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Could Melphalan be Useful for Elderly Patients with Myelodysplastic Syndrome or Secondary Acute Myelogenous Leukemia?

ABSTRACT & COMMENTARY

Source: Denzlinger C, et al. *Br J Haematol* 2000;108:93-95.

Myelodysplastic syndrome (mds) and secondary acute myelogenous leukemia (sAML) are diseases with few satisfying treatment options. In this study from Germany, 21 patients with MDS or sAML were treated with oral melphalan 2 mg each day. If progressive disease occurred after four weeks of treatment, patients were taken off study. Melphalan was held in cases of a complete peripheral response, and was restarted upon relapse.

The patients' ages ranged from 59 to 84 years with a median of 71 years. Patients were classified according to the French-American-British (FAB) classification as having the following subtypes: chronic myelomonocytic leukemia (CMML) (n = 1), refractory anemia with excess blasts (RAEB) (n = 8), refractory anemia with excess blasts in transformation (RAEB-t) (n = 5), or sAML (n = 7). A complete peripheral response required a hemoglobin (Hb) more than 12, platelet count more than 100,000, neutrophil count (ANC) more than 1500, and the absence of blasts. A partial peripheral response was not precisely defined but only two patients fell into this category.

Pretreatment patient characteristics were presented in a table, including the blood counts, karyotype, bone marrow cellularity, percent blasts in the bone marrow, and FAB subtype. Patients with sAML had blast counts that ranged from 35-90%. The mean pretreatment Hb, platelet count, and ANC were 8.3, 54,000, and 700, respectively. The cellularity of the bone marrow was described as normal, hypo-, or hypercellular, with no strict definitions of these three categories provided. Nevertheless, no patient with a hypercellular marrow or a complex cytogenetic karyotype responded to melphalan. By excluding these patients, a subgroup of patients with MDS or sAML was identified that collectively had a response rate of 75% (9/12 patients).

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Within 4-16 weeks, there were seven complete and two partial peripheral responses. In all of these patients, improvement was noted within the first month. The responses in peripheral blood counts lasted for a median of 25 weeks (12+ to 55). All five patients characterized as having a complete response were retreated upon relapse, although exact criteria for relapse were not presented. Four of them again achieved a complete response lasting 18 to 53+ weeks. Overall toxicity was described as mild, consisting of a transient worsening of cytopenias, but no infectious or bleeding episodes requiring hospitalization.

COMMENT BY KENNETH W. KOTZ, MD

This is an interesting report because melphalan, a drug that has long been available, has not been considered a treatment option for patients with MDS or sAML. Denzlinger and colleagues pursued this approach based on a single prior report from Japan.[1] In that report, the decision to try melphalan in MDS was based on activity seen with a conjugate of human IgG and melphalan that may accumulate more selectively and last longer in malignant cells. When activity was seen, it was then hypothesized that the activity of the conjugate in MDS could be reproduced with melphalan alone.[1] In fact, of the 21 patients (median age, 65 years) with MDS (6 with RAEB and 15 with RAEB-t) receiving melphalan at 2 mg a day, an astonishing 12 patients responded (7 complete), with a median duration of response of 14.5 months. They also observed negligible toxicity.[1]

It is not known whether the total response time would be longer with intermittent or continuous melphalan administration, as was done in the studies from Germany and Japan, respectively. In the study by Denzlinger et al, most complete responders did respond again when rechallenged but it is not clear from the article how long patients were followed off therapy after their first response. Therefore, a "total response" time cannot be calculated. As mentioned, patients with complex cytogenetic changes and hypercellular marrows did not respond at all. However, the classification of the underlying disease was not predictive of a response, as patients with both MDS (6/14) and sAML (3/7) responded. Denzlinger et al plan a placebo-controlled, prospective clinical trial restricted to those with normal or reduced bone marrow cellularity. ❖

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Sentinel Lymph Node Biopsy: What's Ahead (and Neck) in Melanoma?

ABSTRACT & COMMENTARY

Synopsis: *In this study, 30 patients with melanoma of the head and neck underwent a sentinel lymph node biopsy. Problems are encountered in this population due to unique aspects of the anatomy of the head and neck.*

Source: Jansen L, et al. *Head Neck* 2000;22:27-33.

Sentinel lymph node biopsy in head and neck cancer can be complicated by unique anatomical difficulties. In the study by Jansen and colleagues, 30 patients with melanoma of the head and neck from two centers in The Netherlands underwent preoperative lymphoscintigraphy and sentinel lymphadectomy ("sentinel node biopsy") between 1994 and 1997. The lesions were required to be greater than 1 mm deep and the therapeutic wide local excision was done after the sentinel node

biopsy. The median Breslow thickness was 3.0 mm with ulceration present in 30%. Locations included the face in six cases, the scalp in eight cases, the ear in four cases, and the neck in 12 cases.

The surgical technique, described in detail in the paper, included the use of preoperative lymphoscintigraphy with Tc-labeled human albumin and intraoperative location of the sentinel nodes using both a gamma probe and visual inspection for blue dye. The average number of sentinel nodes removed was 2.6 per patient, although in three cases no sentinel nodes were identified. Fifty-three percent of these nodes were both blue and radioactive, 43% were radioactive only, and 4% were blue only.

One problem unique to the head and neck is the presence of sentinel lymph nodes within the parotid gland. Four nodes within the parotid gland identified by preoperative lymphoscintigraphy in this study were not removed. However, of the 70 total lymph nodes excised, 13 came from the parotid gland. Another problem in the head and neck region is that not all sentinel lymph nodes can be seen preoperatively due to their anatomical proximity to either the injected site or another sentinel node. This difficulty helps explain 18 harvested sentinel nodes that were not identified on lymphoscintigraphy because of their location relative to the primary tumor (2 nodes) or other nodes (16 nodes).

Sentinel nodes were processed with six permanent histologic sections (12 if the node was larger than 1 cm) and stained with H&E, S100, and HMB45. This led to eight of these high-risk patients having a positive result. A formal lymph node dissection was performed in six patients. It is not reported if any patients received postoperative adjuvant therapy. Nevertheless, with an average follow-up of nearly two years, five of eight patients (62.5%) with a positive sentinel node were disease-free compared with 15 of 19 patients (78.9%) with a negative sentinel node.

COMMENT BY KENNETH W. KOTZ, MD

While it is clear that preoperative lymphoscintigraphy with sentinel lymphadenectomy is feasible and can provide prognostic information, has it been proven to provide a therapeutic advantage? Also, at what Breslow's depth is the probability of finding a positive sentinel node likely enough to warrant performing a sentinel node biopsy? And how much of a wide local excision can be performed before the normal lymphatic pathways are disrupted, thereby eliminating any useful information from the mapping procedure?

One cannot assume that a positive sentinel node has the same prognostic value as a random single positive lymph node found on an elective lymph node dissection. A sentinel lymphadenectomy will yield an average of about 1.7 nodes[1] that the pathologist can then study with serial sectioning and immunohistochemistry, techniques that are impractical to apply to the multiple nodes removed during an elective lymph node dissection. Therefore, the technique of sentinel node mapping may lead to patients who otherwise would not have been identified as node-positive.

An essential question is whether sentinel lymphadenectomy ultimately improves the outcome for patients with melanoma. In the Multicenter Selective Lymphadenectomy Trial, patients with melanoma more than 1 mm are randomized to wide local excision alone or wide local excision plus preoperative lymphatic mapping and sentinel lymphadenectomy.[2] A complete lymph node dissection is done for those patients whose sentinel nodes are positive.

In the Sunbelt Melanoma Trial, patients with melanoma more than 1 mm whose only positive node is a single sentinel node are randomized to observation or one year of standard interferon (all other node-positive patients get one year of interferon).[3] Patients whose sentinel node is histologically negative but reveals "sub-microscopic" disease (vide infra) are randomized to either observation (the standard arm), complete lymph node dissection, or a complete lymph node dissection followed by one month of high-dose interferon. "Submicroscopic" involvement with melanoma is identified by the reverse-transcriptase polymerase chain reaction for tyrosinase mRNA. These two studies should help define the role of the sentinel node biopsy in melanoma.

The study by Jansen et al excluded patients whose melanoma was less than 1.0 mm. Lesions between 0.75 mm and 1.0 mm are associated with positive sentinel nodes in 4% of cases.[4] Therefore, melanomas that are 0.75 mm or deeper can be considered for a sentinel node biopsy. In terms of timing, a sentinel node biopsy is optimally performed after the local biopsy but before the wide local excision disrupts the normal lymphatic channels. However, a sentinel node biopsy may still be informative if a wide local excision was less than 2.0 cm and not in a region of ambiguous drainage such as the trunk or head and neck.[5]

Sentinel lymph nodes identified within the parotid gland present a problem unique to melanoma of the head and neck. Fortunately, the majority of intraparotid lymph nodes are in the superficial portion of the gland (2-20 nodes) with only 1-4 nodes lying deep to the facial nerve.[6] Therefore, when dissection is necessary, superficial parotidectomy with preservation of the facial nerve is usually recommended.[6] ❖

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Follow-up Recommendations for Patients with Stage I-III Malignant Melanoma

ABSTRACT & COMMENTARY

Synopsis: *There are more than 44,000 new cases of malignant melanoma diagnosed each year in the United States and more than 80% of these cases will be localized. A major clinical problem is the development of rational follow-up recommendations for this increasingly large group of patients. Investigators from the Yale Melanoma Unit retrospectively reviewed the records of patients who were seen and followed according to their surveillance protocol to determine the time interval between initial visit and recurrence and the most common method of detecting recurrences. The five-year survival rates for stages I, II, and III were 95%, 72%, and 52%, respectively. Seventy-nine percent of recurrences were detected within the first two years of follow-up. Based on this experience, the authors recommended a schedule for follow-up.*

Source: Poo-Hwu WJ, et al. *Cancer* 1999;86: 2252-2258.

Patients in this study were followed by a multidisciplinary team of dermatologists, medical oncologists and plastic surgeons, according to a uniform protocol that combined frequent, comprehensive examinations with extensive patient education. Patients received instructions in performing self-examinations of the skin and a list of signs and symptoms of recurrence that should alert them to contact their physician. Pamphlets and videotapes were used to educate patients and family members regarding photoprotection. At each follow-up visit, a history, physical examination, complete blood count (CBC), and liver function tests including lactate dehydrogenase (LDH) were performed. Chest x-rays were obtained annually for stage I and II patients and every six months for stage III patients during the first five years of follow-up. Patients with stage III disease had a baseline computed tomography (CT) for complete staging examination. Follow-up CT scans were obtained only if there were abnormal findings initially that were not clearly indicative of metastatic disease.

The charts of 419 patients were reviewed, 46 of which were excluded primarily because patients had inadequate follow-up at Yale. Of the 373 patients whose charts were reviewed, 78 developed disease recurrence. Patient-reported symptoms resulted in detection of recurrence in 34 patients (44%), while the remaining 44 patients (56%) were diagnosed by procedures performed during a scheduled visit. Of the 44 physician-detected recurrences, 57% were identified by either history or physical examination; 18% were detected by chest x-ray and 23% were detected by CT or magnetic resonance imaging (MRI) scanning. The latter group, CT and MRI scans, were obtained because of abnormal findings on the baseline scans or suspicious findings on physical examination. There was only one patient (2%) in whom an abnormal laboratory result (elevated LDH) was the sole indicator for recurrent disease. The recurrences were evenly divided between distant and local regional metastases. Based on the hazard ratios for recurrence by stage, Poo-Hwu and colleagues recommend annual follow-up for patients with stage I disease and six months follow-up for the first two years for stage II with annual follow-up thereafter. For stage III, Poo-Hwu et al recommend follow-up every three months during the first year, every four months during the second year, every six months for years 3-5, and then annually thereafter.

COMMENT BY MICHAEL J. HAWKINS, MD

With the increasing incidence of early stage malignant melanoma, it is extremely important to develop rational, evidence-based follow-up programs. In patients with stage I disease, detection of second primaries or premalignant lesions is equally, if not more, important than screening for systemic recurrence.

Annual follow-up with liver function tests including an LDH and chest x-ray seems sufficient for these patients. Close, ongoing surveillance for second primaries is best determined by the patient's dermatologist and will depend upon the number of moles present and whether any of the moles exhibit atypical features. In this series, nine out of 493 patients with stage I disease developed recurrences, seven of which were physician detected. Thirty-five of 117 patients with stage II malignant melanoma developed recurrent disease. Detection in this group was equally divided between patient and physician. Since most recurrences occur within the first two years, Poo-Hwu et al recommend follow-up every six months with these patients. Many clinicians are uncomfortable with this interval, especially in young patients with deep primary lesions, and would tend to use the guidelines specified for stage III patients.

Clinical studies to date, however, have not shown a benefit for any follow-up protocol. This is in part due to the lack of effective therapies that can have a positive effect on survival once recurrence has occurred. Some patients who develop locoregional recurrence of their malignant melanoma will have long-term disease-free survivals following surgery with or without adjuvant systemic therapy. In this study, 60% of locoregional recurrences were detected by the patient. Single-arm studies of aggressive chemoimmunotherapy regimens have reported a 20% complete remission rate in patients with metastatic malignant melanoma.[1] The usefulness of immunotherapy in this context is currently being evaluated in a large-scale randomized trial comparing chemotherapy alone vs. chemoimmunotherapy.[2] Should effective systemic therapies become available and make early detection of systemic relapse desirable, follow-up programs would need to strongly consider the use of noncontrast CT scans of the chest instead of chest x-rays. However, trials of Interleukin-2 in metastatic renal cell carcinoma and Rituximab in non-Hodgkin's lymphoma have demonstrated tumor responses in patients with large-volume disease and have not seen a clustering of responses in patients with smaller tumor burdens.[3,4] ❖

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A Rare Event Imaging System for Detection of Cancer Cells in Blood and Bone Marrow

ABSTRACT & COMMENTARY

Synopsis: *An automated microscope system is described for the detection of rare cancer cells in samples of blood and bone marrow. The Rare Event Imaging System could detect rare cancer cells (1 in 1 million) in hematopoietic tissue samples. The Rare Event Imaging System facilitated analysis for minimal residual tumor (MRT), and additional correlations of rare event imaging and patient disease status are eagerly awaited.*

Source: Kraeft SK, et al. *Clin Cancer Res* 2000;6: 434-442.

Improved detection strategies are needed for the evaluation and monitoring of patients with cancer. Identification of microscopic subclinical disease in blood or bone marrow may identify patients in need of systemic therapy at a time prior to clinical presentation with disseminated disease. In addition, identification of malignant cells with a demonstrated capability to spread to blood and bone marrow has significant implications for the patient, as disseminated disease is a major cause of cancer-related mortality.

Several strategies have been used to detect minimal residual tumor cells in the blood of patients with cancer. These strategies include attempts to grow, culture, and characterize tumor cells,[1] molecular approaches such as reverse transcription PCR,[2,3] and immunological approaches to identify and characterize circulating malignant cells.[4,5] While flow cytometry can evaluate a large number of cells in a matter of minutes, it remains important to confirm the malignant nature of positive events detected by flow cytometry. Thus, an automated system to identify and analyze rare malignant cells in blood and bone marrow could have significant potential clinical applications.

The manuscript by Kraeft and colleagues describes an automated microscopic system (Rare Event Imaging System) for the detection and analysis of cancer cells in samples of peripheral blood and bone marrow. Samples are obtained from blood and bone marrow, red cells are lysed, and peripheral blood mononuclear cells (PBMC) or nucleated bone marrow (BM) cells are counted and allowed to attach to adhesive slides. The adhered cells are

then analyzed by immunological methods for possible tumor cells. The instrumentation required for this analysis include an automated fluorescence microscope (Nikon Microphot-FXA) with a cooled, charged, coupled device camera and a 60-MHz Pentium personal computer.

Kraeft et al initially described the efficiency of the cell deposition method following analysis of PBMC from normal donors and cancer patients, as well as BM samples from cancer patients and stem cell samples from cancer patients. The efficiency of cell deposition did vary, with 89% recovery from normal donor peripheral blood samples, 64% recovery from cancer patient peripheral blood samples, 58% recovery from cancer patient bone marrow samples, and 73% from cancer patient stem cell samples. The sensitivity of the rare event imaging system was then evaluated by spiking breast cancer cells into PBMC samples. The anticytokeratin antibody could readily detect the breast cancer cells in PBMC samples. A serial dilution analysis was performed, and breast cancer cells were detected at the lowest tested dilution corresponding to a detection of one breast cancer cell in 1 million PBMC. To allow additional phenotypic characterization of these cancer cells, and to improve the specificity of the rare event detection analysis, a staining procedure involving double labeling of tumor cells was developed. The double-labeling procedure consisted of labeling with an antibody specific for a surface molecule expressed on various malignancies and combining that analysis with staining for intracellular cytokeratin. The antibodies used included an antibody reactive with epithelial cell adhesion molecule (Ep-CAM) (breast, ovarian, colon, and lung carcinoma antigen) and an antibody reactive with disialo-ganglioside (GD2) antigen (small-cell lung carcinoma, neuroblastoma, and melanoma antigen). Visualization of the MCF-7 breast cancer cells were shown with the Ep-CAM/cytokeratin double-stained approach, and the SW2 small cell lung cancer cell line was shown to have double staining with the GD2/cytokeratin labeling. Thus, dual characterization with a surface molecule and intracellular cytokeratin was clearly demonstrated with these cancer cell lines.

The specificity of the single- and double-staining protocols was evaluated with peripheral blood samples from healthy donors. Sixteen to 18% of the normal donor peripheral blood samples had a low level of cytokeratin-positive cells that ranged from one to 26 labeled cells per 106 white blood cells. In contrast, use of the double-labeling protocol almost entirely eliminated the background positivity, with only a single double-positive cell detected in a total of 77 peripheral blood samples.

Three hundred fifty-five peripheral blood, bone marrow, and stem cell samples were then evaluated from patients with breast cancer before autologous bone marrow transplantation but after high-dose chemotherapy using the single cytokeratin labeling method. Cytokeratin-positive cells were detected in 52% of the bone marrow cells, 34% of peripheral blood samples, and 27% of stem cell samples. The frequency of these cytokeratin-positive cells in the positive samples ranged from one to 1020 cytokeratin-positive cells per million cells evaluated. To control for background reactivity in the normal donor samples, a threshold cut-off value was defined as the mean number of cytokeratin-positive cells plus two times the standard deviation as observed in the control sample. Kraeft et al then report cytokeratin positivity in 40% of the bone marrow samples, 24% of the peripheral blood samples, and 12% of the stem cell samples.

COMMENT BY MARK R. ALBERTINI, MD

The Rare Event Imaging System was demonstrated to be a sensitive means of detection of rare cancer cells (1 in 1 million) in samples of peripheral blood and bone marrow. The double-labeling protocol resulted in a significant reduction in false-positive determinations. This analysis allowed phenotypic characterization of tumor cells with the double-labeling analysis. Thus, the double-staining protocols for cytokeratin/Ep-CAM and cytokeratin/GD2 can detect rare cancer cells in hematopoietic tissues from cancer patients.

The Rare Event Imaging System appears ready for clinical testing to determine correlations between positivity with this analysis and subsequent clinical outcome. The current article describes and validates the ability of this system to detect rare malignant cells. However, clinical implications of this finding require further investigation. The proposed monitoring system appears ready for this clinical testing, and studies analyzing clinical samples from cancer patients are eagerly awaited. Potential incorporation of events detected with the Rare Event Imaging System together with traditional cancer outcome measurements would provide valuable testing of this technology.

Kraeft et al also describe potential additional phenotypic analysis of samples with markers that are correlated with metastatic potential. The use of this Rare Event Imaging System with additional markers requires further investigation. However, the use of a double-staining procedure with additional surface marker analysis appears to be a logical extension of this technology.

In summary, Kraeft et al describe an exciting technology to identify rare malignant cells in samples from peripheral blood and bone marrow. Additional clinical testing will be required to determine potential use of this monitoring strategy for patients with cancer. ❖

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Age at the Time of Hodgkin's Disease Treatment and the Occurrence of Second Malignancies

ABSTRACT & COMMENTARY

Synopsis: *With the advent of effective chemotherapy and radiotherapy approaches for the treatment of Hodgkin's disease introduced several decades ago, there is now a large cohort of patients with a remote history of such treatment. In this report of a large series of such survivors, second malignancies of all types (including lung, colon and breast, as well as leukemia) were discovered at an increased rate. The risk of developing second malignancies was greatest for those who were treated for their Hodgkin's disease at a young age. Patients cured of Hodgkin's disease are at increased risk for second malignancy, and the risk appears to increase rather than recede with time.*

Source: Swerdlow AJ, et al. *J Clin Oncol* 2000;18: 498-509.

Inasmuch as curative therapies for hodgkin's disease have been available for over three decades, the long-term side effects of treatment are now becoming increasingly apparent. To further describe the later consequences of treatment, a large cohort of British patients (n = 5519) treated from 1963 to 1993 were evaluated for the development of second malignancy and mortality. The data, derived from the British National Lymphoma Investigation, the Royal Marsden Hospital, and St. Bartholomew's Hospital registries, were available for 97% of patients.

There were 322 second malignancies in this group. All major types of tumors were more frequent in Hodgkin's disease survivors than the general population. For example, the relative risks of gastrointestinal, lung, breast, and of leukemia increased significantly. Although the absolute excess risks of second malignancy were greater for older patients, the relative risks (RR) were more pronounced for individuals who had Hodgkin's disease treated at a young age. Furthermore, there now emerges a trend toward certain types of second tumors depending on the type of Hodgkin's disease therapy. For example, after mixed modality treatment, the relative risk for gastrointestinal cancer was 3.3 (95% CI, 2.1-4.8), whereas the risk of lung cancer was greater for those that received chemotherapy alone (RR = 3.3; 95% CI, 2.4-4.7) and the risk of breast cancer was increased for those that had received radiotherapy (without chemotherapy) (RR = 2.5; 95% CI, 1.4-4.0).

As mentioned, these risks were greater after treatment at younger ages: for patients treated at ages younger than 25 years, there were RRs of 18.7 (95% CI, 5.8-43.5) for gastrointestinal cancer after mixed-modality treatment, 14.4 (95% CI, 5.7-29.3) for breast cancer after radiotherapy, and 85.2 (95% CI, 45.3 to 145.7) for leukemia after chemotherapy (with or without radiotherapy).

This analysis highlights the major effect of age at treatment on the appearance of second malignancy after Hodgkin's disease. The association of type of treatment and the occurrence of specific second tumors is an observation that may eventually provide clues to the mechanisms of tumor development in those organ systems.

COMMENT BY WILLIAM B. ERSHLER, MD

This analysis is by far the most comprehensive description of second malignancies in Hodgkin's disease survivors. Treatment-related leukemias have been appreciated for many years,[1-3] and most believe that alkylating agents are primarily responsible.[4] These leukemias tend to occur within a few years of Hodgkin's disease treatment. Solid tumors occur more gradually, but eventually constitute the great majority of second malignancies.[5,6]

There have been other reports that would suggest that, at least for certain cancers, the risks are greater after childhood than after adult Hodgkin's disease treatment.[7-9] This comprehensive report supports this conclusion. It is curious that gastrointestinal malignancies seem to occur more commonly in individuals treated with mixed modalities, whereas breast cancer occurs more commonly in patients previously treated with radiation alone. Chemotherapy is clearly associated with the development of leukemias and probably lung cancer as well. Why this should be the case is clearly conjecture at this point, but the roles of specific treatments in the etiology of second malignancies needs further and intense exploration.

The report also highlights the importance of patient age at the time of treatment, and now, with many survivors having been treated 30 or more years ago, there is an emergence of lung and gastrointestinal second malignancies with rates that exceed those for leukemia. It may well be that the increased risk for these solid tumors will increase even more with succeeding decades.

The take-home message for clinicians is that patients cured of Hodgkin's disease are in a high-risk category for just about all types of cancer, and such patients should be examined and screened as rigorously as rigorously as any high-risk group. ❖

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CME Questions

12. Regarding the study of MDS and sAML, which one of the following is true?

a. Patients with a hypercellular bone marrow responded well to melphalan.
b. Patients with MDS responded better to melphalan than patients with sAML.
c. Responses to melphalan occurred only at high doses.
d. Improvement was usually noted within a month in patients who responded.

13. Which one of the following is true?

a. In melanoma, a sentinel lymph node biopsy should be performed in lesions of any depth.
b. Sentinel nodes within the parotid gland are usually negative and therefore need not be removed.
c. Anatomical considerations can complicate the location of sentinel nodes in the head and neck.
d. Performing sentinel lymph node biopsies has been proven to prolong survival in melanoma.

14. Which one of the following statements about the Rare Event Imaging System is *false*?

a. Cytokeratin-positive cells can be detected in peripheral blood samples from healthy donors.
b. The double-labeling protocol can improve the specificity of rare event detection by combining analysis for intracellular cytokeratin with an analysis for epithelial cell adhesion molecule (Ep-CAM).
c. The detection of cytokeratin-positive cells following cytokeratin single-staining is a specific marker for cancer cells.
d. The double-labeling protocol can improve the specificity of rare event detection by combining analysis for intracellular cytokeratin with an analysis for disialo-ganglioside (GD2) antigen.

15. In patients with stage I-III cutaneous malignant melanoma who develop disease recurrence, three-fourths of these recurrences will have occurred within what time from diagnosis?

a. 1 year
b. 2 years
c. 3 years
d. 5 years

16. Which of the following statements about the risk of second malignancy after treatment for Hodgkin's disease is *not* true?

a. The older the patient at the time of treatment, the greater the risk for leukemia development.
b. Younger patients have a greater relative risk for the development of solid tumors.
c. Lung, colon, and breast cancer occur at increased frequency in Hodgkin's disease survivors.
d. Solid tumors occur later after Hodgkin's disease therapy than do leukemias.

In Future Issues:

DNA Microsatellite Instability:
A Favorable Indicator in Colon Cancer