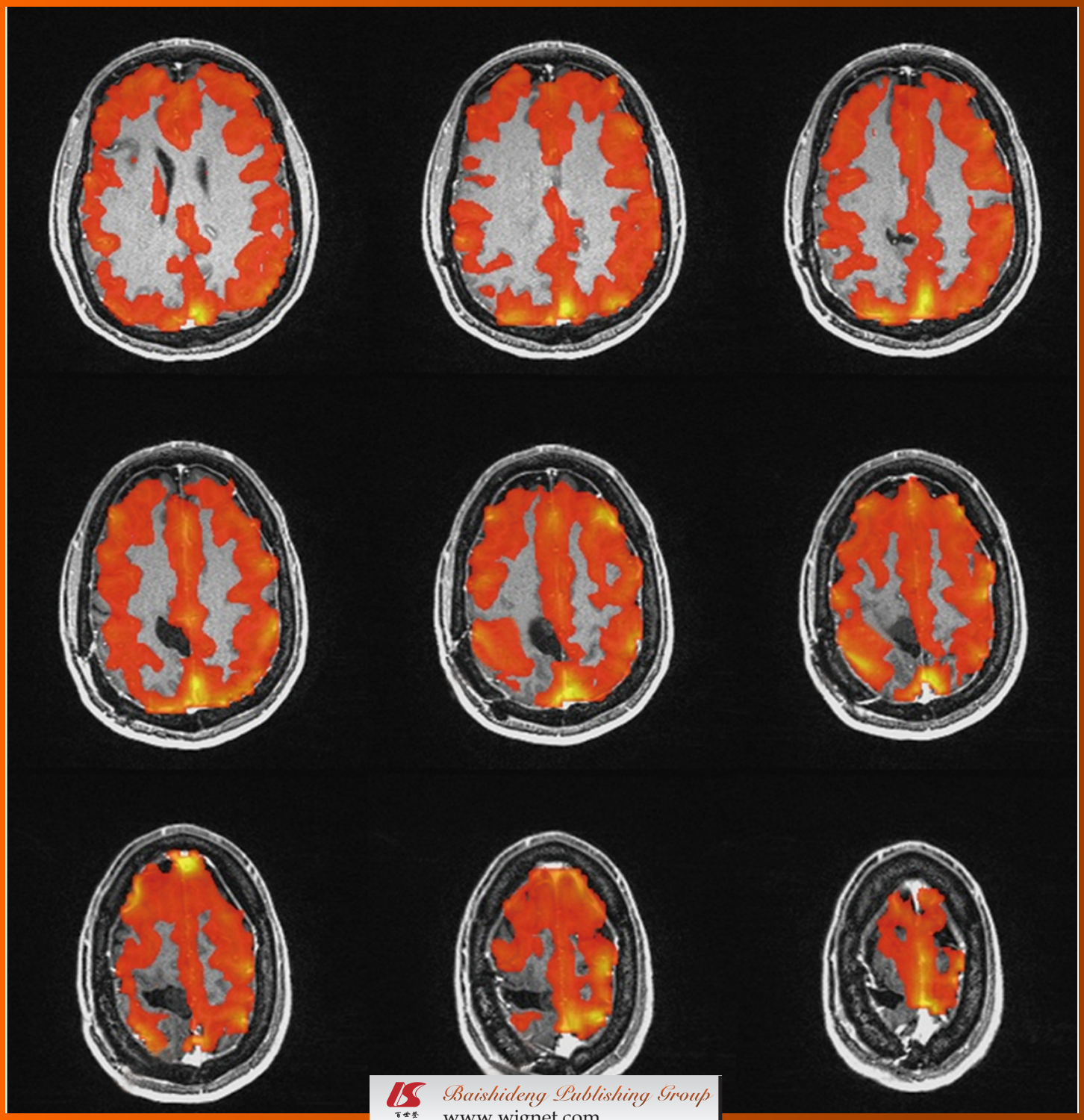

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EDITORIAL

Rituximab maintenance in follicular lymphoma patients

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Abstract

Rituximab maintenance (RM) therapy following successful induction has recently emerged as a highly effective treatment for follicular lymphoma (FL). Randomized trials analyzing the impact of RM compared to observation alone have demonstrated a significantly better outcome in terms of progression-free survival (but not overall survival) in patients (pts) who received as first-line treatment single-agent rituximab, standard chemotherapy (CVP) and recently also immunochemotherapy (R-CHOP, R-CVP or R-FND), as shown by preliminary results of the PRIMA trial. Also in the setting of relapsed disease, RM has shown significant benefit either after chemotherapy or immunochemotherapy. RM has been generally well tolerated, and treated pts developed only mild toxicity, mainly a small increased rate of neutropenia, hypogammaglobulinaemia and self-limiting upper-respiratory tract infections. Moreover, no cumulative or unexpected toxicities were observed and quality of life was not affected. These data have established RM therapy as an important part of multi-modal therapeutic strategies in patients affected by FL.

Key words: Follicular lymphoma; Immunochemotherapy; Maintenance; Rituximab

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INTRODUCTION

In last 10 years, the introduction of the chimeric anti-CD20 monoclonal antibody rituximab (R) has emerged as one of most important advances in the treatment of patients affected by B-cell non-Hodgkin's lymphoma (NHL), and especially diffuse large B-cell lymphoma and follicular lymphoma (FL). R selectively binds the CD20 surface antigen on B lymphocytes, and subsequently induces the killing of coated cells though a combination of different immuno-mediated effector mechanisms of action, namely complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and induction of apoptosis[1]. Although the efficacy of R was initially demonstrated when employed as a single agent[2], in patients affected by advanced FL the major benefits have been observed when combined with chemotherapy. In fact, as demonstrated in six randomized trials, the addition of R to every effective chemotherapeutic combina-

tion (CVP[3, 4], CHOP[5-7], CHVP[8], MCP[9] and FCM[10]), resulted in a significant increase in response rate, complete remission (CR) rate, progression-free survival (PFS) and even overall survival (OS) with respect to chemotherapy alone (Table 1), without relevant acute and long-term toxicities.

However, as indicated by continuous declination of PFS curves at long-term follow-up in these trials, relapses seem to continue after immunochemotherapy in these patients and none can be considered cured. Thus, eventual relapse remains an important clinical issue for the majority of patients with FL, and defining further ways to extend the period of remission remains an essential goal. An important way to achieve this goal is the concept of maintenance therapy, offering continued treatment to patients after successful induction therapy in attempt to prevent the re-emergence of disease. An early study of oral chlorambucil for 2 years demonstrated that this maintenance therapy was associated with significant prolongation of disease control, but without any improvement in OS[11]. For this reason, considering the adverse effects associated with prolonged exposure to alkylating agents, maintenance chemotherapy strategies were abandoned. The most extensively studied maintenance therapy for FL is the immunomodulatory agent interferon-alpha. A meta-analysis of 10 randomized studies which compared interferon-alpha maintenance with observation clearly demonstrated a significant improvement of 10% in the likelihood that patients would remain in ongoing remission at 5 years and 10 years ($P < 0.001$) and an 8% improvement in their likelihood of survival at 5 years and 10 years ($P = 0.004$) with interferon-alpha maintenance[12]. However, the adverse effects of prolonged interferon-alpha exposure and the resultant impairment of quality of life have resulted in this therapy being infrequently used in current clinical practice.

The ideal maintenance agent would have proven efficacy as monotherapy in FL, minimal acute and long-term toxic effects, simple administration, favourable treatment schedules, and require minimal monitoring of the patient. R has many of these characteristics and its use as a maintenance therapy for FL is very appealing. In particular, pharmacokinetic studies showed that R maintains a serum concentration considered active (25 g/mL) for a median time of 3-3.5 mo after infusion, suggesting that almost all patients would maintain this concentration with a dosing interval of 2 mo[13]. However, the optimal dosing schedule of RM has not been determined and the several phase II and randomized phase III studies performed so far have employed different maintenance schedules, mainly a single infusion every 2 or 3 mo for 2 years or 4 weekly administrations repeated at intervals of 6 mo for 2 years.

Considering the heterogeneity of maintenance schedules, of prior induction treatments, and the phase of disease in which maintenance is applied (onset or relapse), the goal of this editorial is to provide a comprehensive overview of RM, illustrating results after single agent R, after chemotherapy and after immunochemotherapy; in addition, we summarize infusional and late toxicity and the cost-effectiveness of R. We also provide discussion of alternative therapeutic strategies as consolidation after an induction treatment.

LITERATURE SEARCH

We searched PubMed (http://www.pubmed.gov) for articles with the keywords 'follicular lymphoma', 'rituximab', 'maintenance', and reviewed all references of the retrieved articles.

Abstracts from the American Society of Hematology, European Hematology Association and American Society of Clinical Oncology since 2007 were searched using the same keywords.

Overall, five major randomized studies have now published their final results on the role of RM in various clinical settings, either after single agent R[14-16], chemotherapy alone[17], or immunochemotherapy at relapse[6,7] (Tables 2 and 3). Preliminary results of a single large randomized trial (PRIMA, Primary R and MAintenance) investigating maintenance treatment after first-line immunochemotherapy have recently been reported[18]. Several of these studies also included patients with other forms of indolent lymphoma, but we will consider only data on the specific subset of patients with FL.

RITUXIMAB MAINTENANCE AFTER SINGLE AGENT RITUXIMAB

In one of the first studies evaluating RM, Hainsworth *et al*[16] randomly allocated patients responding to a previous standard 4-week course of R to receive either maintenance R given weekly for 4 wk every 6 mo for 2 years or R re-treatment (with the same schedule) at the time of lymphoma progression. The median PFS was 31.3 mo in the maintenance group compared with 7.4 mo in the re-treatment group ($P = 0.007$). However, the duration of R benefit (defined as the time to next anti-lymphoma treatment) was similar in the maintenance and in the re-treatment groups (31.3 *vs* 27.4 mo, P = NS); moreover, there was no difference in OS between the two cohorts (72% *vs* 68% at 3-years, P = NS).

Ghielmini *et al*[14] investigated maintenance R (a total of 4 infusions every 2 mo) following treatment with single-agent R in 202 patients with FL. The study was recently updated with long-term follow-up data (median 9.5 years)[19]. Overall, RM was associated with an improvement of 11 mo in median event-free survival (EFS) *vs* observation (24 *vs* 13 mo, $P < 0.001$). The best outcome was observed in previous untreated patients responding to R induction (8-years EFS 45% for the maintenance arm *vs* 22% for the observation arm; $P < 0.001$). In univariate analysis, baseline features predicting longer EFS were: disease diameter < 5 cm, being chemotherapy naïve, Ann Arbor stage lower than IV, and a VV phenotype at position 158 of the Fc gamma receptor RIIIA. At multivariate analysis, the only favourable prognostic factor for EFS was the maintenance treatment (HR 0.59, 95% CI 0.39

Table 1 Randomized trials comparing Rituximab-chemotherapy *vs* chemotherapy alone in follicular lymphoma patients

Reference	Year	Prior treatment	Treatment	No of patients	ORR	OS	PFS
Marcus *et al*[3, 4]	2005, 2008	No	R-CVP *vs* CVP	321	81% *vs* 57% ($P < 0.001$)	83% *vs* 77% at 4-years ($P = 0.029$)	27 *vs* 7 mo ($P < 0.001$) [1]
Hiddeman *et al*[5]	2005	No	R-CHOP *vs* CHOP	428	96% *vs* 90% ($P = 0.001$)	95% *vs* 90% at 2 yrs ($P = 0.016$)	91% *vs* 79% at 2 yrs ($P < 0.001$)[1]
van Oers *et al*[6, 7]	2006, 2010	Yes	R-CHOP *vs* CHOP	465	85% *vs* 72% ($P < 0.001$)	82% *vs* 79% at 3 years ($P = 0.09$)	33 vs 20 mo ($P < 0.001$)
Forstpointner *et al*[10]	2006	Yes	R-FCM *vs* FCM	125	95% *vs* 71% ($P = 0.01$)	Not available[2]	Not available[2]
Herold *et al*[9]	2007, 2010	No	R-MCP *vs* MCP	358	92% *vs* 75% ($P < 0.001$)	86% *vs* 74% at 5 years ($P = 0.02$)	86 *vs* 35 mo ($P < 0.001$)
Salles *et al*[8]	2000	No	R-CHVP-I *vs* CHVP-I	358	94% *vs* 85% ($P < 0.001$)	84% *vs* 79% at 5-years ($P = 0.15$)	53% *vs* 37% at 5 years ($P < 0.01$)

ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; [1]Time-to-treatment-failure; [2]Data not available because of protocol design (double randomization).

Table 2 Randomized trials comparing rituximab maintenance *vs* observation after single agent rituximab

Reference	Year	Prior treatment	Maintenance schedule	No. of patients	Median F-up	PFS	OS
Haisworth *et al*[16]	2005	R x 4 (weekly)	R x 4 (weekly) every 6 mo x 4 *vs* R x 4 weekly at relapse (retreatment)	62	41 mo	31.3 *vs* 7.4 mo ($P = 0.007$)	72% *vs* 68% at 3 years (P = NS)
Ghielmini *et al*[14] Martinelli *et al*[19]	2004 2010	R x 4 (weekly)	R every 2 mo x 4 *vs* observation	185	9.5 years	24 *vs* 13 mo ($P < 0.001$)	68% *vs* 54% ($P = 0.081$)

to 0.88, $P = 0.009$). Analysis of OS showed a borderline advantage for the maintenance arm (68% *vs* 54%; HR for death 0.63, 95% CI 0.37 to 1.06, $P = 0.0813$).

RITUXIMAB MAINTENANCE AFTER CHEMOTHERAPY OR IMMUNOCHEMOTHERAPY

The efficacy of RM therapy has also been investigated after treatment with different chemotherapy regimens. Hochster *et al*[17] randomly allocated 228 patients with previously untreated FL who had stable disease or better after CVP chemotherapy to either maintenance R (four weekly infusions every 6 mo for 2 years) or observation. Maintenance R was associated with greatly prolonged median PFS *vs* observation (4.3 years *vs* 1.3 years; $P < 0.001$) and borderline increased 3-year OS (91 *vs* 86%; $P = 0.08$). OS improved significantly only for patients with high tumour burden ($P = 0.03$).

In the setting of relapsed disease, two studies utilized a '2 X 2' factorial design to explore the benefits of the addition of R to multi-agent salvage chemotherapy, and also the role of RM. Forstpointner *et al*[10] randomly allocated patients with relapse of FL to FCM or R-FCM, followed by randomization to maintenance or observation. Response duration was longer with maintenance therapy (estimated median PFS not reached *vs* 16 mo in the observation group, $P < 0.001$); however, estimated OS at 3 years for the entire cohort, which also included patients affected by mantle cell lymphoma, was 77% in the group that received maintenance therapy and 57% in those assigned to observation ($P = 0.1$). Van Oers *et al*[6] randomly allocated pre-treated patients to CHOP or R-CHOP, with a secondary randomization to maintenance R or observation. In their initial report, at a median follow-up of 33 mo, maintenance therapy was associated with prolonged PFS (51.5 *vs* 19.4 mo $P < 0.001$) and with improved 3-yr OS (85.1 *vs* 77.1, $P = 0.011$). However, when follow-up was extended to 6 yrs, while the advantage of RM on PFS was confirmed (median 3.7 *vs* 1.3 years, $P < 0.001$), the beneficial effect on OS was not so evident (5-year OS 74% *vs* 64%, $P = 0.07$)[7]. This discrepancy might be partially due to the effect of the unbalanced use of R in the post-protocol salvage regimen. In fact, R was used most frequently in patients who had neither received R during induction treatment nor as maintenance.

An unplanned sub-analysis of 40 patients with relapsed FL who underwent RM after response to treatment with Fludarabine-R or Bendamustine-R in the context of the German Stil phase III NHL 2-2003 trial, showed that RM significantly prolonged OS and PFS[20]. Finally, in a large study 420 R-naïve patients were randomized to receive no R before and autologous stem cell transplantation (ASCT) (no R), R purging (weekly for 4 wk) before

Table 3 Randomized trials comparing rituximab maintenance *vs* observation after chemotherapy or immunochemotherapy

Reference	Year	Prior treatment	Maintenance schedule	No. of pts	Median F-up	PFS	OS
Hochster *et al*[17]	2009	CVP (1st line)	R x 4 (weekly) every 6 mo x 4 *vs* observation	228	3.7 years	Median: 4.3 *vs* 1.3 years At 3 years: 64% *vs* 33% ($P < 0.001$)	At 3 years: 91% *vs* 86% ($P = 0.08$)
Forstpointner *et al*[10]	2006	FCM or R-FCM (relapsed disease)	R x 4 (weekly) every 6 mo x 2 *vs* observation	105	26 mo	Median: Not reached *vs* 16 mo ($P < 0.001$)	At 3 years (estimated): 77% *vs* 57% ($P = 0.1$)
van Oers *et al*[6, 7]	2006 2010	CHOP or R-CHOP (relapsed disease)	R every 3 mo x 8 *vs* observation	334	6 years	Median: 3.7 *vs* 1.3 years At 3 years: 59% *vs* 28% ($P < 0.001$)	At 5 years: 74% *vs* 64% ($P = 0.07$)
Salles *et al*[18, 23]	2010	R-CHOP, R-CVP, R-FCM (1st line)	R every 2 mo x 12 *vs* observation	1018	25 mo	At 2 years: 79% *vs* 60% ($P < 0.001$)	At 2 years: NS

high-dose therapy BEAM conditioning (Rp), RM after ASCT (every 3 mo for 2 years) (RM) or both (Rp + RM). At a median follow-up of 6.4 years, 5-year PFS was 62.9% for patients receiving Rp + RM *vs* 37.6% for patients receiving no R ,while 5-yr OS was not different[21].

META-ANALYSIS

In 2009 a meta-analysis of the five randomized controlled trials[6, 10, 14, 16, 17] that compared RM therapy with observation or R at relapse was performed[22]. Data for 985 patients with FL were available for the meta-analysis of OS. Patients treated with maintenance R had statistically significantly better OS than patients in the observation arm or those treated at relapse (HR for death = 0.60, 95% CI= 0.45 to 0.79). Patients with refractory or relapsed disease had a survival benefit with maintenance therapy (HR for death = 0.58, 95% CI= 0.42 to 0.79), whereas previously untreated patients did not (HR for death = 0.68, 95% CI= 0.37 to 1.25). There was no significant difference between patients treated with different maintenance schedules (i.e. 4 weekly infusions every 6 mo or a single infusion every 2-3 mo). These results strongly support the benefit of RM in the setting of relapsed disease after successful induction therapy. A recent update of this meta-analysis, including the published extended follow-up data of previous studies and the data of an additional 2 trials[21,23] (2283 patients), confirmed all the previous conclusions (significant improvement in OS in the whole cohort and in relapsed/refractory patients with, no significant benefit on OS in previously untreated patients and a significant improvement in PFS in every group of patients)[24].

RITUXIMAB MAINTENANCE AFTER FIRST-LINE IMMUNOCHEMOTHERAPY

The role of R as maintenance therapy following first-line immunochemotherapy was addressed by the PRIMA trial, whose preliminary results were recently reported at American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) 2010 Congresses[18], and updated with an additional year of follow-up at the 2010 American Society of Hematology meeting[23]. The PRIMA trial is an international effort conducted by the French Group d'Etude des Lymphomas de l'Adulte (GELA) in 223 centres from 25 countries in untreated FL (grade 1, 2 and 3a) patients requiring therapy. Induction consisted of R for 8 infusions combined with either CHOP for 6 cycles, CVP for 8 cycles, or FCM for 6 cycles. Patients responding to induction therapy were subsequently randomized to either maintenance R 375 mg/m^2 every 2 mo for 24 mo or observation. A total of 1217 patients were enrolled in the study, with 1,018 patients randomized after a response (CR/PR) to induction treatment. FLIPI risk groups were as follows: low risk 21%, intermediate 36%, and high risk 43%. R-CHOP was used in 75% of patients, R-CVP in 22% and R-FCM in 3%. CR/Cru was obtained in 71% of patients and PR in 29%. After a median follow-up of 36 mo, RM therapy reduced the risk of lymphoma progression by 45% (hazard ratio = 0.55, 95% CI=0.44 –0.68, $P < 0.001$), with 2-year PFS of 79% in RM (n = 505) compared to 60% in observation (n=513). Subgroup analysis demonstrated improvements across all age categories, FLIPI risk scores, induction chemotherapy choice, and response to induction chemotherapy. The magnitude of risk reduction was greater for patients in PR (55% risk reduction) than in CR/CRu (48% risk reduction). The risk of requiring next anti-lymphoma treatment or chemotherapy was reduced by 40% with maintenance R. Adverse events were more frequent in the maintenance R arm, including grade 3-4 adverse events in 24% compared to 17%; grade 3-4 neutropenia and infection both occurred in 4% compared to less than 1%. There was no increase in deaths related to treatment arm and quality of life was not diminished with RM. In summary, the PRIMA trial demonstrates that addition of maintenance R every 2 mo for 2 years following first-line immunochemotherapy resulted in a significant improvement in PFS with acceptable toxicity. The follow-up time was too short to see any improvement in OS.

The British Columbia Cancer Agency (BCCA) reported a retrospective population-based analysis of 251 patients affected by FL, who were treated between 2004 and 2010 with first-line R-CVP, since 2006, patients responding to induction treatment, underwent RM (every 3 mo for 2 years). At a median follow-up of 3 years, PFS was signifi-

Table 4 Toxicities in trials comparing rituximab maintenance *vs* observation in follicular lymphoma

Reference	No of. patients	Grade 3-4 AE	Neutropenia (grade 3-4)	Grade 3-4 Infections
Haisworth *et al*[16]	62	9% *vs* 4%	2% *vs* 0%	0
Ghielmini *et al*[14]	185	28% *vs* 20%	18% *vs* 17%	NA
Martinelli *et al*[19]				
Hochster *et al*[17]	228	NA	3% *vs* 1%	1% *vs* 1%
Forstpointner *et al*[10]	105	NA	13% *vs* 6%	4% *vs* 3%
van Oers *et al*[6]	334	NA	10.8% *vs* 5.4% (P = 0.07)	9% *vs* 2.4% (P = 0.009)
Salles *et al*[18, 23]	1018	23% *vs* 16%	4% *vs* 1%	4% *vs* 1%

cantly improved in patients receiving RM compared to patients on observation alone, while OS did not, also confirming in a population-based approach the data of clinical trials[25].

MOLECULAR BASIS

Few and still controversial data have been published on the benefit of RM based on molecular status (persistence or disappearance of Bcl2/IgH positivity in bone marrow and/or peripheral blood) after induction treatment. The only study that investigated this topic found no difference in PFS in patients who were Bcl2/IgH positive or negative before beginning RM, which conversely determined improvement in outcome regardless of pre-maintenance molecular status[26]. However, some criticisms have been raised in this study: first of all, only major breakpoint rearrangement (MBR) has been investigated and, most importantly, patients with unknown molecular status (not informative for Bcl2/IgH rearrangement) were included in the group without evidence of blood and marrow involvement[27].

TOXICITY

Several concerns regarding the prolonged use of R have been raised and evaluated. The first issue is the prolonged B-cell depletion associated with this clinical practice. As discussed before, based on pharmacokinetic analysis and assuming a R serum level of 25 mcg/mL for maintaining B-cell depletion[13], the single infusion of R every 2-3 mo appears to be the most appropriate. However, this schedule produces the maximum B-cell depletion, and the increased risk of low immunoglobulin levels alongside with possible additional infectious complications remain a concern. In the study by van Oers *et al*[6], patients in the RM arm had a median IgG level of 6.3 g/L, compared with 7.3 g/L in the observation arm. Maintenance was omitted in two patients with IgG levels < 3 g/L. Another side effect reported with the use of R is the development of neutropenia (Table 4). In the same trial, neutropenia was reported in 10.8% of patients in the R arm compared with 5.4% in the observation arm (P = 0.07). The increased incidence of hypogammaglobulinaemia and neutropenia may both have contributed to an increased rate of grade 3-4 infection (9% *vs* 2.4%, P = 0.009), most of which were in the ear-nose-throat area. Six patients were hospitalized; however, they all fully recovered and there were no deaths related to RM. Based on cumulative data reported in three trials, the previously cited meta-analysis confirmed that patients who underwent RM therapy had more infection-related adverse events than patients in the observation arm (RR=1.99, 95% CI= 1.21 to 3.27). When only grade 3 or 4 infection-related adverse events were included in the analysis, this effect was even more pronounced (RR 2.90, 95% CI=1.24 to 6.76)[22].

The phase Ⅲb study MAXIMA, specifically evaluated the safety of RM (every 2 mo for 2 years) given either as the standard infusion rate or as a rapid infusion (≤ 90 min) in FL patients (first-line 395 patients, relapsed/refractory 150 patients) responding to induction treatment. The full course of RM was completed by 407 patients (58 patients discontinued due to progression, 16 patients due to toxicity). R-related adverse events were reported in 57 patients, the most common being infections (22 patients)[28].

On the other hand, in an analysis of 215 patients from Memorial Sloan-Kettering Cancer Center, hypogammaglobulinaemia was registered in 39% of patients with normal baseline levels following exposure to R, and 10% needed intravenous immune globulin replacement for symptomatic hypogammaglobulinaemia[29].

COST-EFFECTIVENESS OF MAINTENANCE

The cost-effectiveness of R in the treatment of patients with FL is an important issue[30]. Regarding the cost-effectiveness of RM, after induction therapy *vs* current standard practice (observation), a lifetime transition model was developed[31] based on PFS and OS obtained from the EORTC 20981 trial. The results tend to show that RM therapy may be a cost-effective strategy in the management of relapsed/refractory FL patients, at least in France. The cost of R was partly offset by the lower cost of relapse due to a longer time in the disease-free health state for patients in the R arm. An analysis concerning the cost-effectiveness of first-line RM in patients with untreated FL has been reported in the perspective of the UK National Healthcare Service[32]. Based on evidence from the PRIMA trial, the simulation of incremental cost-effectiveness ratios (ICERs) demonstrated that the superior clinical benefits of first-line RM are sufficient to justify the additional costs over observational practice.

ALTERNATIVE STRATEGIES

An alternative consolidation strategy could be the use of radioimmunotherapy (RIT). Morschhauser and colleagues[12] have reported results of the FIT trial: in this study patients who entered first remission with chemo-

therapy or immunochemotherapy were randomized to ^{90}Y ibritumomab or to observation. There was a significant improvement in the failure-free survival rate for RIT consolidation in patients who had received induction therapy with only chemotherapy. Nevertheless, RIT may be an attractive consideration in elderly patients where anthracycline induction is not desired and the burden of every-8-week therapy for 2 years is too much.

DISCUSSION

RM has emerged in recent years as a very appealing therapeutic strategy in patients affected by FL responding to induction treatment, as all randomized trials concordantly demonstrated that this practice is safe, has an acceptable toxicity profile and significantly improves response duration and PFS. However, many features of this topic have not yet been fully elucidated and have to be critically discussed. First of all, every single trial was unable to support a significant OS benefit, even after considerable follow-up. Probably the main reason for this is that patients with FL retain sensitivity to chemo-immunotherapy for long periods and those who did not undergo RM could often be effectively rescued with salvage R-containing treatments.

Although the meta-analysis recently published demonstrated a survival benefit for maintenance treatment, especially in relapsed patients, the limitations of this type of analysis that pool data obtained in different settings of patients (first-line or relapsed, R naïve or not), treated with different induction regimens (R alone, chemotherapy alone, or chemo-immunotherapy) cannot permit definitive conclusions. Moreover, none of the studies comprised in the meta-analysis explored the effect of RM after the first-line current standard of care in patients affected by FL, i.e. immunochemotherapy. For this reason the striking preliminary data of the large international PRIMA study on RM after frontline immunochemotherapy (R-CVP, R-CHOP, R-FM), that confirmed the efficacy of this strategy on PFS (with halved risk of relapse at 2-years) without any relevant toxicity, seem to open the door to the acceptance of this strategy as a new standard of care[18]. However, other alternative post-induction consolidation strategies, such as radio-immunotherapy[12], have been developed and demonstrate an improvement in PFS similar to that of PRIMA, albeit with a chemotherapy only induction approach in the majority of patients: for these reasons future studies directly comparing these different options are needed. Moreover, a new generation of monoclonal antibodies, such as the new anti-CD20 monoclonal antibody GA-101, is now coming from the bench to the bedside, and could eventually be incorporated in future maintenance strategies.

At the present time, the best chemotherapy regimen in combination with R in first-line treatment (CHOP, CVP, FM or Bendamustine) is not known, and it is not clear whether RM could have different efficacy after different immuno-chemotherapeutic regimens. Some ongoing trials are trying to address these issues.

Another important issue is that the best schedule (4 weekly infusions every 6 mo or a dose every 2 or 3 mo) and the optimal duration of RM (8 mo, 2 years or until progression) has not been determined, as the different schedules and treatment durations have not been directly compared. An ongoing Swiss study is comparing 2 years *vs* 5 years of maintenance: preliminary safety data after a median maintenance time of 3.3 years seem to suggest that RM beyond 2 years is feasible without evidence of increased toxicity, even if it is too early to draw definitive conclusions about the safety of RM administered beyond 2 years[33].

In conclusion, RM has shown to be effective and well tolerated in the majority of patients. Current available results of randomized trials support the benefit of RM in all relapsed patients responding to 2nd line treatment and not candidates for intensive approaches (autologous stem cell transplantation) and this strategy has been approved by regulatory organisations in many countries. Finally, preliminary results of the PRIMA study seem to open the door to incorporate RM after successful induction immunochemotherapy in the comprehensive standard 1st line therapeutic strategy for patients affected by advanced FL requiring treatment. Definitive data of the PRIMA trial and future comparative studies with other alternative post-induction consolidation or alternative maintenance strategies (i.e. with new monoclonal antibodies), are ultimately needed to define the standard of care in the near future for untreated patients affected by FL.

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REVIEW

Cerebrovascular reactivity mapping for brain tumor presurgical planning

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Abstract

This article provides a review of Blood Oxygen Level Dependent functional magnetic resonance imaging (BOLD fMRI) applications for presurgical mapping in patients with brain tumors who are being considered for lesion resection. Initially, the physical principle of the BOLD effect is discussed, followed by a general overview of the aims of presurgical planning. Subsequently, a review of sensorimotor, language and visual paradigms that are typically utilized in clinical fMRI is provided, followed by a brief description of studies demonstrating the clinical impact of preoperative BOLD fMRI. After this thorough introduction to presurgical fMRI, a detailed explanation of the phenomenon of neurovascular uncoupling (NVU), a major limitation of fMRI, is provided, followed by a discussion of the different approaches taken for BOLD cerebrovascular reactivity (CVR) mapping, which is an effective method of detecting NVU. We then include one clinical case which demonstrates the value of CVR mapping in clinical preoperative fMRI interpretation. The paper then concludes with a brief review of applications of CVR mapping other than for presurgical mapping.

Key words: Blood oxygen level dependent; Brain tumor; Cerebrovascular reactivity; Functional magnetic resonance imaging; Neurovascular uncoupling; Presurgical

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INTRODUCTION

Blood Oxygen Level Dependent functional magnetic resonance imaging (BOLD fMRI) is a brain mapping technique using deoxyhemoglobin contained in the blood vessels as an endogenous contrast agent to produce functional activation maps[1].

Neural activation induces a transient increase in regional oxygen extraction from the blood that is coupled with a much larger increase in cerebral blood flow (CBF) and cerebral blood volume (CBV). This influx of oxygenated hemoglobin results in a net decrease in regional deoxyhemoglobin concentration. This drop in paramagnetic deoxyhemoglobin concentration leads to an increase in the magnetic relaxation times T2 and T2*. The mapping of eloquent areas is thus obtained by acquiring T2 or T2*-weighted images consecutively while the subject is at rest or performing a task, and detecting the signal increase related to the local reduction of deoxyhemoglobin concentration accompanying the functional activation relative to baseline.

fMRI studies are carried out using a gradient echo sequence with echo planar readout[2]. This sequence is very sensitive to the static local magnetic field inhomogeneities and therefore is suitable for detection of T2* related signal changes, and at the same time allows scanning of the whole brain within one repetition time (TR) of 2-3 s. The subject performs a cognitive, sensorimotor or visual paradigm inside the bore of the MRI scanner during image acquisition. In a typical clinical fMRI paradigm, a block design is used consisting of 20-30 s blocks (a.k.a., epochs) of rest or control tasks alternating with blocks of active tasks. In this way the subject's brain activity is usually monitored for a total duration of 200-300 s by acquiring whole brain MR images with a good spatial (typically 3 mm × 3 mm × 3 mm) and temporal resolution (e.g. 2 s). Four dimensional (3D+time) datasets are created where a signal time series is recorded and stored for each voxel. Functional activation maps are obtained by detecting areas of the brain showing a statistically significant signal increase due to the executed active task relative to the resting or control task.

To achieve this goal, a series of processing steps needs to be carried out on the fMRI dataset[3]. First the raw images are initially time shifted so that all the slices in each whole brain acquisition (volume) that occur in one TR result as if they were acquired at the same time. Then all the volumes are registered to a reference volume to correct for small head motions. A further preprocessing step consists of spatially smoothing each voxel signal time series in order to reduce low and high frequency noise.

At this point a statistical analysis is carried out that aims to determine, voxel by voxel, the "goodness of the fit" of the signal time series to a theoretical hemodynamic response function obtained by convolving the paradigm timing with an impulse response function (Figure 1). The "goodness of the fit" can be expressed through several statistical parameters, such as *P*-value, Z or t score or cross correlation coefficient.

Activation maps are generated choosing a threshold (significance) on the statistical score. The suprathreshold regions are visualized as "hot spots," often overlaid in color and coregistered on a higher resolution anatomical MR image (Figure 2).

The neurobehavioral paradigms used for functional MRI studies can be divided into two categories, block-design and event-related design. Block design paradigms, which are more commonly used clinically, utilize consistent and repeated blocks of stimuli (active task) and rest (control task), often of the same duration.

In the event-related paradigm design single events are used as stimuli instead of epochs of consecutively administered multiple stimuli. Each trial is considered separately as being time locked to the beginning of the stimulus, and signal changes are explored in relation to the onset of the event generated by the trial.

Block design paradigms provide higher sensitivity for detection of statistically significant signal changes between the control and active conditions as well as allow for better patient compliance, and for these reasons are generally preferred for clinical fMRI studies[4].

Introduced in the early nineties by Ogawa *et al*[5], BOLD fMRI has become an extensively used imaging technique in the neuroscience community.

BOLD fMRI has been applied to the study of a broad spectrum of brain functions from simple motor and visual activities to complex language, memory and emotion and even higher-level reasoning tasks such as abstract mathematical reasoning[6].

In the last decade it has made the transition from a purely research imaging technique to a viable clinical technique used primarily for presurgical planning in patients with brain tumors and other resectable brain lesions.

CLINICAL FMRI FOR PRESURGICAL PLANNING

The goal of surgical treatment of brain lesions is the maximization of lesion resection with simultaneous minimization of damage to eloquent surrounding normal brain tissue in order to minimize the risk of postoperative neurological deficits[7,8]. Several studies have demonstrated that patient survival and quality of life improve with the extent of resection, provided that there is an absence of surgically-induced permanent neurologic deficits[9]. For this reason it is of paramount importance to identify the eloquent cortical areas within the lesions or in close spatial proximity to its borders that are at risk of being damaged during surgery, as well as to avoid the interruption of "eloquent" white matter fiber tracts that can also lead to loss of neurological function. These areas are usually identified using more invasive brain mapping techniques, such as the gold standard ECS (intraoperative electrocortical stimulation mapping) for localization of critical functional areas during awake or asleep craniotomy, the implantation of a subdural grid for brain mapping using electrocorticography[10], the recording of intraoperative somatosensory or motor evoked potentials. The somewhat less invasive Wada test used for the identification of the dominant language hemisphere (but not eloquent cortical localization) is also not without risks. In contrast, BOLD fMRI is performed preoperatively, is completely non-invasive and safe, allows for whole brain mapping and in conjunction with high resolution MR structural images can depict with accuracy the spatial relationship between the margin of a lesion and functionally viable brain tissue.

BOLD fMRI for presurgical planning provides the neurosurgeon with a valuable tool because it allows for accurate assessment of risk of postoperative motor, cognitive (including language), visual and somatosensory deficits, which is very useful for both surgical decision-making with respect to extent of resection and informed discussions with patients regarding risks and benefits of surgical resection[11]. Furthermore, in cases for which a decision in favor of resection has been made, BOLD fMRI can determine the safest surgical trajectory to the lesion.

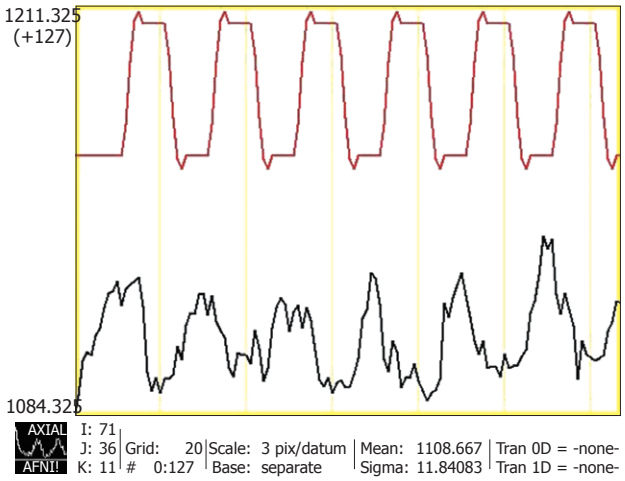

Figure 1 Magnetic resonance signal time series (black line) in an activated voxel. Subject was engaged in a language phonemic task over a time period of 260 s. The red line curve represents the ideal hemodynamic response function the voxel time series was fitted to. Very good correlation between the two curves can be easily seen. AFNI software (afni.nimh.nih.gov) was used for data processing.

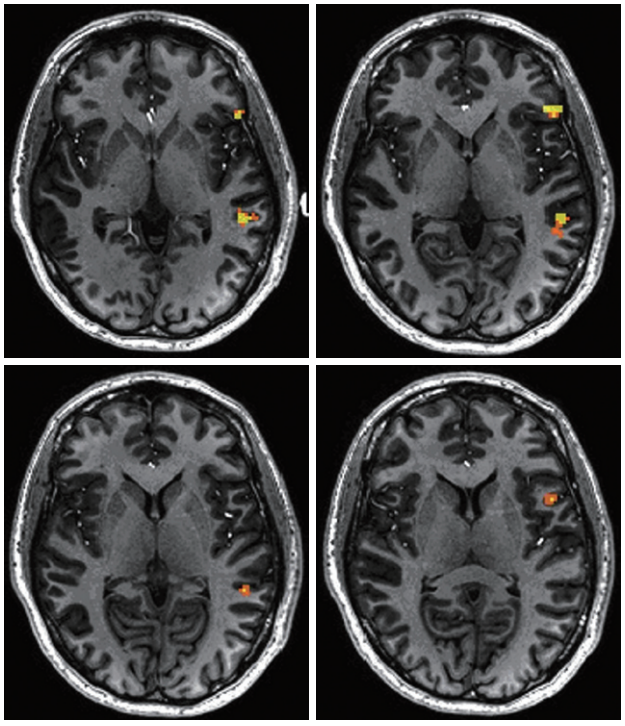

Figure 2 Activation (colored voxels) in the Broca's and Wernicke's areas in a normal subject performing a phonemic fluency task. The t-score map was thresholded at 4.0 value ($P < 0.001$) and superimposed on a high resolution T1 weighted MPRAGE image. AFNI software (afni.nimh.nih.gov) was used for data processing.

Preoperative fMRI activation maps can guide the intraoperative cortical stimulation (ICS) mapping, reducing the total surgical time and associated risk of morbidity related to invasive mapping as reported in the literature[12,13].

Performance of clinical fMRI studies in patients suffering from brain tumors or other resectable brain structural lesions, who are often neurologically impaired,

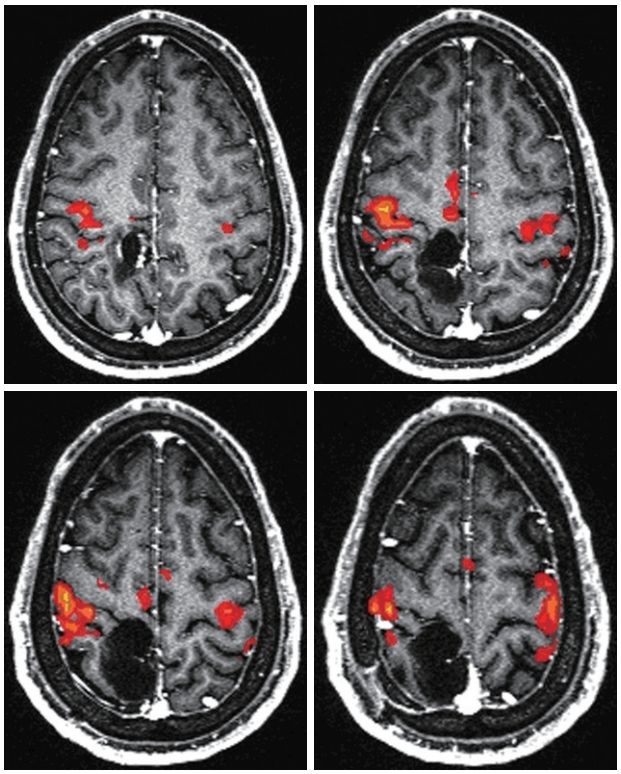

Figure 3 Hand Motor mapping in a patient with a lesion located in the right perirolandic region. Images were acquired on a 3 T magnetic resonance imaging scanner. AFNI software (afni.nimh.nih.gov) was used for data processing.

requires special considerations with respect to patient preparation, neurobehavioral evaluation and paradigm selection, which would not be necessary in normal volunteer research fMRI studies.

The choice of paradigms depends mainly on the location of the lesion and the patient's ability to adequately perform individual tasks[14]. For example if a brain tumor is adjacent to the inferior frontal gyrus, one or more expressive language tasks should be performed by the patient in order to determine the proximity of functional Broca's area to the lesion. Similarly, if the lesion is perirolandic in location, tasks that are known to reproducibly activate the primary motor cortex (PMC) should be used (Figure 3). In both cases, the exact task (s) chosen will depend on the patient's ability to adequately perform each of a battery of available tasks in each category, as assessed during a prescan training session.

A combination of neuroradiologist review of available prior structural brain MR imaging studies and prescan interview by a neuroradiologist or other physician (through which medical/neurological history is obtained and gross functional deficits are determined) determines the battery of likely useful BOLD fMRI paradigms for a particular patient. Once this battery has been selected, it is necessary to perform a prescan training session in which the patient is instructed regarding each task and asked to practice each task to objectively assess performance capability and assess for subtle cognitive or sensorimotor deficits that might impair task performance.

Currently, clinical BOLD fMRI for presurgical plan-

ning is used to map the motor, language and the visual eloquent cortex utilizing a variety of well-documented paradigms from the fMRI literature and multicenter clinical experience that have demonstrated consistent efficacy in mapping eloquent cortex[15]. Below a brief description of the most commonly used paradigms for presurgical mapping by fMRI is reported.

SENSORIMOTOR PARADIGMS

Paradigms to map the sensorimotor areas have been used since the first days of clinical fMRI. Most patients are able to perform these tasks, and these tasks do not require special equipment. These paradigms are used during a clinical fMRI exam when brain lesions are in proximity to the PMC. They are usually implemented with a simple block design in which blocks of complete absence of any body movement alternate with blocks of continuous movement of the specific part of the body whose cortical representation area needs to be determined. A unilateral or bilateral finger tapping task is most often used for the localization of the PMC because the hand representation area comprises a large portion of the motor homunculus and yields a robust BOLD signal[16]. These paradigms also yield robust activation of the supplementary motor area (SMA) and the premotor cortex. A hand grasp task can also be run for the same purpose. Furthermore, if the lesion is anatomically located more superomedially along the PMC in a parasagittal or midline convexity location, a toe or ankle movement task is needed in order to determine the foot representation area of the PMC[17], whereas if the lesion extends more inferiorly, involving the frontal opercular region, a tongue or lip movement task can be performed to localize the face representation area of the PMC. It is worth mentioning that these motor paradigms also elicit activation in the ipsilateral cerebellar hemisphere.

LANGUAGE PARADIGMS

The main goals of language presurgical mapping by fMRI are to provide the neurosurgeon with information about cerebral hemispheric language lateralization as well as precise localization of critical eloquent language cortex with respect to the margins of potentially resectable brain lesions. A large number of effective research-level language activation paradigms have been reported in the literature, and given the variety of approaches used for fMRI language mapping across different institutions, there still remains a need for standardization for clinical use[18]. However, we will describe in this article a series of paradigms that have been frequently used in the clinical setting.

Phonemic verbal fluency or phonological tasks are administered mainly with the purpose of localizing Broca's area in the frontal lobe which is responsible for speech production. Silent Word Generation or Verb Generation are two tasks well documented in the clinical fMRI literature that activate expected expressive language cortex including the dorso-lateral prefrontal cortex, inferior frontal gyrus, variably cingulate language regions, SMA, premotor and motor regions[19]. In performing these tasks patients are asked to produce nouns or verbs associated, respectively, with a presented letter or noun. Control tasks for these paradigms usually consist of simple fixation. The Rhyming paradigm is an interesting example of a dual choice phonological processing task[20]. During the active block of this task, pairs of words are displayed visually and patients are required to press a button on a response pad if the words rhyme, whereas during the control block two rows of stick figures are shown and patients are required to press the button if the two rows match. The verbal fluency and rhyming tasks have also been demonstrated to effectively lateralize hemispheric language function[21,22].

Another expressive task often used both for presurgical fMRI and intraoperative mapping is object naming, which requires the patient to name presented pictures in blocks alternating with periods of fixation. This task is a poor lateralizing task because of its tendency to activate nonessential as well as essential eloquent cortex, often in a bihemispheric pattern representative of the global language network.

Receptive paradigms are useful to localize Wernicke's area (posterior aspect of the superior temporal gyrus) and other eloquent cortical areas in the dominant temporal-parietal region such as supramarginal gyrus, angular gyrus, inferior temporal gyrus and middle temporal gyrus. These paradigms generally include language comprehension tasks such as sentence reading or listening comprehension and can be designed to be forced choice paradigms in which patient performance can be monitored using recordings of button presses on a response keypad. Another very useful receptive language task is a passive story listening task, in which patients are asked simply to passively listen to blocks of garbled speech alternating with blocks of meaningful stories[23].

Semantic paradigms constitute another category of language tasks. They are designed to be useful for language lateralization and localization of inferior frontal as well as temporoparietal language areas in the dominant cerebral hemisphere. Typical semantic paradigms require the association between a noun and a category (e.g. dog-animal) or a noun and a verb (e.g. dog-bark)[20]. These paradigms are also designed to be forced choice in order to monitor patients response. During the control block, patients are engaged in dual choice tasks not involving language processing.

VISUAL PARADIGMS

The most efficient and complete method to map the visual cortex is to use expanding (or contracting) checkered rings to activate retinal locations at successively greater eccentricities and to use a rotating checkered wedge or hemifield to map successive angular positions[24].

In doing so, each quadrant of the visual field can be identified and the central vision can be distinguished

from the peripheral vision, the latter being essential for reading.

Neurons responding preferentially to visual stimulation at different locations in the visual field are activated at different times during each of the stimulus sequences. Activation maps can be displayed color coding the delay in activation relative to each quadrant of the visual field and/or the relative eccentricities. Many other visual stimulation tasks can be used to simply activate the primary visual cortex without providing sensitive retinotopic mapping; most of these tasks incorporate some kind of flashing checkerboard-type stimulus.

CLINICAL VALIDATION AND SURGICAL IMPACT

The early era of clinical functional imaging validation studies were conducted comparing the results of preoperative fMRI with those obtained using intraoperative 'gold standard' brain mapping techniques. Excellent concordance has been reported between the pattern of activation revealed by fMRI and ICS mapping for motor mapping[25-30]. A high degree (between 80% and 100% in most series) of concordance between these two techniques has also been found for language mapping[31-33]. For example, a recent study by Bizzi and colleagues found 83% sensitivity and 82% specificity for BOLD imaging localization when compared to ICS[34]. Moreover, several studies have demonstrated the effectiveness of fMRI for determining language lateralization because of the agreement (90%-100% in most series) between the results of fMRI and the Wada test or neuropsychological testing[31].

BOLD fMRI can have a remarkable impact on surgical management of brain tumor patients. Petrella and colleagues demonstrated how the results of presurgical fMRI altered the surgical treatment plan in 19 out of 39 patients ($P < 0.05$), allowing in most cases a more aggressive approach than that which would have been taken without access to the results of fMRI, and surgical time was also reduced in the majority of cases[12]. A similar study by Medina *et al*[13] suggested an impact of preoperative fMRI on not just the overall surgical plan but specifically the intraoperative mapping plan in 52% of cases. fMRI also eliminated the need for performance of further preoperative diagnostic studies, including the Wada test. In another study the positive impact of fMRI on patient outcome was demonstrated in a group of 22 patients who underwent preoperative motor fMRI; only 6 experienced mild postoperative neurological deficits but they all fully recovered within 3 mo[35].

BOLD fMRI offers several advantages compared to ICS. However, these two techniques play a complementary role because of their different nature and the respective limitations. BOLD fMRI is a positive activation technique, whereas ICS allows more specific detection of only critical, but not nonessential participatory, eloquent cortical regions by inducing the arrest or disruption of normal function. Thus, fMRI is more capable of depicting the global language network at the expense of producing 'false positives' with respect to essential eloquent cortical mapping when compared to ICS, which only indicates such essential functional cortex[36].

LIMITATIONS OF BOLD FMRI AND ROLE OF BOLD CEREBROVASCULAR REACTIVITY MAPPING

The significance of neurovascular uncoupling

Activation maps obtained by BOLD fMRI are based on the coupling between neuronal firing and hemodynamic changes such as increased blood flow, blood volume and oxygenation occuring in the vasculature adjacent to activation areas. However, in many brain diseases the neurovascular coupling has been reported to be altered. Examples include, but are not limited to carotid occlusion, transient global ischemia, penumbra of cerebral ischemia, subarachnoid hemorrhage, epilepsy and Alzheimer's disease (AD)[37-42]. In brain tumors this relation is often severely altered because it has been demonstrated both in angiographic as well as in MRI studies that tumor vasculature responds much less vigorously to physiological stimuli than vessels in normal cerebral cortex[43-45]. The inability of such aberrant microvasculature to display a normal BOLD response to neural stimulation is referred to as neurovascular uncoupling (NVU). Hence, in the setting of NVU, false negatives can be seen on activation maps, thus limiting the ability of fMRI to adequately define areas of eloquent cortex in the vicinity of or actually within a lesion where loss of normal cerebrovascular autoregulation occurs. It is not uncommon to observe eloquent cortex in regions of impaired cerebrovascular reactivity (CVR), and multiple published studies have reported unreliable results of presurgical mapping, both in terms of reduced activation measured in the hemisphere ipsilateral to the tumor and in terms of incorrect assessment of language dominance, which can be attributed to NVU[45-47]. Decreased BOLD fMRI activation volumes in the tumor ipsilateral hemisphere have also been shown to correlate with increased rCBV in patients with high grade gliomas demonstrating the loss of autoregulatory capability in tumor neovasculature[48]. This is a critical issue in presurgical mapping using BOLD fMRI, since false negative activation may result in inadvertent surgical resection of functional cortex, with resultant permanent postoperative neurological deficits. Since the aim of neurosurgical intervention is the maximization of resection of diseased (e.g. tumor or epileptogenic zone) brain tissue with simultaneous maximal preservation of eloquent cortex, surgical decision-making based on preoperative fMRI activation maps relies heavily on the absence of false negative activation. NVU potential must, therefore, be adequately assessed in order to provide accurate activation maps for surgical planning purposes.

CVR mapping

Since the relaxation of arterial smooth muscle, which

strongly depends on the blood CO_2 partial pressure (PCO_2), is thought to be responsible for maintaining the blood flow in the microcirculation distal to large feeding vessels, the cerebrovascular autoregulation can be investigated by manipulating the PCO_2 level in the blood. The CVR is then defined as the change in blood flow per unit change in PCO_2.

CVR can be measured by different imaging modalities, including Transcranial Doppler, Single Photon Emission Computed Tomography, Positron Emission Tomography and MRI. Early imaging-based measurements of CVR detected the magnitude of blood flow change in response to the administration of a contrast agent[49-51].

However, MRI has become the preferred choice because of its noninvasiveness and good spatial resolution. Furthermore, qualitative and quantitative CVR measurements can be obtained by using BOLD MR sequences identical to the ones used in functional MRI that do not require use of exogenous contrast agents.

As mentioned in the introduction of this review, the BOLD contrast arises from the decrease of deoxyhemoglobin (dHb) resulting from neuronal activation. Since increases in PCO_2 cause dilation of cerebral blood vessels without increasing the metabolic rate of brain parenchyma, and changes the dHb concentration in the cerebral vasculature, BOLD MR imaging can be used to test vascular reactivity following a hypercapnia challenge[52].

Hypercapnia can be induced by various approaches. In general, these methods can be categorized into two types[53-61]: breath-hold (BH), and inhalation of CO_2-manipulated air. For the first category, the subject is instructed *via* visual or auditory cues to hold his breath for a short period (normally 10-20 s), which is interleaved with normal breathing periods for a total paradigm duration of approximately 4-5 min. The best reproducibility has also been reported for a breath hold task of 15-20 s duration compared to longer and shorter periods[62]. Data are pre-processed similar to BOLD functional imaging data, and maps of percentage signal change or cross correlation with an expected hemodynamic response function are provided for assessment of CVR. The typical hemodynamic response used for neuronal activity-based signal change can be used to model BH related signal change; however, a more accurate model has recently been developed accounting for a slower signal change for BOLD-related respiratory response[63]. The hypercapnia condition is established a few seconds into the BH period, and increased BOLD signal can be detected in normal brain regions. After BH, the subject quickly recovers to normocapnia during the normal breathing period. A brief inspiration or expiration is commonly performed before the start of BH. In general, there is no significant advantage found for inspiration or expiration BH techniques[64]. It has been suggested that inspiration BH is preferable for easier patient tolerance and larger BOLD signal change[64]. Nevertheless, at ultra-high field, it is found that altered oxygen concentration in the nasal cavity during end-inspiration may result in artifactual signal changes, which confound the interpretation of the CVR measurement[65]. The main advantage of the BH method is that it does not require sophisticated equipment and can be easily performed during a routine clinical MR imaging session, but the main drawback of this method is the impossibility of quantitation of CVR using this approach.

The second category of methods involves administration of air with altered CO_2 or O_2 levels[55,57,59-61]. The main advantage of this approach is that it allows precise control of the content of inhaled air, and end tidal (ET) CO_2 can be monitored during the experiments, which furnishes a quantitative measure of the induced hypercapnia condition that can enable a quantitative assessment of CVR. In addition, the detected BOLD signal is less likely to be contaminated by BOLD signal changes related to neuronal activation secondary to visual or auditory processing that would typically affect BH-based methods. On the other hand, it normally takes longer to build up a hypercapnia condition that produces sufficient BOLD signal changes with these types of stimuli. The equipment setup time and patient training needed for use of such gas delivery systems could be relatively problematic for routine clinical use, especially with debilitated patients, but a few groups have proposed and built specialized systems for clinical applications[55,57]. These methods typically require the use of a facial mask and the setup of experimental apparatus to control the CO_2 delivery, but it offers the advantage that by continously monitoring the change of ET CO_2 level in the blood, quantitative CVR measurements can be performed[66]. Protocols to detect CVR by a CO_2 inhalation task usually include the administration through a mask of air and a CO_2/air mixture for induction of artificial hypercapnia, with CO_2 concentration varying from 5% to 10%[67-69]. The ET-CO_2 levels are monitored by using infrared devices. The paradigm design for alternate delivery of air and gas mixture is similar to the block design used to study brain activation. Still there is lack of standardization of epoch duration; however, a recent study by Yezhuvath *et al*[57] demonstrated that a paradigm with air breathing for 1 min interleaved with 1 min CO_2 breathing, repeated three times is sensitive enough for CVR measurement because the results were not significantly different from the ones obtained with longer epochs of air and CO_2 breathing. More importantly, a recent study has suggested that inspiration of 4% CO_2, 21% O_2 and balanced N_2 is the preferred method to induce hypercapnia, because BH and inhalation of CO_2/O_2 mixture without N_2 could elicit unwanted metabolic activities in the brain[55].

Following standard BOLD fMRI preprocessing steps and correcting for dephasing between the BOLD signal and the recorded pressure of end-tidal CO_2 (PET-CO_2), signal quantitative CVR maps are computed voxel by voxel by the ratio between MR signal change due to CO_2 inhalation over the related pCO_2 changes and are expressed in units of percentage MR signal change/mmHg CO_2 (Figure 4). The rationale for this definition comes from the proportionality between the BOLD signal and CBF, as well as the definition of CVR as the change in

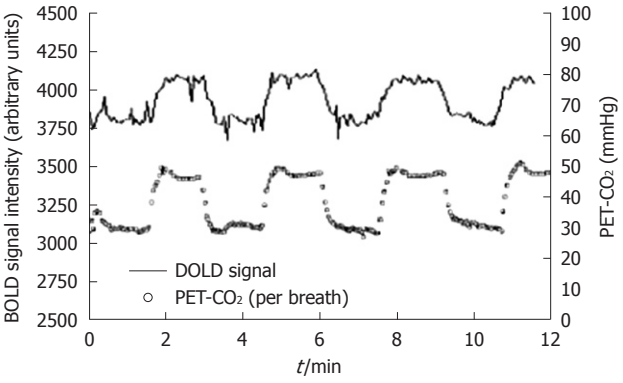

Figure 4 Example of cerebrovascular reactivity measurement using administration of air with altered CO_2 or O_2 levels: after time shifting the Blood Oxygen Level Dependent signal pattern closely follows pressure of end-tidal CO_2 (end tidal pressure of carbon dioxide) pattern (from Vesely *et al*[69]). Blood Oxygen Level Dependent magnetic resonance imaging and pressure of end-tidal CO_2 ($PET\text{-}CO_2$) signals are reported in arbitrary units. BOLD: Blood Oxygen Level Dependent.

CBF per unit change in PCO_2. However, the simple administration through a mask of air and CO_2 is more likely to provide semiquantitative rather than purely quantitative CVR maps. It is, indeed, necessary to control and modify the CO_2 level rapidly and precisely in order to gain the required square wave changes in $PET\text{-}CO_2$, and when patients are simply inhaling CO_2 through a mask they hyperventilate in order to blow off the CO_2. For this reason, long experimental times are also needed to reach a steady $PET\text{-}CO_2$ level before hypercapnia measurements can be effectively performed.

In order to overcome the above-mentioned problems relating to standard, a special device has recently been developed that offers some advantages towards a more accurate measurement of CVR[70]. This device consists of a rebreathing circuit that rapidly changes the PCO_2 between two steady levels keeping constant the ET oxygen levels (ETO_2) during BOLD image acquisition[69]. In this way, a controlled reproducible physiologic stimulus is applied that allows truly quantitative CVR measurement. Experimental applications of this tool have been carried out in patients affected with Moyamoya and stenoocclusive diseases and the results have been validated by comparison with different imaging modalities[55,71,72]. However, to date, no such applications of such a device have been performed in brain tumor patients, and concerns have been raised regarding such patients' ability to tolerate such methods.

CLINICAL EXAMPLE OF NVU DETECTED WITH BH CVR MAPPING

A 39-year-old male with previous surgical resection of a grade II well differentiated diffuse astrocytoma presented with tumor recurrence at the surgical bed. As shown on the axial precontrast T2 FLAIR and postcontrast T1 weighted 3D MPRAGE images, a nonenhancing, FLAIR hyperintense nodular mass is seen along the medial aspect

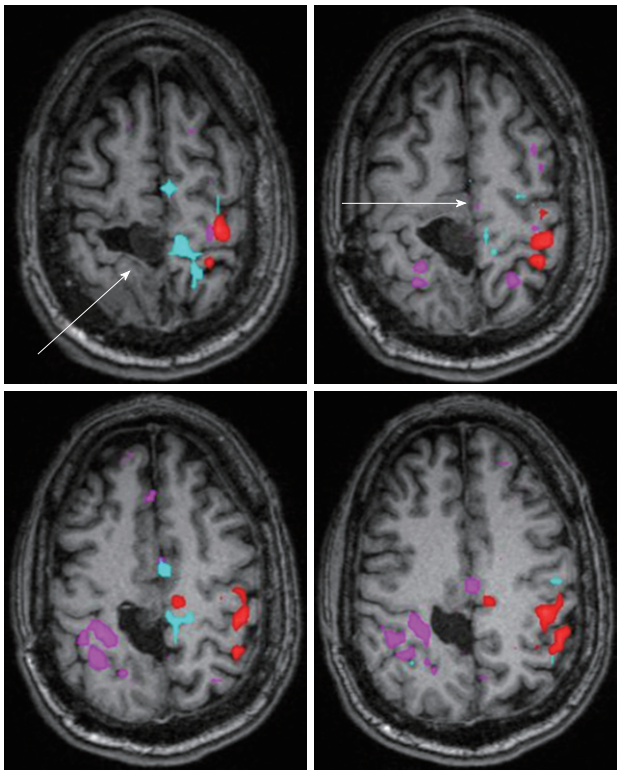

Figure 5 Color coding of Blood Oxygen Level Dependent activation map, overlaid on noncontrast T1-weighted 3D MPRAGE axial images, is as follows: magenta refers to left hand motor task activation (hand opening/closing), thresholded at a T value of 4.6, while red refers to the right hand motor task, thresholded at a T value of 4.5, and cyan/light blue refers to bilateral foot motor task (toe flexion/extension), thresholded at a clustered cross-correlation value of 0.50. Note the striking absence of any activation on the foot motor task in the foot representation area of the right (ipsilesional) primary motor cortex as well as absence of activation in the superior frontal gyrus (supplementary motor area), while the contralateral homologous regions demonstrate expected activation, as seen color-coded in cyan.

of the surgical resection cavity. The patient presented with distal left lower extremity weakness, with specifically left foot weakness with respect to plantar flexion and extension, but did not demonstrate any upper extremity or facial weakness. Presurgical BOLD fMRI demonstrates expected activation in the hand representation area of the PMC, but absent activation is seen in the foot representation area of the PMC more superomedially (Figure 5). The corresponding BH CVR map demonstrates abnormally reduced regional CVR in this area, suggesting NVU and high risk of false negative activation (Figure 6). In this case, susceptibility artifact from the previous surgery is also likely to be at least partially contributory, but NVU likely represents the main reason for false negative activation. Given the presence of intact motor strength in the left lower extremity including some degree of preserved mobility of the foot, this does not represent true negative activation due to complete absence of eloquent cortex and resultant complete loss of function, but rather represents false negative activation; although functional cortex remains, it is impossible to elicit BOLD activation in the foot representation area of the PMC due to NVU. Based on this detection of NVU, a decision was made by the

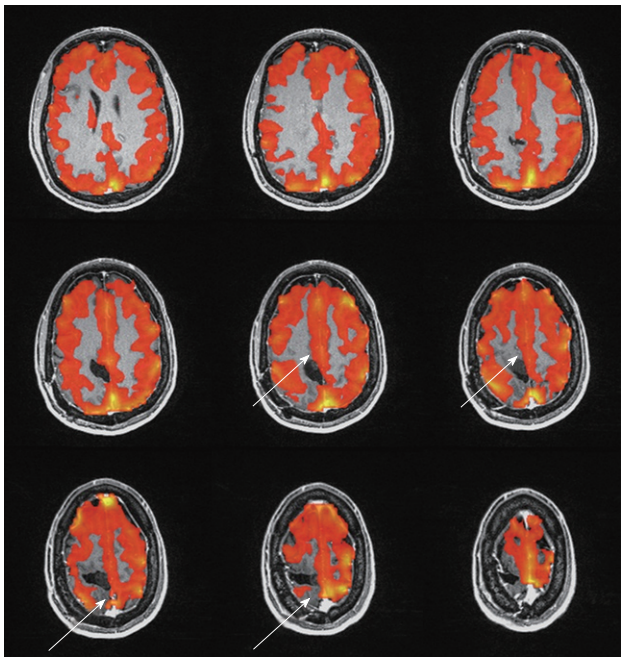

Figure 6 Blood Oxygen Level Dependent breath-hold cerebrovascular reactivity map, overlaid on postcontrast 3D MPRAGE anatomic axial images. The Blood Oxygen Level Dependent cerebrovascular reactivity (CVR) map was thresholded at positive 0.25% signal change. Note the absence of CVR just anterior and posterior to the surgical resection cavity in the right frontal convexity (in the expected location of the foot representation area of the primary motor cortex, as well as decreased CVR along the medial right frontal convexity, corresponding to the supplementary motor area.

neurosurgeon to approach the resection of the recurrent lesion cautiously and to perform intraoperative cortical stimulation mapping for adequate determination of the location of the foot representation area of the PMC. The activation maps were useful, however, to delineate the hand representation area, and this did affect the extent of craniotomy needed for adequate intraoperative mapping.

OTHER CLINICAL APPLICATIONS OF CVR MAPPING

While CVR is considered a sensitive indicator for assessing the brain's ability to dynamically adjust its energy supply, the clinical applications of CVR mapping (aside from presurgical mapping) are yet to reach their full potential, mainly due to technical constraints. In recent years, with the development of various advanced approaches, viable clinical applications of CVR mapping have emerged.

CVR mapping in cerebrovascular disease is emerging as a promising tool for clinicians involved in the evaluation of patients at risk for stroke. A few studies have been reported using hypercapnia induced BOLD MRI signal response to probe CVR in patients with arterial steno-occlusive diseases such as carotid artery stenosis[55,71,72]. For example, a patient with right middle cerebral artery occlusion and Moyamoya phenomenon secondary to aplastic anemia showed paradoxical CVR values in the right middle cerebral artery territory in the cortex[55].

CVR mapping is also a powerful method to detect abnormal neurovascular coupling and physiological effects of pharmacological agents in the brain. For instance, quantitative CVR approaches have been used to monitor CVR changes in the brain from caffeine consumption[73-75]. The coupling ratio between CBF and the cerebral metabolic rate for oxygen was found to be significantly decreased in both visual and motor cortices[73-75].

Another important application of CVR mapping is in the research of aging and neurodegenerative diseases. The blood vessels' ability to dilate, which is reflected by CVR, may be a more sensitive biomarker than resting state perfusion. A recent study has demonstrated that CVR declined with age in a healthy adult cohort[76]. The decrease in CVR was shown to be steeper and spatially more extensive in the brain than resting state perfusion alterations. CVR in a mild AD patient group and age-matched controls has also been assessed[77]. Significant brain CVR deficits were found in early AD subjects. The spatial distribution of CVR reduction was different from that of resting perfusion alterations, but appeared to be consistent with *in vivo* amyloid mapping findings. The magnitude of CVR reduction correlated well with the volume of leukoaraiosis.

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CASE REPORT

An oral fluoropyrimidine agent S-1 induced interstitial lung disease: A case report

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Abstract

A 66-year-old Japanese man with pancreatic cancer received eleven courses of gemcitabine monotherapy. The tumor responded to gemcitabine until metastatic liver tumors progressed. Subsequently, he was treated with S-1, an oral fluoropyrimidine anticancer agent, as salvage chemotherapy. Forty-two days after initiating S-1, he presented with dyspnea and fever. Chest computed tomography showed diffuse interstitial lesions with thickening of the alveolar septa and ground glass opacity. Serum KL-6 level was elevated to 1,230 U/mL and he did not use any other drugs except insulin. Thus, the development of interstitial lung disease (ILD) was considered to be due to S-1. Arterial blood oxygen pressure was 49.6 Torr in spite of oxygen administration (5 L/min). Steroid therapy improved his symptoms and the interstitial shadows on chest radiograph. Although S-1-induced ILD has mostly been reported to be mild, clinicians should be aware that S-1 has the potential to cause fatal ILD.

Key words: Corticosteroid therapy; Interstitial lung disease; Pancreatic cancer; S-1

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INTRODUCTION

Most anti-neoplastic drugs have the potential to induce pulmonary toxicity, involving lung parenchyma, airways, pleura, and the pulmonary circulation. The mainstay of treatment of drug-induced pneumonia is to identify and eliminate the causative agent as soon as possible. Gemcitabine, a key drug for treating pancreatic cancer (PC)[1],

frequently induces interstitial lung disease (ILD). S-1, an oral fluoropyrimidine agent which can inhibit cell growth and induce apoptosis, was reported to be active against various malignancies in East Asian countries. Because S-1 is active against gemcitabine refractory PC, as well as chemotherapy naive PC, the quantity of S-1 consumed increases every year. However, only a few case reports have warned that S-1 may induce ILD during the treatment of a variety of malignancies including PC. Here, we report a case of S-1-induced ILD and a review of the literature.

CASE REPORT

A 66-year-old Japanese man with a history of smoking 2 packs of cigarettes per day for 45 years was admitted to our hospital because of back pain and appetite loss over the previous 2 mo. He had diabetes mellitus and had been treated with insulin self-injection for 10 years. Computed tomography (CT) scan revealed a mass in the pancreatic tail. He was diagnosed with PC (cT2, cN0, cM0) and underwent curative distal pancreatectomy (pT2, pN0, pM0). Nine months after resection, an abdominal CT scan revealed tumor recurrence with multiple liver metastases. He received eleven courses of gemcitabine (GEM) monotherapy (1000 mg/m^2 on days 1, 8, and 15, every 4 wk) as first-line chemotherapy and obtained a partial response. Chest CT scan at the time of recurrence showed emphysematous lungs without ILD. After the eleventh course, abdominal CT scan revealed the progression of metastatic liver tumors. Therefore, we decided to replace GEM with S-1 (80 mg/m^2 per day, administered for 4 wk with 2 wk rest). Forty-two days after initiation of S-1, he experienced dyspnea on exertion and high fever (39.0℃) He was hospitalized due to hypoxemia (49.6 Torr) in spite of oxygen administration (5 L/min). Physical examination revealed no abnormalities except for bilateral fine crackles on auscultation. Laboratory data showed increased leukocyte counts: 20.1 × 10^9/L with mild eosinophilia (6.5%) and monocytosis (13%) which were not observed during treatment with GEM; elevated levels of lactate dehydrogenase (569 U/L), C-reactive protein (9.0 mg/mL) and KL-6 (1230 U/mL). Chest radiograph showed reticular and dense infiltrative shadows on both lung fields (Figure 1A), and chest CT scan revealed diffuse interstitial lesions with thickening of the alveolar septa and ground glass opacity, predominantly in subpleural lesions without findings of lung volume loss (Figure 1B and C). Sputum culture for bacteria and fungus was unremarkable. Tests for polymerase chain reaction of *Pneumocystis jiroveci* DNA in sputum, cytomegalovirus antigen and *Mycoplasma pneumoniae* antibodies were all negative. The patient received only two drugs, S-1 and insulin, which he had been receiving for 10 years. Thus, we diagnosed S-1-induced ILD in this patient. S-1 was immediately discontinued and high-dose methylprednisolone (500 mg/d, intravenously for 3 consecutive days) followed by oral prednisone (1 mg/kg per day) was administered. Two days after initiating steroid therapy, his symptoms improved considerably. The interstitial shadows on chest radiograph and CT scan were substantially resolved 16 d after starting steroid therapy (Figure 2A and B).

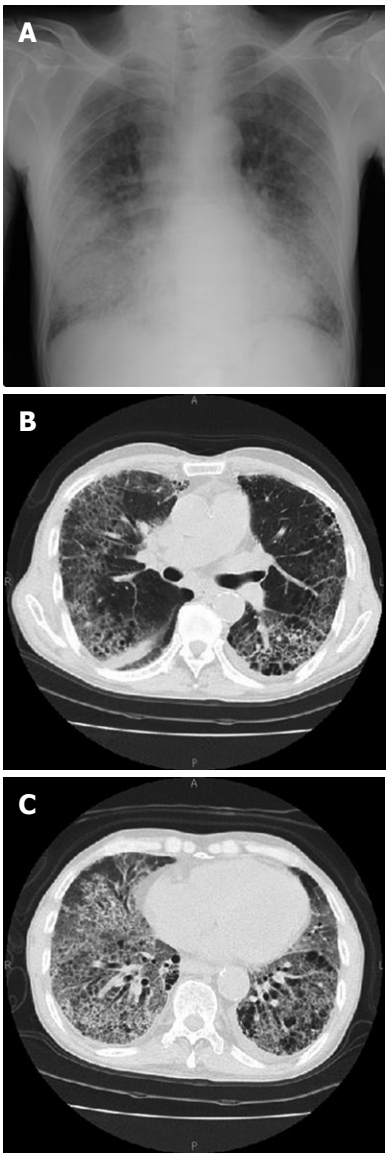

Figure 1 Chest radiograph and computed tomography findings on admission. Chest radiograph (A) showed bilateral interstitial shadows mainly in the middle to lower lung field on both sides. Chest computed tomography (B, C) revealed diffuse interstitial lesions with thickening of the alveolar septa, bilateral airspace consolidation, and ground glass opacity.

However, his general condition gradually worsened due to tumor progression and he died of hepatic failure 45 d after hospitalization.

DISCUSSION

PC is responsible for approximately 5% of all cancer-related deaths and is the eighth most common cause of cancer-related death in both genders worldwide[2]. In a palliative setting, GEM has been the standard treatment for advanced PC because it was shown, a decade ago, to result in superior beneficial responses and survival

Table 1 Reported severe cases of S-1 induced interstitial lung disease

Ref.	Age (yr)/sex	Disease	Regimen	The latency from the 1st use (d)	Outcome
Kurakawa *et al*[8]	70/M	Gastric	S-1 single	36	Good/recovery
Shitara *et al*[9]	37/F	Gastric	S-1 single	150	Poor/dead
Tada *et al*[10]	72/M	Tongue	S-1 single	18	Good/recovery
Nohara *et al*[11]	75/M	Colon	CDDP + S-1	360	Good/recovery
Yamamoto *et al*[12]	80/M	Gastric	S-1 single	22	Good/recovery
Ueyama *et al*[13]	80/F	Breast	S-1 single	5	Good/recovery
Present case	66/M	Pancreas	S-1 single	45	Good/recovery

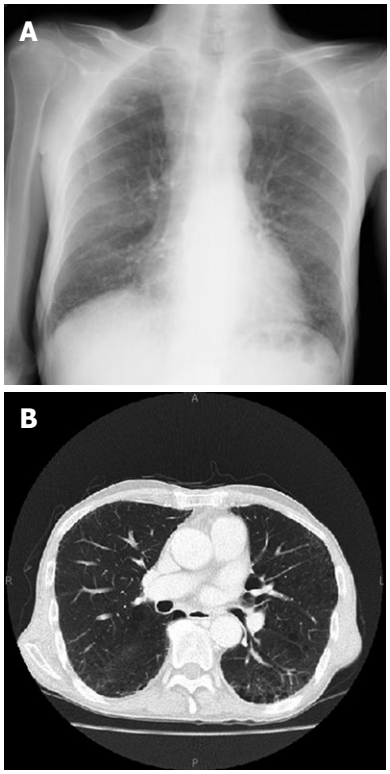

Figure 2 Chest radiograph and computed tomography findings 16 d after initiating steroid therapy. Chest radiograph (A) and computed tomography (B) findings were substantially improved 16 d after initiating steroid pulse therapy.

compared with bolus 5-fluorouracil[1]. In Japan, several retrospective studies[3-5] clearly demonstrated the efficacy and impact of S-1 as second-line chemotherapy for advanced PC following GEM failure. The methodology of single-agent systemic chemotherapy, i.e. GEM as first-line treatment followed by S-1, should be regarded as the established treatment for inoperable, advanced PC in Japan as well as other East Asian countries[4]. ILD is the most common GEM-induced lung injury, and various GEM-induced pulmonary toxicities have been reported in cancer chemotherapy. Roychowdhury *et al*[6] reported that the incidence of dyspnea and that of other serious GEM-induced pulmonary toxicities was 0.45% and 0.27%, respectively. S-1 is an orally administered anti-neoplastic agent composed of tegafur, 5-C-2,4-dihydroxypyridine, and potassium oxonate. Tegafur is a 5-fluorouracil prodrug which has been a key drug in the treatment of gastrointestinal cancers in Japan and other East Asian countries[7]. The other two components are combined to enhance anti-tumor cytotoxicity and suppress adverse events of the gastrointestinal tract. Pulmonary toxicity due to S-1 has rarely been reported. Case reports of severe ILD[8-13] are summarized in Table 1. Only one of 7 cases including the present study resulted in a fatal outcome due to ILD (9). The patient was a 37-year-old female with advanced gastric cancer with disseminated intravascular coagulation at the time of treatment initiation. S-1-induced ILD seemed to occur relatively early (5 to 45 d) after initiation of treatment with the exception of two cases, who developed ILD 150 d and 360 d after treatment with S-1.

Camus *et al*[14] reviewed drug-induced ILD and insisted that acute and chronic eosinophilic pneumonia (EP) were well known manifestations. EP is most commonly observed in association with methotrexate, sulfasalazine, para-aminosalicylic acid, nitrofurantoin, or nonsteroidal anti-inflammatory drugs. EP is histologically characterized by the accumulation of eosinophils in the alveolar airspaces, with infiltration of the adjacent interstitial space by eosinophils and variable numbers of lymphocytes and plasma cells. Chest radiography and high resolution CT demonstrate bilateral airspace consolidation, which mainly involves peripheral lung regions. In our patient, mild eosinophilia and bilateral air space consolidation were observed, and a good clinical outcome was achieved leading us to conclude that our case was consistent with EP as the type of ILD. From radiological findings, diffuse alveolar damage (DAD) seemed to be one of the differential diagnoses. Unfortunately, since we could not perform BFE, no definitive supporting evidence for EP or DAD could be obtained. For S-1-induced ILD, steroid therapy was an effective treatment worth trying.

Other cytotoxic fluoropyrimidines such as 5-fluorouracil and Uracil/Tegafur have been reported to cause mortality due to lung injury[15,16]. To best of our knowledge, PC cases with S-1-induced ILD have not been reported elsewhere in the English literature.

As the use of S-1 becomes more common, especially in the field of PC chemotherapy for East Asian patients, the incidence of S-1-pulmonary toxicity may increase proportionally.

In conclusion, all clinicians should be aware that S-1 may cause ILD and fatal outcome.

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Events Calendar 2011

January 13-14, 2011
3rd Breast-Gynecology International Cancer Conference BGICC, Cairo, Egypt

January 15-16, 2011
Melanoma 2011: 21st Annual Cutaneous Malignancy Update, San Diego, CA, United States

January 15, 2011
Current Trends in Breast Cancer: Updates From the 2010 San Antonio Breast Cancer Symposium, Dallas, TX, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011, San Francisco, CA, United States

January 21-23, 2011
8th Meeting of the EAU Section of Oncological Urology, London, England, United Kingdom

January 27-28, 2011
2nd National Conference: Recent Advances in Renal and Bladder Cancer, London, United Kingdom

January 27-28, 2011
8th Annual Cancer Drugs Research & Development, San Diego, CA, United States

February 10-12, 2011
17th Annual NOCR Meeting, Las Vegas, NV, United States

February 19-22, 2011
Scripps Cancer Center's 31st Annual Conference: Clinical Hematology and Oncology, San Diego, CA, United States

February 24-26, 2011
European Multidisciplinary Conference in Thoracic Oncology (Lung 2011-EMCTO), Lugano, Switzerland

February 25-27, 2011
7th European Congress on Hematologic Malignancies: From Clinical Science to Clinical Practice, Budapest, Hungary

March 02-05, 2011
64th Society of Surgical Oncology Annual Cancer Symposium 2011, San Antonio, TX, United States

March 04-06, 2011
8th Annual Oncology Nursing Advanced Practice: Innovation through Practice, San Diego, CA, United States

March 07-09, 2011
9th International Symposium on Targeted Anticancer Therapies, Paris, France

March 09-13, 2011
16th National Comprehensive Cancer Network Annual Conference (NCCN 2011), Hollywood, FL, United States

March 11-12, 2011
12th European Congress: Perspectives in Lung Cancer, Torino, Italy

March 14-18, 2011
Oncology Imaging Update in Costa Rica, Guanacaste, Costa Rica

March 17-19, 2011
International Cancer Prevention Update Symposium, New York, United States

March 18-22, 2011
Vienna, Austria 26th Annual EAU Congress

April 02-06, 2011
AACR 102nd Annual Meeting, Orlando, FL, United States

April 08-10, 2011
Asian Oncology Summit 2011, Hong Kong, China

April 20-23, 2011
9th International Gastric Cancer Congress, Seoul, South Korea

April 29-30, 2011
Cancer Survivorship Conference, Minneapolis, MN, United States

May 23-24, 2011
4th International Conference on Ovarian Cancer Screening, London, United Kingdom

June 03-07, 2011
47th American Society of Clinical Oncology Annual Meeting, Chicago, IL, United States

June 20-23, 2011
7th EADO Congress European Association of Dermato-Oncology, Nantes, France

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer, Barcelona, Spain

June 23-25, 2011
"MASCC/ISOO 2011 International Symposium, Athens, Greece

July 03-07, 2011
14th World Conference on Lung Cancer, Amsterdam, Netherlands

July 14-17, 2011
3rd World Congress of the International Academy of Oral Oncology 2011, Singapore, Singapore

August 15-17, 2011
International Conference and Exhibition on Cancer Science & Therapy, Las Vegas, Nevada, United States

September 1-3, 2011
Tri-Society Head and Neck Oncology, Singapore, Singapore

September 7-10, 2011
Hallmarks and Horizons of Cancer, Lausanne, Switzerland

September 23-27, 2011
Joint 16th ECCO and 36th ESMO Multidisciplinary Cancer Congress, Stockholm, Sweden

October 06-07, 2011
Current Status and Future of Anti-Cancer Targeted Therapies, Buenos Aires, Argentina

November 30-December 03, 2011
AORTIC 2011-Entering the 21st Century for Cancer Control in Africa, Cairo, Egypt

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INSTRUCTIONS TO AUTHORS

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2218-4333/g_info_20100723153305.htm.

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Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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