Expansion of Palliative Care in the Gulf Area
Original Articles /Studies

Impact of BMI on Locoregional Control among Saudi Patients with Breast Cancer after Breast Conserving surgery and Modified Radical Mastectomy ......................................................................................................................................07
E.F. Al Saeed, A.J. Al Ghabban, M.A. Tunio

A statistical quantification of radiobiological metrics in Intensity Modulated Radiation Therapy evaluation ..........15
A. Surega, J. Punitha, S. Sajitha, BS Ramesh, A. Pichandi, P. SasiKala

A method for assessment of radiation treatment chain of cervical cancer with combined external and brachy radiation therapy ................................................................................................................................................................................24
A. Chaparian, P. Shokrani

Role of Lymphadenectomy and Its Impact On Survival In Endometrial Carcinoma – An Institutional Experience ..........30
S. Suchetha, P. Rema, S. Vikram, P.S. George, I. Ahmed

Breast Cancer—Epidemiology, Risk Factors and Tumor Profiles in Bangladeshi underprivileged women..........................34
M. Rahman, A. Ahsan, F. Begum, K. Rahman

Early hematological effects of chemo-radiation therapy in cancer patients and their pattern of recovery- A prospective single institution study ..................................................................................................................................................43

Platinum-based chemotherapy in metastatic triple negative breast cancer: Experience of a tertiary referral centre in India ..................................................................................................................................................................................52

A Single Institution 18-Years Retrospective Analysis of Malignant Melanoma ..........................................................................................................................58
A. Mukherji, A.K. Rathi, P.K. Mohanta, K. Singh

MRI and ultrasonography for assessing multifocal disease and tumor size in breast cancer: Comparison with histopathological results.............................................................................................................................................................65
V. Rudat, A. Nour, N. Almuraikhi, I. Ghoniemy, I. Brune-Erber, N. Almasri, T. El-Maghryb

Patient’s Compliance On the Use of Extended Low Molecular Weight Heparin Post Major Pelvic Surgeries in Cancer Patients at King Hussein Cancer Center ..................................................................................................................................................73
M. Baba, M. Al Masri, M. Salhab, M. El Ghaneem

Can we use Sorafenib for advanced Hepatocellular Carcinoma (HCC) Child Pugh B? ..............................................82
K. Rasul, A. Elessam, S. Elazzazi, R. Ghasoub, A. Gulied

Case Reports

The external auditory canal as an unusual site for metastasis of breast carcinoma: A case report ........................................85

Primary Mixed Cellularity Classical Hodgkin lymphoma of the Lumbar spine – An unusual presentation ...............................88
K.R. Anila, R. A. Nair, S. Prem, K. Ramachandran

Subdural hematoma during therapy of gastro-intestinal stromal tumor (GIST) with Imatinib mesylate ........................................92

Conference Highlights /Scientific Contribution

- Workshop Highlights –The Second Regional Training Of The Trainers’ (TOT) Workshop On Palliative Care, Kuwait, 23-26 November 2014 ..................................................................................................................................................96
- News Notes................................................................................................................................................................................102
- Advertisements.............................................................................................................................................................................107
- Scientific events in the GCC and the Arab World for the 1st Semester of 2015.................................................................108
Early hematological effects of chemo-radiation therapy in cancer patients and their pattern of recovery - A prospective single institution study

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Abstract

The purpose of this prospective study is to understand the early hematological effects of chemo-radiation therapy in cancer patients, their pattern of recovery and to ascertain their prognostic value.

Methods

255 diagnosed cancer patients planned for definitive treatment with radiation therapy alone or with chemotherapy were included in this two year prospective study. A complete blood count was done at baseline, weekly during the course of therapy and thereafter, monthly for a period of 6 months. For the purpose of grading clinical toxicity, the Common Toxicity Criteria, CTCAE v2.0 was used while RECIST criteria was used to define the tumor response rates. This study was statistically analyzed using SPSS software.

Results

255 patients were included in the study wherein head and neck cancers comprised the major patient population (28.6%) followed by cervix (18.8%) and breast (15.7%). Out of these, 37% in head-and-neck cancer subgroup, and 58.3% in cervix had anemia at start of treatment. 92.2% cases with chemoradiation developed anemia during treatment, while with radiation alone it was 95.5%. This was statistically significant in patients with cancer uterine cervix (p < 0.01). At the end of treatment 65% patients with normal hemoglobin had complete responses (CR), while 58.3% with mild anemia and 33.3% with moderate anemia had CR (p=0.1).

Conclusions

Severe anemia during treatment is a poor prognostic indicator and is usually a sign of advanced disease. Leucopenia and thrombocytopenia occur more commonly during chemoradiotherapy as against radiotherapy alone, but improves with supportive management.

Key words: anemia, chemotherapy, radiation therapy, hematology, cancer

Introduction

It is a well-known fact that in malignancy, tumor cells tend to compete with the normal host cells and ablate the immune system causing nutritional deficiencies manifesting as anemia and resulting in deranged hematological parameters. Additionally, management of cancer itself incurs myelosuppression as an adverse event of period after therapy.\textsuperscript{(1)} Hence, a thorough knowledge of the cancer patient’s hematological profile before, during and after treatment is vital.

Combined modality therapy is currently the standard of care for head-and-neck cancers, breast carcinoma, lymphomas, esophageal carcinoma, carcinoma cervix, colorectal and anal period after carcinomas.\textsuperscript{(2)} They are usually associated with higher rates of tumor control, but also carry an increased risk of myelosuppression than single modality therapy.\textsuperscript{(3)}
Tumour and treatment related myelosuppression induces tumour hypoxia which is associated with resistance to radiation therapy and chemotherapy. This may lead to poor local control of tumors, thereby reducing survival and subsequent impaired quality of period after life.\(^{(4,5)}\)

Besides the erythroid series, other hematological cell lines essentially leucocytes and platelets have a prognostic profile in oncological settings. Cytotoxic therapies induce a suppression of these sensitive cell lines leading to a generalized impairment of cellular period after immunity.\(^{(6,7,8)}\)

This prospective study was designed to understand the hematological profile of patients at three intervals: before treatment, during the course of chemo-radiation therapy, and in post treatment follow-up phase.

**Materials and Methods**

This prospective longitudinal study was undertaken at the Department of Radiotherapy, Christian Medical College and Hospital, Ludhiana between June 2002 and January 2004. The study presented is a part of dissertation approved by the Institutional Review Board of the Christian Medical College and Hospital.

**Initial plan and Patient characteristics**

Previously untreated cancers were studied in our research protocol and the common sites with the most number of patients were categorized, viz. head and neck, cervix, breast, lung, CNS and rest as “others”. Any patient who had received prior chemotherapy or radiotherapy, or presenting with any co-existing primary hematological disorder or on any anticoagulant therapy were excluded from the study. Each patient was given anti helminthic treatment prior to starting treatment, and all the patients were maintained on oral hematinsics, and vitamin supplements until the conclusion of the study. Blood transfusions were done as and when indicated.

**Treatment**

The prevalent institutional site and stage-wise cancer management protocols were adopted in our study either with radiation therapy alone or concurrent chemoradiation therapy. Patients were given external beam radiotherapy by Theratron 80R® Cobalt-60 photons and planned with non computerized conventional radiation therapy portals.

**Hematological assessment and Toxicity grading**

A complete blood count was done at baseline, weekly during the course of therapy and thereafter, monthly for a period of 6 months. 

Blood tests were done with the help of Auto Blood Cell Counter. Blood film was stained using Leishman’s stain and then analyzed. Bone marrow erythropoiesis was assessed weekly from reticulocyte count in every patient with the help of Brilliant Cresyl blue staining. In cases of suspected leukemoid reaction, a LAP scoring was done.

For the purpose of assessing the grade of clinical toxicity caused by anemia, leukocytopenia or thrombocytopenia, the Common Toxicity Criteria (NCI, USA), CTCAE v2.0 was used. At the end of study, tumor response was assessed with the RECIST criteria.\(^{(9)}\)

**Statistical analysis**

The haematological profile over the different time intervals were analysed graphically and through application of repeated measures of analysis of variance (one-way ANOVA Post Hoc range tests). Chi square test was employed to ascertain the difference in percentages and proportions of variables. Additionally, students’ \(t\) test was used for binary variable statistical assessment. Values were considered significant at an alpha level of 0.05. This study was statistically analyzed using SPSS software (version 15.0; SPSS, Inc., Chicago, IL).

**Results**

**Patient and treatment characteristics**

Table 1 shows the patient and treatment related characteristics. 255 patients were included in the study wherein head and neck cancers comprised the major patient population (28.6%) followed by cervix (18.8%) and breast (15.7%).
were 50.52% patients with stage III disease and 15.81% patients with stage IV disease in their respective sites.

Concurrent chemo-radiotherapy schedules were commonly employed in head and neck cancers (69.9%), cancer cervix (54.2%) and esophageal carcinomas (76.9%), while 57.5% of breast cancer patients received chemotherapy in sequential form.

**Baseline Hematological Profile**

**Hemoglobin**

The baseline hematological profile is depicted in Table 2. Out of the 255 patients, 37% in head-and-neck cancer subgroup, 58.3% in cervix, 55% in breast and 61.9% with lung cancer had anemia at start of treatment. Mean hemoglobin levels in cervix patients (11.2±1.79) were significantly lower than head and neck cancer patients (12.4±1.73), p=0.00.

**Peripheral Blood Film**

The majority of patients in all the sites: 59.3% in head and neck, 60.7% in cervix, 63.6% in breast, 53.9% in lung and 70% in brain had iron deficiency picture on peripheral blood film.

237 patients (93%) were maintained on oral hematins, 9 (3.5%) were initiated on oral hematins along with injectable iron while 9 (3.5%) received blood transfusions before the start of treatment.

**Leucocytes**

Leucopenia was seen in 18 (24.5%) head and neck cancer patients, 16 (33.3%) carcinoma cervix patients, 7 (17.5%) breast carcinoma patients and one patient each with lung and CNS malignancies. Remaining majority had leucocytes within normal range.
Hematological effects of chemo-radiation therapy in cancer patients, H.N. Lee, et. al.

**Platelets**

Overall, 183 (71.8%) patients had platelet counts within normal limits. Twenty (27.4%) with head and neck area cancers, 11 (22.9%) with cancer of the cervix, 7 (17.5%) with breast cancer, 7 (33.3%) with lung cancer, 5 (25%) with CNS malignancies and 7 (13.2%) with malignancies in other sites had thrombocytosis.

In the head and neck patients, hemoglobin levels showed a decreasing trend while mean reticulocyte counts showed an increase. This was found to be statistically significant ($p < 0.05$) at the third week and on subsequent follow-ups. 92.2% cases with chemoradiation developed anemia during treatment, while with radiation alone it was 95.5%.

Among the carcinoma cervix patients, there was a decrease in hemoglobin levels along with an increase in reticulocyte count. This was not significant during treatment but was statistically significant ($p < 0.01$) in the 3rd month of follow-up. All cases with chemoradiation had anemia, while 95.5% cases with radiation alone had anemia.

In breast cancer patients, a decrease in mean hemoglobin levels and an increase in mean reticulocyte count was seen as highly significant ($p < 0.05$) in the 2nd month of follow-up. 95.7% cases with chemoradiation developed anemia, while 88.2% cases with radiation alone had developed anemia while undergoing treatment.

Among the lung cancer patients, a decrease in mean hemoglobin levels and an increase in mean reticulocyte counts were seen in the last week of treatment. This was found to be statistically significant ($p < 0.01$).

In patients with CNS malignancies, there was a decreasing trend in weekly hemoglobin levels and an increase in the mean reticulocyte counts. This was found to be statistically highly significant ($p < 0.01$) in the 2nd month of follow up onwards.

Among the other patients studied, hemoglobin levels showed a decreasing trend while reticulocyte counts showed an increase. This was significant in the last week of treatment.

There was a greater fall in the total leukocyte count from the baseline value in the chemoradiotherapy group as compared to the patients in the radiotherapy-alone group (Figure 1). The fall in the total leukocyte count was shown to be statistically highly significant in chemoradiotherapy group from week 2 onwards ($p < 0.01$), which continued until the last month of follow up. In the radiotherapy alone group, fall in TLC was found to be statistically significant from week 3 onwards ($p < 0.05$), which continued until the last week ($p < 0.01$) and thereafter the fall in TLC was found to be not significant.

Patients with carcinoma cervix were divided into two groups: one receiving chemoradiation and the other receiving radiotherapy alone. Fall in the total leukocyte count was statistically highly significant ($p < 0.01$) from week 2 onwards in the chemoradiotherapy group, which continued up to the last month of follow up, whereas fall in TLC was statistically significant ($p < 0.005$) from week 2 onwards up to the 3rd week in the radiation only group. Thereafter the TLC changes were found to be statistically not significant.

Two patients with grade 4 toxicity died during the course of treatment despite conservative management, while 1 patient with grade 3 toxicity continued to have grade 2 toxicity on last follow-up.

Figure 1. Total leucocyte count (TLC/cmm, x 1000) trend in head-and-neck cancer (HNC) and carcinoma cervix patient population (with and without chemotherapy (chemo))
For patients with cervical cancer, 90% with normal hemoglobin have complete response while 76.5% with mild anemia and 70% with moderate anemia have complete responses (Table 3, p = 0.1). At the end of treatment among the head and neck cancer patients, complete response was seen in 63% of patients with hemoglobin > 12 g/dl, 58.3% in patients with mild anemia and 33.3% in patients with moderate anemia (Table 4, p = 0.1). At last follow up, 39.1% had

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### Table 3. Baseline anemia and response to therapy in carcinoma cervix patients

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>CR</td>
<td>18</td>
<td>90.0</td>
<td>13</td>
<td>76.5</td>
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<tr>
<td>PR</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>17.6</td>
</tr>
<tr>
<td>NR</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>D/L</td>
<td>2</td>
<td>10.0</td>
<td>1</td>
<td>5.9</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100</td>
<td>17</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 4. Baseline anemia and response to therapy in head-and-neck cancer patients

<table>
<thead>
<tr>
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<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. %</td>
</tr>
<tr>
<td>CR</td>
<td>29 (63.0)</td>
<td>14 (58.3)</td>
<td>1 (33.3)</td>
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</tr>
<tr>
<td>PR</td>
<td>5 (10.9)</td>
<td>6 (25.0)</td>
<td>1 (33.3)</td>
<td>-</td>
</tr>
<tr>
<td>NR</td>
<td>-</td>
<td>3 (12.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PD</td>
<td>1 (2.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D/L</td>
<td>11 (23.9)</td>
<td>1 (4.2)</td>
<td>1 (33.3)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>46 (100)</td>
<td>24 (100)</td>
<td>3 (100)</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. %</td>
</tr>
<tr>
<td>CR</td>
<td>18 (39.1)</td>
<td>12 (50.0)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>PR</td>
<td>1 (2.2)</td>
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</tr>
<tr>
<td>NR</td>
<td>2 (4.3)</td>
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<tr>
<td>PD</td>
<td>4 (8.7)</td>
<td>7 (29.2)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>D/L</td>
<td>21 (45.7)</td>
<td>5 (20.8)</td>
<td>3 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>46 (100)</td>
<td>24 (100)</td>
<td>3 (100)</td>
<td>-</td>
</tr>
</tbody>
</table>

EOT, Response at end of treatment; LFU, Response at last follow-up; CR, Complete response; PR, Partial response; NR, No response; PD, Progressive disease; D/L, Died / Lost to follow-up
Hematological effects of chemo-radiation therapy in cancer patients, H.N. Lee, et. al.

complete response. At the end of study, 39.1% patients with normal hemoglobin had CR and 8.7% had progressive disease, while 29.2% patients with mild anemia had progressive disease. This was found to be statistically not significant (p = 0.1).

Discussion

The present study is aimed to know the incidence of the hematological abnormalities in cancer patients, and state the effects of radiotherapy with or without chemotherapy on these patients. In our study, the prevalence of anemia was nearly 50.2% (128) at baseline with nearly 58.3% (28) of cancer cervix patients having anemia followed by 61.9% patients with lung carcinoma, 55% (22) of patients of breast carcinoma and 36.9% (27) of patients with head and neck cancers being anemic at baseline. Few studies reported that cervical patients have the highest prevalence of anemia at baseline (75%) and most remained anemic during the course of radiotherapy. The documented incidence of anemia is as high as 80% and nearly 48% of head and neck patients present with anemia (hemoglobin <12g/dl) and a total of 57% ultimately became anemic by the end of therapy. (10, 11, 12)

Radiation oncologists need to be aware of the possibility of anemia in cancer patients undergoing radiotherapy so that timely intervention can be instituted whenever anemia is diagnosed. (13) Non-laboratory toxicity (presenting as oral mucositis, dermatitis, nausea, vomiting) and hematologic toxicity (leukopenia, anemia, thrombocytopenia) are adverse effects of chemoradiotherapy treatment for cancers. (14, 15) Anemia often defined as a hemoglobin level <12 g/dl—is common in patients presenting for radiation therapy (resulting from the underlying disease and/or previous treatment), with an estimated incidence of up to 40%- period after 60%. (16, 17) The ability of radiation therapy to eradicate malignant cells critically depends upon the intratumoral content of molecular oxygen, a potent radiosensitizer involved in mediating DNA damage. In fact, intratumoral oxygen level is arguably the most important determinant of response among tumors of the same type treated with a single fraction of ionizing radiation therapy. (18, 19)

In our study, among the patients with head and neck cancers, 59.3% of anemic cases had iron deficiency anemia while 3 (11.1%) patients had a megaloblastic blood picture. Among the patients with cancer cervix, 47.1% have normal peripheral blood picture while 47.1% have mild anemia, 77.8% with moderate anemia and 100% of patients with severe anemia have microcytic hypochromic picture. 22.2% patients with moderate anemia have a megaloblastic picture.

In cases of cancer, anemia is mainly due to dietary deficiency, malabsorption or blood loss. In women, the most common cause is blood loss; usually menorrhagia (> 80 ml / cycle) or GI bleeding. In males, bleeding from the tumor site, malabsorption and peptic ulcers are the most common causes of iron deficiency anemia as seen on peripheral blood film. Treatment with iron replacement, e.g., Ferrous Sulphate 200 mg Q8h, should cause a rise in hemoglobin of 1 gm/dL/week, accompanied by reticulocytosis, which needs 3 months to replenish stores. (11)

Reticulocytosis with counts greater than 1.5% is seen in cases of post anemia treatment with folate, iron and vitamin B12 supplementation. Reticulocytopenia, which signifies decreased red cell production, is seen in aplastic anemia, bone marrow suppression or failure following chemotherapy or radiotherapy and also in cases of disordered red cell maturation due to iron deficiency, folate or vitamin B12 deficiency and in anemia of chronic diseases. (20)

In our study, there was a decrease in hemoglobin levels during the course of treatment in all the patients while the reticulocyte counts showed an increase during treatment. All our patients received oral iron, folate and vitamin supplements during therapy.

In our study, at the end of treatment among the head and neck cancer patients, complete response was seen in 63% of patients with hemoglobin > 12 g/dl, 58.3% in patients with mild anemia and 33.3% in patients with moderate anemia. At last follow up, 39.1% have complete response. In our study of patients with cervical cancer, 90% of
patients with normal hemoglobin have complete response while 76.5% with mild anemia and 70% with moderate anemia have complete responses. At the end of treatment, 70% with normal hemoglobin have complete response, 58.8% with mild and 40% with moderate anemia have complete responses, while 80% patients with severe anemia who received blood transfusions have progressive disease. This implies that a decrease in hemoglobin level has an adverse effect on treatment outcome.

During the course of our study, 9 patients received blood transfusion during treatment of which 5 patients belonged to the carcinoma cervix group. Four (80%) of these 5 patients have progressive disease in the form of lung metastasis, liver metastasis and locoregional failure. A retrospective study noted the influence of hemoglobin concentrations and blood transfusions before and during treatment on occurrence of distant and/or local regional failures in cancer uterine cervix patients\textsuperscript{(21)} It is concluded that blood transfusions might be beneficial when given before treatment and although not significant, blood transfusion given during treatment tended to be an adverse prognostic factor suggesting that blood transfusion might not have completely offset acute anemia prior to transfusion.

There was one patient in each of the following groups of head and neck, lung, genitourinary and esophageal carcinoma who received transfusions. Of these 4 patients, 1 died and 3 have progressive disease.

Further to our study, distant failure was as high as 75% in patients having severe anemia, on the contrary, the locoregional failure was 17.6% which was attributed to locally advanced tumor and residual disease after EBRT.

Pre-treatment hemoglobin did not have an effect on disease outcome in lung cancer patients showing that lung carcinoma has overall poor prognosis. This is supported by a similar study in NSCLC wherein median survival in three groups from lowest to highest hemoglobin was 17.5, 18.4, 16.3 months. No significant effect of pretreatment hemoglobin concentration was seen in predicting overall local disease-free or metastasis-free survival rates\textsuperscript{(22)}

Leukocytosis was seen in 13.3% among our patients and this was attributed mainly to infections. All these patients responded to antibiotic treatment.

Leukocyte counts decreased during the course of treatment in all groups of patients, more in the chemoradiotherapy group as compared to radiotherapy alone group. This signified a combined toxicity of chemotherapy and radiotherapy on the leukocytes. Leukocytes were shown to normalize by 3rd week of treatment and subsequently on follow-up. A sudden dip in leukocytes was seen in the 2nd month in chemoradiotherapy groups in head and neck, cervix and breast carcinoma with a possible likelihood of bone marrow suppression and subsequent rise in leukocytes signifying a recovery.

Thrombocytosis may be a part of paraneoplastic syndrome or may be due to secretion of thrombopoietic factors stimulating the activity of platelet production.

Also in our study, 7 (33.3%) patients with lung cancer have thrombocytosis. Thrombocytosis is associated with poor survival outcomes in cervix, and lung malignancies\textsuperscript{(23, 24, 25)} Thrombocytopenia was seen only in 5.9% of our patients.

In summary, our study shows that most of the patients presented with locally advanced disease and that 50.4% have anemia at baseline. 20.6% of our patients have poor nutritional status while 48.8% have borderline nutritional status which may have contributed to the anemia. Other causes include excessive blood loss especially in carcinoma cervix patients and the malignancy itself. Radiotherapy and chemotherapy also contributed to the development of anemia. An attempt was made to improve the nutritional status with iron, folic acid and vitamin supplementation along with control of infection and correction of anemia with blood transfusions.

Finally, our study showed that response to therapy was better in head and neck and cancer cervix patients who have no anemia, as against
Hematological effects of chemo-radiation therapy in cancer patients, H.N. Lee, et. al.

those with anemia and this was found to be statistically significant in carcinoma cervix patients. Lung carcinoma in general had a poor outcome and baseline anemia did not have any prognostic influence.

Conclusions

Severe anemia during treatment is a poor prognostic indicator and is usually a sign of advanced disease. Leucopenia and thrombocytopenia occur more commonly during chemoradiotherapy as against radiotherapy alone, but improves with supportive management. Paraneoplastic syndrome seems to be an important part of clinical manifestations and may present as anemia, thrombocytosis or leukemoid reactions. More rigorous studies involving larger number and randomized group of patients, and longer follow-up are required to further our understanding into this vital aspect of oncology.

Note by authors: This study was presented during the CARO-ACRO (Canadian Association of Radiation Oncologists) Annual Conference 2012 in Ottawa, Canada.

References


