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Adjuvant Radiation for Malignant Melanoma: The KUMC Experience

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Abstract

Background. The role of external beam radiation in the treatment of melanoma remains controversial. While melanoma is no longer considered radio-resistant, the indications and outcomes for adjuvant radiation therapy in melanoma patients are still evolving.

Methods. A retrospective review was conducted of patients diagnosed with malignant melanoma and treated with postoperative radiation therapy at the University of Kansas Medical Center.

Results. Forty-five patients (27 male; 18 female) with a diagnosis of malignant melanoma were treated with external beam radiation therapy for curative intent between 1985 and 2005. Local control at the treatment site was achieved in 42 of 45 patients and was maintained in 35 patients (78%) at a median follow-up of 14 months. The median time for freedom from any disease progression was 12 months.

Conclusions. Radiation therapy is an effective option for management of patients with malignant melanoma with local control being achieved and maintained in the majority of patients. *KJM 2008; 2(1):1-7.*

Introduction

The role of radiation in the treatment of malignant melanoma often is palliative to relieve the symptoms of widespread metastatic disease. However, there is a possible role of radiation in the curative setting. While surgical resection remains the standard primary treatment, a significant number of completely excised lesions will recur, especially in patients with high-risk features.

Some of the adverse prognostic factors for overall survival include tumor thickness and ulceration[1], while extra-capsular extension, cervical lymph node involvement, and excised lymph nodes larger than 3 cm are prognostic factors for lymph node failure.[2] Patients who test positive for these factors can have local failure rates after surgery alone as high as 50%.[3] These high local failure rates have prompted the search for ways to achieve better local control. Although interferon initially looked promising[4], further studies have not shown this modality to be as beneficial as first thought.[5]

Radiation therapy is another option in the adjuvant treatment of malignant melanoma. Several studies have examined the role of radiation in the non-palliative setting. The results of these studies indicated that adjuvant radiotherapy may be beneficial for patients with high risk features, both for reducing failure at the primary site[6,7] and failure in the lymph node basins[7-13].

This report will examine the results of and possible indications for post-operative radiation therapy in the management of patients with malignant melanoma.

Methods

A retrospective review of the malignant melanoma patients receiving radiation therapy at the University of Kansas Medical Center (KUMC) between 1985 and 2005 was conducted. Approval for this study was granted by the KUMC Institutional Review Board.

The KUMC tumor registry identified all patients with a diagnosis of melanoma who received radiation as a component of their treatments. Patients who were treated for palliation and those who received radiation by means other than external beam (such as brachytherapy) were excluded from this review. After exclusion, 45 patients and a total of 47 treatments were available for analysis. One individual received three separate treatments over a time span of 19.2 months; only the first treatment is considered.

Statistical analysis was performed with SPSS for Windows (Release 16.0, SPSS Inc, Chicago, IL). Categorical variables were summarized by frequencies and percentages, and quantitative variables were summarized by medians and ranges. The duration of follow-up was calculated from the time of completion of radiation treatment until the date of event or last known follow-up. Time to event (overall survival, freedom from disease progression, and freedom from local recurrence) was analyzed by Kaplan-Meier survival plots and univariate analysis by the log-rank test.

For univariate analysis, categorical variables were compared by the log-rank test and/or continuous variables by Cox proportional hazards analysis. Multivariate analysis by Cox regression analysis was then performed. Probability values of $p<0.05$ were considered to be statistically significant. No corrections for multiple comparisons were made.

Results

The study population consisted of 27 males and 18 females with a median age of 60.3 years (range 14 to 85 years). All patients had surgery as the initial component of their therapy. The primary tumor sites were head and neck (16 patients, 36%), upper extremity (6, 13%), lower extremity (15, 33%), and trunk (6, 13%); with two patients (4%) having an unknown site. The tumor stage and nodal status at diagnosis is provided in Table 1**.**

All patients had surgery as the initial component of their therapy prior to radiotherapy. Thirty-three of the radiation treatments (73%) were to the site of resected primary disease; of which 12 (27%) were at the time of original presentation and 21 (47%) were at the time of recurrence. Lymph node regions were included in the treatments of 26 patients (57%), 9 (20%) at the time of original presentation and 17 (38%) at the time of recurrence. Fifteen patients (33%) received radiation treatment to both the primary site and the lymph nodes. One patient (2%) was treated later to another site other than lymph nodes.

Table 1. Tumor stage and nodal status at diagnosis.

Tumor Stage	Nodal Status				
	0	**1**	**2**	**3**	**Total**
Tx*	4**	2	1		7
T1	7				7
T2	5	2	1		8
T3	6	1			7
T4	6	4	3	3	16
Total	28	9	5	3	45

*Tx denotes a primary tumor that could not be assessed.

**One patient was M1a.

External beam radiation varied in terms of both dose per fraction and fractions per week. The majority of patients (28, 60%) were treated on a daily basis, Monday through Friday, for five fractions per week. Other fractionation schemes included three times per week (9 patients, 20%), twice per week (7 patients, 16%), and one patient was treated twice daily (10 times per week). Dose also was variable with 33 treatments at four gray (Gy) per fraction, seven treatments at six Gy per fraction, and five treatments at 2-3 Gy per fraction. Total dose ranged from 24 to 66 Gy, but was centered at 32 Gy. Twenty-three (51%) of the patients were treated with eight fractions of four Gy. Moreover, these eight fractions were delivered over an interval that included one weekend, for a total treatment time of nine days. Four others were treated over one additional weekend for a total treatment time of 11 days.

Systemic therapies included interferon and chemotherapy. Eight (18%) patients received interferon as an initial aspect of treatment and five (11%) received interferon after recurrence or progression. Chemotherapy was used initially in two (4%) patients and as secondary treatment in six (13%) patients.

The median follow-up from completion of radiation treatment for all patients analyzed was 23 months with a range of 2.4 to 136 months. At last follow-up, 24 patients were alive with a median follow-up of 32 months (range 13 to 136 months). For the 21 patients who had died, the median follow-up was 13 months with a range of 2.4 to 44 months. Of the 24 patients alive, 11 (24%) had evidence of disease and 13 (29%) had no evidence of disease. Two expired patients and one patient still alive never achieved disease-free status after completion of treatment.

The median disease free survival (DFS) for all patients was 12 months (Figure 1). For 26 patients (including the three with persistent disease) that had evidence of malignancy, the median time to progression was six months. Of the three patients that had residual local disease after treatment, one had persistent stable disease but experienced distant failure and died at seven months; two patients had progressive local disease but no distant failure (one dead at seven months and one alive at 13 months). An additional seven patients had a subsequent recurrence within the radiation field; all but one also had distant failure concurrent with the local failure. For the seven local failures, the median time to disease recurrence was 12 months. Overall, local control was achieved and maintained in 35 patients (78%), with a median time to recurrence not being reached (Figure 1).

A total of 26 patients had a recurrence outside the radiation field with a median time to distant failure of seven months. Of the 26 distant failures, six patients (as described above) had concurrent local failures leaving 21 patients with isolated distant failures. The median time for failure for these 21 patients was nine months. The most common site of distant failure was the central nervous system with 13 patients or half of all distant failures.

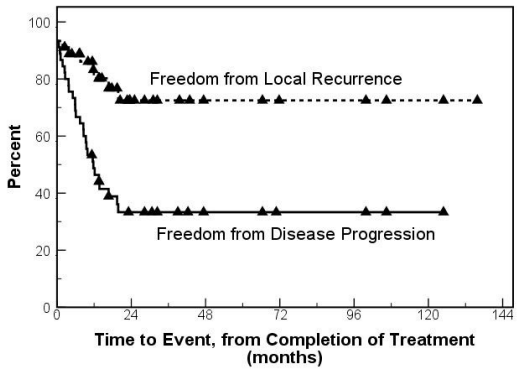

Figure 1. Comparison between Freedom from Local Recurrence (dashed line) and Freedom from Disease Progression (solid line). The triangles indicate times at which patients were censored.

Table 2. Analysis of factors associated with outcome.

Factor		**Number of Patients**	**Freedom from Disease Progression**		**Freedom from Local Recurrence***
			Median, months	**p value**	**p value**
Gender	Male	27	17	**0.010**	0.078
	Female	18	6		
Prior treatment	Primary radiotherapy	16	12	0.90	0.77
	Secondary radiotherapy	29	12		
Lymph nodes at time of treatment	Positive	25	9	0.19	0.39
	Negative	20	14		
Age	< 60 years	19	9	0.79	0.45
	> 60 years	26	12		
Total dose	< 32 Gy	11	6	0.090[a]	0.26[a]
	32 Gy	23	20	**0.010****	**0.001****
	> 32 Gy	11	7	**0.002**[b]	**0.010**[b]
Depth (initial)	Tis-T2 (0-2 mm)	22	10	0.77	1.0
	T3-T4 (> 2 mm)	23	10		
Lymph nodes at initial diagnosis	Positive	17	14	0.96	0.64
	Negative	28	12		
Treatment time	≤ 12 days	24	14	0.042	**0.001**
	> 12 days	21	9		

*Median times for Freedom from Local Recurrence were not reached except for the sub-groups of Total dose > 32 Gy and Treatment time > 12 days, both of which were 12 months.

**Global analysis for difference: [a]Comparison between <32 Gy and 32 Gy; [b]Comparison between 32 Gy and >32 Gy.

Multiple factors were examined for a possible effect on freedom from disease progression (Table 2). The only factors that were statistically significant predictors by univariate analysis were gender (p=0.010), with males doing better, and total dose (p=0.010 overall), with better outcome being exhibited when the dose was exactly 32 Gy, compared to doses <32 Gy (p=0.090) or >32 Gy (p=0.002). There were no statistically significant differences in clinical presentation (age, T-stage, nodal status, histology, etc.) between the three dose groups (<32 Gy, 32 Gy, >32 Gy). There was a marginal influence of total treatment time, with patients treated in 12 days or less exhibiting better outcome than patients whose treatment required longer than 12 days (p=0.042). By multivariate Cox regression analysis, both total dose (p=0.006) and gender (p=0.019) were retained as independent predictors of freedom from disease progression.

Similarly, factors influencing freedom from local recurrence were examined (Table 2). As with freedom from disease progression, total dose influenced the outcome (p=0.001 overall), with patients that received >32 Gy exhibiting a poorer outcome (6/11 patients recurring, 55%) than

patients that received exactly 32 Gy (4/23 patients, 17%), which was statistically significantly different (p=0.010). However, patients that received <32 Gy actually exhibited a better outcome (none of the 11 patients recurred) than patients who received 32 Gy, although the difference was not statistically significant (p=0.26). Only for the >32 Gy group was a median time to event reached (12 months). Also, overall treatment time was a factor (p=0.010) with patients treated in less than 12 days doing better than patients whose treatment required >12 days. Again, only for the latter group was median time to event reached (12 months). By multivariate Cox regression analysis, the overall treatment time was retained (p<0.001) and gender (p=0.050) was added as independent predictors of freedom from local recurrence. However, if overall treatment time was not included, then only total dose was identified as a predictor (p=0.001).

Discussion

As with any retrospective review, these data need to be interpreted with caution. There is an inherent bias in patients that are referred for adjuvant radiation treatment and also patients who elect to undergo radiotherapy. Despite these limitations, outcomes data such as these are valuable in estimating the possible benefit to patients in terms for local control and overall-survival.

Our outcomes, with a median time for freedom from disease progression and DFS of 12 months and a local control rate of 78%, were consistent with some of the ranges reported in the literature. Stevens et al.[6] found a local recurrence rate of 11% and median disease free survival of 25 months in 174 high-risk patients. Ang et al.[7] reported a 5-year 88% local control rate and survival rate of 47%, with a hypofractionated treatment regiment for high-risk head and neck melanoma. Ballo et al.[8] reported on treatment of 89 consecutive patients with axillary radiation, finding a 13% failure rate in the treated axilla and in a separate report of 160 patients with cervical radiation, a 9% local failure rate at 10 years.[9] Cooper et al.[10] had a five-year actuarial failure rate of 16% in a review of 40 patients treated with elective post-operative radiation. Corry et al.[11] described a 74% treatment failure rate at five years in their treatment of high-risk nodal areas. One explanation for the wide range of results for adjuvant radiation was the different institutional indications for treatment, thus different patient populations.

We analyzed the data to see if certain patient subsets had better outcomes. For freedom from disease progression, gender was a significant factor, with males having a more favorable prognosis. This finding was contrary to other authors who have found male gender to be an adverse prognostic factor.[1] This result may reflect a type I statistical error due to the small number of patients in our study. In addition, the total dose delivered had a significant impact on outcome, with those patients receiving 32 Gy in eight fractions of four Gy each (51% of all patients) exhibiting superior outcomes compared to patients that received total doses less than or greater than 32 Gy.

For freedom from local recurrence, similar findings were obtained, with a better prognosis for those patients treated with 32 Gy than for those patients that received >32 Gy total dose. These analyses are confounded by the fact that a large proportion (51%) of patients were treated with the same regimen, eight fractions of four Gy for a total dose of 32 Gy. Of the ten additional patients treated with four Gy fractions, two received a total dose <32 Gy and eight received a total dose >32 Gy. Likewise, of the 23 patients that received a total dose of 32 Gy, all but four required a total treatment time of 12 days or less. Thus, there were close correlations between

total dose, dose per fraction, and treatment time, with the consequent potential for one variable to confound the impact of another variable in the analysis. None-the-less, the results suggested that overall the KUMC "standard" regimen of 8 x 4 Gy in less than two weeks was effective for achieving and maintaining local control.

Many institutions have reported results using a hypofractionated (giving the same total dose of radiation over fewer fractions) radiation scheme, typically 30 Gy in five twice-weekly fractions[6-10] although this has not been proven to be superior to more conventional fractionation schemes. Chang et al.[15] retrospectively compared hypo-fractionation and conventional fractionation in 56 cutaneous melanoma patients and did not find any difference in the two regimens. While a larger series may reveal a patient subset that benefits from higher overall treatment dose, caution should be used in higher fraction doses since this will predispose patients to a greater degree of radiation side effects, especially lymphedema.

Post-operative radiation therapy appears to provide good local control but it may not affect survival since the majority of patients have distant failures despite good local control. In this series of patients, there were no isolated local failures. The implications for future treatment directions should thus focus on more systemic therapies. While it is possible that more aggressive use of radiation for the initial primary tumors and lymph node basins could destroy microscopic disease before it has a chance to spread distantly, it is possible that such treatment would only provide improved local control and that patients would eventually succumb to distant failures.

While a randomized trial would give the best level of evidence for the usefulness of postoperative radiation, our data indicated that adjuvant radiation in a post-operative setting appears to reduce local recurrence and should be considered for patients with malignant melanoma at high risk for local failure.

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Keywords: melanoma, radiation, adjuvant radiotherapy, Kansas

TMP-SMX Induced Aseptic Meningitis

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Introduction

Aspetic meningitis secondary to drug adverse effects is a rare but serious disorder, most commonly reported with non-steroidal anti-inflammatory drugs and trimethoprim and sulfamethoxazole (TMP-SMX). Early diagnosis is important, since the cessation of the problem drug leads to rapid clinical improvement. We report a case of TMP-SMX induced meningitis.

Case Report

A 24-year-old previously healthy man was admitted after a four-day history of severe headaches, neck stiffness, nausea, vomiting, and low grade fever and chills. He had been taking TMP-SMX for 18 days for a suspected community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) abscess of his right groin. In addition, he noticed sudden onset of a diffuse maculo-papular rash on the day of presentation sparing only his face and palms.

The patient denied any history of contact with infected individuals, cough, or sinus discharges. His past medical history was negative. He had never taken TMP-SMX. He smoked cigarettes, but did not report any alcohol or illicit drug use. He had no known medication allergy. On presentation, he was awake and oriented.

On physical examination, the patient showed a positive Brudzinski sign and the rash as described above, as well as a painful, 2x2 cm, right groin abscess. Vital signs were remarkable for a temperature of 103°F and a heart rate of 103 bpm.

A Complete Blood Count (CBC), Comprehensive Metabolic Profile, urinalysis, chest xray, and a brain CT scan were normal. Lumbar puncture was significant for 427 WBCs with 93% segmented neutrophils, protein of 51, normal glucose, and and no organism on gram stain. The following tests were negative: *Rickettsia rickettsi* serology, human immunodeficiency virus (HIV) antibody, *Erlichia chaffensis* serology, Lyme disease serology, herpes simplex virus polymerase chain reaction (PCR) on cerebrospinal fluid (CSF), Enterovirus PCR on CSF, Tularemia serology, cryptococcal antigen, *Bartonella* serology, venereal disease research laboratory (VDRL) test. Bacterial, viral, acid fast, and fungal cultures and stains also were negative. TMP-SMX was stopped on admission and the patient recovered within three days.

Discussion

TMP-SMX induced meningitis has been well reported in literature. The reaction is idiosyncratic.[1] The described symptoms can occur in patients naïve to TMP-SMX as well as previous users. These symptoms can occur hours to weeks following administration of the drug. Meng et al.[2] reported recurrent aseptic meningitis following TMP-

SMX use for urosepsis four times in the same patient.

The pathogenetic mechanism of this disease is still uncertain. Possible mechanisms include hypersensitivity reaction, direct drug toxicity, and immune complex deposition. Antonen et al.[3] suggested IL6 as a possible mediator.

Symptoms usually include mild headache, low grade fever, and neck stiffness, although hemodynamic compromise and respiratory failure requiring intubation and admission to the intensive care unit also have been reported.[1] Cerebrospinal fluid analysis suggestive of TMP-SMX induced meningitis includes a neutrophilic pleocytosis and mildly elevated protein along with normal glucose and negative gram stain.[1]

Some reports suggested that CSF fluid findings alone cannot differentiate between TMP-SMX induced meningitis and partially treated bacterial or viral meningitis.[4] Brain CT scan is normal in most case reports. Blumenfeld et al.[5] described MRI findings consistent with diffuse bilateral T2 signal abnormalities of the white matter of the cerebral hemispheres.

Recovery after discontinuation of the drug, and negative viral, bacterial, and fungal cultures are strongly suggestive of TMP-SMX induced meningitis. Fortunately, recovery is complete most of the time and uneventful within 3 to 11 days, even in the case of most severe symptoms.

Conclusion

The incidence of TMP-SMX induced meningitis is unknown. It does not appear to be dose or time related. Neutrophilic pleocytosis and negative cultures are essential for the diagnosis. Treatment is discontinuation of the drug. Prognosis is usually excellent.

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Keywords: trimethoprim-sulfamethoxazole combination, aseptic meningitis, adverse effects, case report

Hypercalcemia and Paraproteinemia in Squamous Cell Bladder Cancer

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Introduction

Squamous cell carcinoma (SCC) comprises about 1.2 - 4.5% of all vesical tumors in the United States.[1] In contrast, it comprises almost 75% of all bladder cancers in areas endemic of *Shistosoma haemotobium.* In non-bilharzial regions of the world, SCC involves chronic irritation, such as prolonged indwelling Foley catheters and chronic urinary tract infections, which confers up to 28-fold increased risk for SCC.[2] There are previous reports of humoral hypercalcemia and paraproteinemia associated with bladder cancers, but not simultaneously.[3-7]

We report the first known case of squamous cell carcinoma of the bladder with paraproteinemia and symptomatic hypercalcemia. We also review the literature on humoral hypercalcemia.

Case Report

A 54-year-old African-American female presented with complaints of weakness, urinary retention, and fever of approximately one-week duration. She had a history of multiple sclerosis with a chronic indwelling Foley catheter secondary to a neurogenic bladder. The initial examination in the emergency department showed an obstructed Foley catheter that when replaced, five mL of grossly bloody urine was returned.

The initial labs were significant for a creatinine of 15 mg/dL, BUN of 125 mg/dL, potassium of 5.7 mmol/mL, white blood cell count of 12900 cells/mm^3, and hemoglobin of 8.5 mg/dL. Iron studies were consistent with anemia of chronic disease.

A computed tomography of the pelvis showed bilateral severe hydro-nephrosis with circumferential thickening of the bladder wall. The patient was started on dialysis. Bilateral ureteral tubes failed to relieve the obstruction. Nephrostomy was necessary to drain the kidneys. After initial stabilization, cytoscopy was performed and a bladder tumor was identified. Pathology revealed a moderately differentiated squamous cell carcinoma with focal necrosis and invasion into the muscle wall.

During the hospital course, the patient had multiple electrolyte abnormalities that were corrected. However, she had persistent increased serum protein and symptomatic hypercalcemia of 12.0 mmol/mL that was unresponsive to intravenous hydration and loop diuretic therapy. The hypercalcemia was controlled by pamidronate.

Parathyroid hormone (PTH) and vitamin D were low. Serum and urine immuno-electrophoresis showed a monoclonal peak of 153 mg/dl of immunoglobulin Kappa light chain confirming paraproteinemia and a clinical picture suggestive of multiple myeloma. However, the bone marrow biopsy showed only 1% plasma cells. A skeletal survey and bone scan were negative. The diagnosis of monoclonal gammopathy of undetermined significance (MGUS) was made. Later, lab results for parathyroid

hormone-related peptide (PTH-rP) were found to be elevated, confirming the diagnosis of humoral hypercalcemia secondary to a paraneoplastic syndrome of the bladder tumor.

Ultimately, the patient was stabilized for surgery and underwent cystectomy, hysterectomy with bilateral oophorectomy, and bladder reconstruction. She had severe adhesions in her abdomen and metastatic disease in her peritoneal cavity. Her PTH-rp level dropped to normal after surgery. The patient declined transfer to a skilled nursing home and was discharged home against medical advice.

Discussion

The pathophysiology of hypercalcemia of malignancy is most commonly the result of two mechanisms, osteolytic and humoral.[8] Osteolytic hypercalcemia occurs by invasion of the tumor into the bone, either by direct invasion or metastatic disease, commonly seen in breast cancer, lymphoma, and multiple myeloma.[9] Interestingly, myeloma cells activate genes that result in a dysregulation of normal bone homeostasis, resulting in simultaneous stimulation of bone resorption and inhibition of bone formation.[10]

Humoral hypercalcemia of malignancy (HHM), first suggested by Albright in 1941,[11] is most commonly due to the secretion of parathyroid hormone–related peptide (PTH-rP) and less commonly a result of secretion of the active form of vitamin D, 1,25-dihydroxyvitamin D.[3] It is commonly seen in squamous cell carcinoma of the lung, renal cancer, ovarian cancer, and endometrial cancer.[9] PTH-rP, genetically different than the native variant, is a peptide that binds to the PTH receptor and stimulates osteoclastic bone resorption causing hypercalcemia.

The work-up for metastatic bone disease and multiple myeloma were negative. This finding is still significant since paraproteinemia, such as MGUS, are associated to solid tumor and are able to bind calcium, causing hypercalcemia.[7,12] Thus, the patient's hypercalcemia could be due to either HHM, a non-calcium-binding mechanism or paraproteinemia, which can be calcium-binding. The distinction was necessary since therapy is not indicated in the latter.

Hypercalcemia secondary to a calcium-binding paraprotein would be expected to be asymptomatic. The ionized calcium would be expected to be within normal limits. Treatment of hypercalcemia does not affect survival, but is necessary to prevent the complications of hypercalcemia in the interim before surgery.[9]

Our patient had increased ionized calcium along with a finding of PTH-rP, confirming HHM and ruling out a calcium-binding paraproteinemia. Even though one study[7] suggested that paraproteinemia may be as high as 1.1% in patients with solid tumors, to our knowledge, this is the first report of a patient with HHM with the etiology of the elevated calcium being confounded by paraproteinemia.

Humoral hypercalcemia of malignancy is not uncommon and is well documented in squamous cell carcinomas of the esophagus, cervix, and lung, but is rarely documented in squamous cell carcinoma of the bladder. There have been prior reports of humoral hypercalcemia of malignancy in squamous cell carcinoma of the bladder, but to our knowledge this is the first reported case of hypercalcemia of squamous cell carcinoma of the bladder with an associated paraproteinemia.

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Keywords: hypercalcemia, paraproteinemia, parathyroid hormone-related peptide, squamous cell carcinoma

Cardiovascular Health Delivery System in Belarus Contrasted to the United States

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Introduction

Health service and resource availability and utilization vary markedly between nations. We contrasted cardiovascular care and technology in Belarus and the United States. One author (Dr. Inna Porter) was a practicing cardiologist in Belarus until 2002.

Belarus is one of the countries of the former Soviet Union which achieved independent status in 1991. It is located in the center of Europe and shares borders with Russia, Ukraine, Poland, Lithuania, and Latvia. Belarus with a territory of 208,000 square kilometers is about the same size as the state of Kansas. With a population of 10.3 million, Belarus has about the same number of citizens as the state of Ohio and about four times more citizens than the state of Kansas.

Minsk is the capital of Belarus and is home to approximately 15% of the population. Over 80% of the population is Belarusian, 10% are Russians, and the remaining 10% are mostly Ukrainian and Polish. The Russian Orthodox religion is predominant in Belarus. There are also small populations of Roman Catholics and Jews.

In the first years after the break up of the Soviet Union, there was a profound economic collapse in Belarus that affected the health system and the health of the population in general. The Chernobyl disaster on the border of neighboring Ukraine also had a direct impact on the health of the people. Life expectancy in Belarus in 2003 was 62.7 years for males and 74.7 years for women.[1] In comparison, life expectancy in the United States in 2002 was 74.5 years for males and 79.9 for females.[2] Cardiovascular disease and cancer are the leading causes of death in both countries. Although medical care now is much improved in Belarus, it still remains inadequate compared to the delivery of health care in most European countries and the United States.

Brief Overview of Belarusian Health Care Delivery System and Its Structure[3]

The delivery of health care, its structure, and organization in Belarus have not evolved much since the declaration of independence. There is free access to health care for all citizens of Belarus that is financed by the government. Regardless of socioeconomic status, everyone is eligible for a comprehensive package of free health care benefits. This package includes all care offered by most state institutions except prescribed outpatient medications, glasses, cosmetic surgery, and some dental services.

There are additional ways to obtain medical services in Belarus. Patients can choose a private clinic and pay for the services out of their own pocket or they can pay directly to a state institution for services that were not requested by the patient's provider. The other way one can obtain enhanced medical care is to pay for supplemental health insurance. This insurance is offered by private companies and is intended to cover expenses not covered by government provided services.

Each citizen of Belarus is assigned to a local polyclinic. This means that each polyclinic must provide care for all of the people living within a designated territory. The patients who require procedures that are

not offered locally are referred to a regional clinic or hospital, where more specialized services are available.

Most pharmaceuticals in Belarus can be purchased without prescription. The medications that must be obtained with a prescription are narcotics, medications used in psychiatry, sedatives, tranquilizers, and tinctures with a high percentage of ethanol. Such access to pharmaceuticals leads sometimes to self-treatment, especially in cases of cough, diarrhea, headache, and any kind of pain.

Cardiovascular Care in Belarus

The system of health care delivery described above works quite well if a patient needs to see a primary care or a specialty doctor, requires general surgical procedures, or needs emergency care. Many changes were made in the past several years to improve medical care in Belarus including building several new fully-equipped hospitals and opening new clinics. Due to economic difficulties, there is a shortage of medical equipment, but most basic procedures are readily available.

Echocardiograms, chemical and exercise stress tests, esophagogastroduodenoscopies, and colonoscopies are available in most of the regional polyclinics and hospitals. Due to the limited availability of magnetic resonance imaging or computed tomography equipment, it is more difficult to get these studies performed and they are not used widely. For the same reason, only one cardiology institution in Belarus offers myocardial perfusion studies. There are only four hospitals in the Republic that offer interventional cardiological procedures.

The availability of heart catheterization and open-heart surgeries has increased in the past few years due to the opening of new cardiology hospitals. There were a total of 1140 coronary angiographies performed in 2004 for the entire population of over ten million people. In comparison, over 50,000 coronary angiographies were performed in the United States per population of over ten million people in 2003. Table 1 contains approximate data of some cardiovascular procedures that were done in Belarus in 2004 and the United States in 2003 per ten million people.[4-6]

The limited availability of interventional cardiology procedures caused by inadequate government funding has led to unspoken rationing when choosing patients for a heart catheterization. The criteria of age, presence of associated severe diseases, untreated alcoholism, or high-risk complications are used when choosing patients for free coronary angiography. A special commission of Health Ministry must approve each free heart catheterization. The age of the selected patients is usually under 65. A patient also can pay the equivalent of $350 (US) out of pocket for diagnostic heart catheterization (The median salary in Belarus is about $150-200 (US) per month). Angioplasty and stenting also could be performed if the patient pays for them, but the cost of these procedures is unaffordable for most patients.

Coronary angiography and angioplasty often are done for the patient only after recovery following myocardial infarction, but not during the acute stage. Absence of an emergent interventional cardiology program is probably the main reason for delay. There also is belief that the more stable the patient, the better the chance that he or she will survive the procedure and would have fewer complications. The patient's decision also plays a big role in whether to proceed with heart catheterization or not. Many Belarusian patients favor more conservative treatments. Occurrence of severe angina may push them finally to have an interventional procedure.

Table 1. Cardiovascular procedures done in Belarus in 2004 and the US in 2003 per 10,000,000 people.

	Cardiac Catheterizations	Cardiac Catheterizations With Angioplasty and/or Stenting	Bypass Surgeries	Valve Replacement Surgeries	Surgeries For Congenital Heart Diseases	Pacemaker Placement
Belarus	1140	74	674	334	423	1600
USA	50,000	18,622	17,859	3225	867	6900

In Belarus, the mortality rate during and after bypass surgery is about 4.6%.[4] This is higher compared to the rate of 2.4% in the United States.[6] Assuming that bypass surgeries are usually done in a lower risk population in Belarus (due to the selection factors noted above), the higher death rate could be related to such factors as inadequate intraoperative and postoperative care due to shortage of nurses, specialized beds, medical supplies, and some medications.

The postoperative mortality rate of valve replacement surgeries is about 4.7% in Belarus.[4] This is lower than in the United States where mortality rate after the same procedure is about 5.8%.[6] This difference could be related to the selection of a lower risk patient population in Belarus.

Patients with myocardial infarction usually receive standard supportive therapy with beta-blocker, aspirin, angiotensin converting enzyme inhibitor, heparin, and thrombolysis if indicated. Inhibitors of platelet glycoprotein 2b/3a receptors almost never are used in Belarus because of the high cost. The statins and anti-platelets like clopidogrel are prescribed widely by doctors. However due to their high cost, most patients cannot afford to buy them.

A cardiac balloon pump is available only in the Republic Cardiology Institute and is not used often due to the cost of its initiation and operation. Patients receive therapy with heparin for about three weeks after an acute event. The average hospital stay after acute myocardial infarction is 14-16 days. After that, patients usually are sent to free rehabilitation centers for 21 more days. Physicians in Belarus are instructed not to discharge the patient unless the most vulnerable period after acute myocardial infarction is over.

The average hospital stay after acute myocardial infarction in the United States is only 3.7 days. These profound differences in post-infarction length of stay may be related to many factors including the use of invasive interventional procedures in the US, the impact of third party insurance and Medicare coverage for hospitalizations, greater impact of evidence-based guidelines in the US, as well as cultural differences between the nations.

About 24 bypass tract ablations a year are performed in the Republic Cardiac Institute. This is the only place where this procedure is performed and patients referred here usually have recurrent arrhythmias due to Wolf-Parkinson-White syndrome. There are only two hospitals in Belarus that offer pacemaker placement. Heart transplant is not available in Belarus.

Lack of interventional procedures in Belarus is probably the main reason why the mortality rate from cardiovascular diseases is much higher than in the US. The hospital mortality of the patients with acute myocardial infarction in Belarus is 8.9% while in the US it is only 2.5%.[4,6]

Interestingly, the mortality rate ratio from coronary heart disease for males and females is similar in both countries: 1.6 to 1 in the US and 1.7 to 1 in Belarus.

Table 2 summarizes the latest available data on mortality from some cardiovascular diseases in the US, Belarus, and countries of the Commonwealth of Independent States (CIS; an organization for economic cooperation composed of several republics of the former Soviet Union) per 100,000 populations in 2003. The mortality from cardiovascular diseases is more than twice as high in Belarus than in the US. In spite of higher mortality rates, the prevalence of cardiovascular diseases and risk factors in Belarus is reported as significantly lower than in the US (Tables 3 and 4), although this may be due in part to less screening and recognition.

In comparison with other CIS countries, the mortality in Belarus is much lower. Belarus is the only country from the former Soviet Union where free medical care still exists and is easily available. This health system may be one of the reasons for the lower mortality rate in Belarus than in other CIS countries.

Table 2. Mortality from cardiovascular diseases in the US, Belarus, and CIS countries per 100,000 people in 2003.

Country	Cardiovascular Diseases	Coronary Heart Diseases	Cerebrovascular Diseases
US	309	163	56
Belarus	694	456	173
CIS countries	821	434	251

Table 3. Prevalence of cardiovascular diseases in the US and Belarus per 100,000 adult populations.

Country	Cardiovascular Diseases	Coronary Heart Diseases	Myocardial Infarction	Angina Pectoris
US (2003)	32,750	6062	397	3903
Belarus (2003)	26,911	8169	169	2226

Table 4. Prevalence of coronary artery disease risk factors in the US and Belarus.

Country	Hypertension	Diabetes Mellitus	Tobacco	Hypercholesterolemia	Physical Inactivity	Overweight/ Obese
US (2003)	32%	7%	21%	50%	61%	65%
Belarus	15% (2003)[4]	2% (2003)[1]	27% (2003)1	36% (1999)[7]	17% (1999)[7]	24% (1999)[7]

A lower prevalence of cardiovascular diseases in Belarus may be related in part to a high mortality rate and a shorter life span compared to the US, in addition to the reporting factors mentioned above. While the accuracy of Belarusian statistical data may account to some degree for the lower prevalence of risk factors, other reasons, such as physical activity and a healthier diet, may contribute to the lower prevalence of risk factors. Belarusian people probably have a more physically active lifestyle than Americans. For example, only about 22% of Belarusian people own a car. Although use of public transportation is common, walking to the places of work or shopping are more typical for Belarusians than for Americans.

It is customary for people in Belarus who live in suburban or urban areas to own a country house, called a "dacha", with a small parcel of land, where people grow vegetables and fruits during spring to fall. City dwellers usually go there on weekends to work on their garden. The garden work involves a lot of physical activity as most is done by hand without any heavy machinery. The produce from the dachas are for personal consumption and rarely sold on the market. Some of the vegetables and fruits are preserved for use during the winter. While no reliable studies have been done in Belarus to evaluate the diet structure, it is more likely that the diet intake of Belarusians is higher in fiber and lower in saturated fats, sugar, and salt, than the diet of Americans.

As shown in Table 4, smoking is more prevalent in Belarus than in the US. According to the surveys, 68% to 83% of all smokers in Belarus are males.[8,9] In the US, the percent of smoking males and females is about the same. High tobacco use among Belarusian males could contribute to their shorter lifetime compare to the Belarusian women.

Preventive cardiovascular medicine in Belarus and in the US is somewhat different. People in Belarus are educated about cardiovascular risk factors and a healthy lifestyle through the mass media, brochures, and lectures that are given in polyclinics. Educational lectures also are held periodically for employees of different factories, schools, and institutions. Education is focused more on a healthy lifestyle rather than on taking lipid-lowering medications.

Lipid profile screening tests are offered at no cost in most polyclinics. Recreation centers are common in big cities, but not in most small towns. Use of statins is significantly lower in Belarus than in the US, but use of herbal medicine and fish oil is very popular. Preventive medicine in the US as contrasted to that in Belaurus may differ in regards to attention to a healthy lifestyle as opposed to pharmacologic intervention, but detailed information regarding these factors is not available. While preventive medicine exists in both countries, the relative effectiveness in prevention of cardiovascular diseases at this point remains unclear.

Summary

Despite the economic crisis that Belarus has experienced after the collapse of the Soviet Union, the Belarusian government has managed to provide a free comprehensive package of heath care to the entire population. Remarkable achievements have been made in providing unlimited access to free services, but lack of available resources and funding remains a significant problem for optimal care. Thus, due to limited finances and a shortage of medical equipment, procedures like heart catheterization and open-heart surgery are available mostly to a selected younger group of patients. Most sophisticated medical services are not readily available in the rural

areas. All these factors lead to a higher mortality rate from cardiovascular diseases. An increased number of interventional procedures may lower the mortality rate, but lack of funding may impede further development of cardiovascular care in Belarus for many years. In this situation, development of an alternative insurance subsidized care plan would be a very important factor in providing the best treatment for cardiac patients.

Although medical care in Belarus lags behind most Western European countries and the US, it is more easily accessible compared to other countries of the former Soviet Union. According to the survey of Balabanova and colleagues[10], 9.4% of Belarusian people did not seek professional care when they experienced an episode of illness. Only 0.7% of those respondents reported that the reason for not seeking care was lack of money. These numbers were significantly lower than in the other former Soviet Union countries that underwent a similar survey. While the health care in Belarus is affordable and easily accessible, there is still concern about its sustainability in the face of economic problems.

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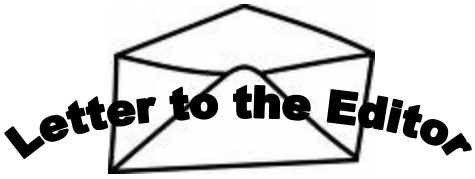

Statins Not Beneficial in Most Chest Pain Admits

Dr. Moore[1] shares two concerns with regard to my commentary[2] that most admitted chest pain patients should not be started on statins. First, he is concerned that a proper cardiac risk stratification for a chest pain patient requires a lipid panel. Secondly, he believes a non-fasting lipid panel may be an acceptable alternative for a fasting lipid panel.

If this patient was an asymptomatic clinic patient being screened for future risk, I would agree with Dr. Moore. But the acutely-stressed patient presenting with "chest pain" is considerably different.

First, lipid levels have not been proven helpful in discriminating the etiology of chest pain. This information may be occasionally helpful to predict risk over 5-10 years, but it does nothing for the "chest pain" patients in the hospital. In fact, few risk factors (discovered in long-term epidemiological studies) have any discriminatory value used prospectively in the ER for chest pain patients.[3,4] Screening all "chest pain" patients in the ED routinely to pick up the rare familial hyper-cholesterolemia is unjustified.

Secondly, there are problems of a non-fasting calculated LDL (and currently no commonly available non-fasting direct measures) as Dr. Moore acknowledges. In addition, a patient who is ill or metabolically stressed may have skewed lipid results (not to mention liver functions).[5]

The place for accurate lipid levels, long-term risk stratification, statin consideration and compliance issues for most "chest pain"
patients is back in the office for a follow-up visit – not the ER.

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