Somatostatin Receptor Scintigraphy of Malignant Lymphoma — Current Status

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Somatostatin receptors have been demonstrated on normal as well as activated human lymphocytes in the circulation and within the reticuloendothelial system such as Peyer's patches and the spleen [1]. Also, lymphocyte function such as proliferation and immunoglobulin synthesis has been showed to be affected by somatostatin [2].

Following the demonstration of the presence of high-density somatostatin receptors in a variety of neuroendocrine derived tumors [3], Reubi et al. subsequently reported visualizing non-Hodgkins lymphoma in four patients imaged with Indium-[111]-[DTPA-D-Phe1]-Octreotide, an analogue of somatostatin [4]. Autoradiography utilizing [125I]-[Tyr3]-Octreotide was used to demonstrate the diffuse distribution of somatostatin receptors in tissue samples of biopsies taken of the involved sites. They suggested that somatostatin receptors could be used as valuable pathobiochemical tissue markers and potentially useful as an in vivo diagnostic tool for human malignant lymphomas. In ten patients studied with malignant lymphoma (Hodgkins disease and non-Hodgkins lymphomas), lymphoma deposits could be demonstrated [5]. In four patients, additional tumor localizations were observed as compared to the results of combined physical and radiological (CT and ultrasound) examinations.

The role of somatostatin receptor scintigraphy (SSR) continued to be studied by the Rotterdam group. Forty previously untreated patients with histologically proven Hodgkins disease and 61 untreated patients with non-Hodgkins lymphoma were consecutively studied [6]. The results of the conventional staging methods were compared to Octreotide scintigraphy in 40 patients with proven Hodgkins disease. In 17 patients, Octreotide scintigraphy was in agreement, in 18 patients it was superior, and in five patients, it was inferior when compared to conventional staging methods. In seven patients, the clinical stage was altered because of Octreotide scintigraphy, raising it in six and lowering it in one. In the non-Hodgkins lymphoma group, 87 percent (53 of 61 patients) had positive scan findings, and in 31 patients, there was agreement. In 17 patients, additional lesions were revealed in Octreotide scintigraphy, which were not demonstrated by conventional staging methods. In five patients, lesions were missed. In 13 of the 61 patients, the Octreotide scintigraphy upgraded the stage of the disease.

The group published some of their results of 56 consecutive untreated patients with histologically-proven Hodgkin's disease and compared the results of SSR with physical and radiological examinations as initial evaluation [8].

Somatostatin receptor scintigraphy was positive in 55/56 (95 percent) of patients at sites of documented disease. In 20 patients, SSR disclosed lymphoma localizations not

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b Abbreviations: SSR, somatostatin based scintigraphy.
revealed by conventional staging. As a result, in 12 patients (21 percent) scintigraphy produced a change of stage, and in seven patients (13 percent), the additional information obtained led to a change of treatment.

A further prospective blinded study was reported more recently by the same group comparing SSR to conventional staging methods [7]. Ninety consecutively previously untreated non-Hodgkins lymphoma (26 low grade, 40 intermediate grade, 21 high grade and three unclassified) underwent scintigraphy. The patient-based analysis revealed an overall sensitivity of 80 percent (72/90). Somatostatin receptor scintigraphy was superior to conventional staging methods in 17 patients (19 percent). In 10 patients (11 percent), the clinical stage was altered. In 14 patients (16 percent), some lesions were not detected. Total agreement between conventional staging and scintigraphy was seen in 38 patients (42 percent). On a lesion-based analysis, overall sensitivity was 66 percent (175/264). Sensitivity was 72 percent (122/169), supradiaphragmatic, and 52 percent (44/85), infra-diaphragmatic. Scintigraphy visualized 22 previously unknown lesions.

Wiseman et al., in a group of 10 patients studied with Indium-111-Pentetreotide, found there was agreement in the staging with conventional methods in seven of the 10 patients, and staging was correctly upgraded in two patients [8]. Twenty-three of 30 sites identified by CT were identified with SSR.

Stoffel et al. performed 22 studies in 17 patients, four with Hodgkins and 13 with lymphoma [9]. On a lesion basis, a sensitivity of 100 percent was found for Hodgkins. It was 64 percent, 80 percent and 78 percent in low, intermediate and high grade lymphomas, respectively.

Although the above-mentioned studies have demonstrated promising results, this has not been universal in the experience of other investigators.

Somatostatin receptor imaging was found to be less sensitive by Sarda et al. in studying 26 patients [10]. These had histologically-proven Hodgkins in three patients and non-Hodgkins lymphoma in 23 patients. Only 50 of the 86 (58 percent) confirmed extramedullary tumor sites were detected by somatostatin receptor imaging. Twelve previously unknown sites were visualized in seven patients. Tumor uptake indices measured in the lesions were found to be highly variable and could even be normal relative to background. As such, they felt that somatostatin receptor imaging was not reliable for the initial staging but could be useful in the diagnosis of residual disease after treatment.

Forty-one consecutive patients were studied by Lipp et al. [11]. Of the 34 patients with confirmed diagnosis, 11 had Hodgkins disease, and 23 had non-hodgkins disease. The sensitivity for detecting Hodgkins disease was 70 percent. When broken down according to site, this translated to 88 percent detection rate for cervical and chest involvement and 13 percent for sites in the abdomen and pelvis. In non-Hodgkins lymphoma, the sensitivity was low, 35 percent, regardless of the location. For high-grade disease, the sensitivity was 44 percent, and in low-grade disease, 29 percent. They also concluded that Octreotide scintigraphy was better suited to characterize somatostatin expressing lymphomas than to localize lesion sites.

Ivancevic et al., in investigating 35 patients with Hodgkins and non-Hodgkins lymphoma, showed that the patient based analysis revealed an overall sensitivity of 88 percent [12]. However, the results of the lesion-based analysis demonstrated a sensitivity of 57 percent for Hodgkins disease, 43 percent for high-grade lymphomas and 35 percent for the low-grade lymphoma. They postulated that this could be due to low receptor densities or the presence of receptor subtypes for which pentetreotide has low affinities.

Bong et al. evaluated 35 patients who had 49 studies [13]. In the patients with Hodgkins disease, overall sensitivity of 91 percent was reported and with non Hodgkins lymphoma, an overall sensitivity of 37 percent. On a per lesion basis, 22 of 28 lesions were found in the Hodgkins disease and 47 of 128 lesions for a sensitivity of 71 percent.
and 37 percent, respectively. O'Brien similarly reported a low sensitivity for non-Hodgkins lymphoma in studying a limited number of patients [14].

Comparison with other radiopharmaceuticals has been looked at by various groups. Cerulus et al., in comparing Gallium-67 to Indium-111-Octreotide in 12 malignant lymphoma patients studied within two to three weeks of each other with both agents reported an overall sensitivity for Ga-67 of 86 percent as compared to 71 percent for the Indium-111-Octreotide [15]. They felt that both the intensity of uptake and the number was generally lower in the lesions on Octreotide scintigraphy than for the Gallium-67.

Van den Anker-Lugenburg et al. [16], on the other hand, reported a better sensitivity for somatostatin based scintigraphy. On the overall, patient-based analysis, a sensitivity of 88 percent for SSR, compared to 63 percent for Ga-67, and on lesion-based analysis, a sensitivity of 60 percent for SSR, as compared to 40 percent for Ga-67, was found.

Bares et al. reported first results of comparison of SSR with Indium-111-labeled Octreotide and glucose metabolism measured by positron emission tomography in 22 patients with suspected or known malignant lymphoma [17]. Metabolic imaging by positron emission tomography yielded a higher rate of detection of lymphoma manifestations (92 percent versus 64 percent) and better tumor contrast.

Recent studies evaluating a somatostatin analog in the treatment of lympho proliferative disorders were reported by Witzig et al. [18]. They demonstrated that 36 percent (10 of 28 patients with low-grade, non-Hodgkins lymphoma) had partial remission and 44 percent (four of nine patients) of patients with cutaneous T cell non-Hodgkins lymphoma had partial remissions. Since it appears that cold somatostatin at a dose of 150 micrograms every eight hours is well tolerated and has activity in these tumors, an imaging method to recognize and follow these tumors appears to be important.

The clinical impact and cost-effectiveness of SSR in limited Hodgkin's disease was studied in 126 previous untreated patients. Somatostatin receptor scintigraphy was compared to standard staging techniques and divided into two prognostic subsets (favorable and unfavorable prognosis) according to standard prognostic factors (e.g., age, sedimentation rate, sex, B symptoms). In both subsets, SSR disclosed lesions not identified by standard staging techniques.

In 21/37 (57 percent) of patients with favorable prognosis, and in 16/44 (36 percent) of patients with unfavorable prognosis, additional lesions were identified. In 11 percent of favorable prognosis patients, the newly detected lesions were outside the subtotal nodal irradiation field, which is the standard therapy for these patients. The authors concluded that these patients would have been managed differently with this added information, reducing the likelihood of relapse and improving life expectancy.

CONCLUSION

Encouraging reports have appeared from various investigators utilizing somatostatin receptor based imaging. These have, in many instances, shown to be better than conventional staging methods. They appear most useful in areas above the diaphragm. Although other reports showing lower sensitivity and specificity have been reported, the reason for these differences is not clear. Various factors may be contributing to this variability including patient selection, limited sample size, variations in acquisition and processing protocols, different doses of radiopharmaceuticals and different levels of interpretative experience.

Whether or not SSR proves to be useful for the detection and staging of disease in lymphoma will require further studies. The results of a recently completed multicenter trial done in the United States has yet to be published. New information regarding factors
influencing the presence and activity of receptors will enhance our knowledge. Since preliminary results showing partial response rates to cold Octreotide in the low-grade lymphomas have been demonstrated, these techniques will be useful as pathobiobchemical tissue markers to select out patients who may respond to this form of treatment.

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