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Research in brief

Are Hodgkin and non-Hodgkin patients at a greater risk of atherosclerosis? A follow-up of 3 years

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Are Hodgkin and non-Hodgkin patients at a greater risk of atherosclerosis? A follow-up of 3 years

Aims and background are to ascertain whether Hodgkin and non-Hodgkin patients are more affected by atherosclerotic process. We studied 96 patients during a period of 3 years (2003–2007). Patients were assessed in the first year soon after receiving radiotherapy and chemotherapy and then reassessed in the third year. All the cases underwent echo-colour Doppler of the carotid axis, and the intima-media thickness (IMT) was measured. When the two time points were compared, the IMT was greater in the arterial district examined at the first assessment; while at the second there was a reduction in the IMT, so patients seemed to improve with time. Flow-mediated dilatation did not improve. Hodgkin and non-Hodgkin patients experience an increase in IMT during treatment, but afterwards they return in their precedent condition. They seem to have a persistently reduced flow-mediated dilatation. Lymphoma therapy probably predisposes patients to early atherosclerosis, and it would be worth trying to reverse this tendency by administering antioxidant therapy.

Keywords: Hodgkin and non-Hodgkin disease, carotid atherosclerosis, intima-media thickness, ultrasound, radiation therapy.

INTRODUCTION

In a recent work, we found that irradiation of the neck of Hodgkin (H) and non-Hodgkin (NH) patients determines a greater intima-media thickness (IMT) of arterial wall than in controls matched for the classic atherosclerosis risk factors, so we concluded that radiotherapy (RT) can influence the atherosclerotic process (Bilora *et al.* 2006). This result is also confirmed by the fact that patients with lymphoma who had RT involving the mediastinum showed an accelerated vascular atherosclerosis (high mortality because of heart attacks) (Renner *et al.* 1999; Basavaraju & Easterly 2002). Cheng examined 130 carotids of irradiated patients during a follow-up of 36 months and concluded that external radiation of the head and neck makes atherosclerosis progress more rapidly than in atherosclerotic arteries unaffected by RT (Cheng *et al.* 2004).

However, other studies have claimed that endovascular RT after balloon coronary angioplasty prevents restenosis by inhibiting myointimal growth and chronic vascular spasm (King *et al.* 1998; Cheng *et al.* 2004).

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Given these conflicting results, we tried to ascertain whether RT truly influences the atherosclerotic process. To do so, we studied a group of lymphoma patients using echo-colour Doppler, in two different times, that is, soon after RT and again 2 years later. We used echo-colour Doppler for these reasons: (1) it is safe (De Groot 2008); (2) it is reproducible (De Groot 2008); and (3) it can find the precocious changes in the artery wall and their modifications after therapy (Crouse *et al.* 2007).

PATIENTS AND METHODS

Over a period of 48 months (March 2003–March 2007), we studied 96 consecutive subjects (male 48, female 48; mean age 59.3 ± 6.5) of them, 54 with NH lymphoma and 42 with H lymphoma, all attending our outpatient clinic for regular check-ups and or treatments. All the subjects had received chemotherapy as well as external beam RT. The last dose of RT was administered a mean of 2 months before the study began (range 4 months to 2 weeks). Radiotherapy included the mantle field, the lymph nodes below the diaphragm and the spleen. The total dose of radiation to the upper body was between 36 and 40 Gy; for the spleen it was between 10 and 20 Gy, and for the paraaortic lymph nodes it was 20 Gy. Patients were given chemotherapy in the years that followed.

All the patients were studied for the common risk factors for atherosclerosis (Table 1). Patients with diseases associated with atherosclerosis, for example, acute myocardial infarction, angina pectoris, transient ischemic attack, murmur, carotid endoarteriectomy, obliterating arteriopathy of the legs, aorta aneurism, were excluded. Patients with autoimmune or thyroid disease and individuals using steroids or contraceptives were also ruled out. All subjects provided their clinical history and underwent physical examination, chest X-ray, electrocardiogram and routine blood tests.

In 2003, all patients had colour Doppler evaluation of the carotid axis using Esaote Technos MP High resolution instrument (Toshiba, Tokyo, Japan) and 7.5-MHz probe for B-mode ultrasound and 6-MHz for pulsed Doppler. This test was repeated 36 months later. The method for studying plaques and IMT is well known (Carpenter *et al.* 1996; Contado *et al.* 1997). In the latter part of the study we also measured flow-mediated dilatation (FMD) (Corrretti *et al.* 2002). All the tests were conducted by an ultrasound technician and were videotaped and reassessed by another ultrasound technician for validation purposes. Contrasting results were further evaluated blindly by a senior expert.

Table 1. Risk factors for atherosclerosis

Risk factors	
Smoking habits	>5 cigarettes/day
Hypertension	Blood pressure 140/90 mmHg or current therapy
Diabetes mellitus	Fasting glycemia >6.1 mmol/L or current therapy
Hypercholesterolemia	Total cholesterol >5.2 mmol/L or current therapy
Obesity	BMI 26 for female BMI 28 for male

BMI, body mass index.

Statistical analysis

Plaques, IMT and FMD were compared using Student's two-tailed *t*-test for matching data.

RESULTS

We examined 96 patients during the first year. The population's risk factors are summarised in Table 2. The number of the plaques and the mean IMT are given in Tables 3 and 4. During the follow-up, 22 patients (21.1%) were lost to follow-up: one had a stroke and became tetraplegic; the others probably went to another centre. Thirty-one patients (29.8%) died. Table 4 shows the reduction in the IMT of carotid axis at the last assessment (the longest time after RT), and Table 3 shows the stability of the plaques, which generally coincided with a degree

Table 2. Risk factors for atherosclerosis in cases

Age (years)	59.3 ± 6.5
Hypertension	20%
Hyperlipidaemia	6%
Body mass index (kg/m^2)	29 ± 1.5
Smoking habitus	25%
Diabetes mellitus	6%
Gender (% male)	50%

Table 3. Percentage of patients with plaques the 2 years considered

Carotid districts	% of patients with plaques in 2003	% of patients with plaques in 2007
Common	19.2	17.3
Bulb	20.2	23
Internal	18.3	17.3

Table 4. Intima-media thickness (IMT) in mm, in the two considered years

Carotid districts	IMT (mm) in 2003	IMT (mm) in 2007	*P*
Common	1.14 ± 0.17	0.8 ± 0.20	<0.05
Bulb	1.23 ± 0.22	0.8 ± 0.15	<0.05
Internal	1.06 ± 0.15	0.7 ± 0.16	<0.05

of stenosis of 30%, while only two patients had plaques causing stenosis of 50%. During 2007, FMD was very low, only 2.56 ± 1.7.

DISCUSSION

Radiotherapy to the neck is believed to predispose to atherosclerosis (Carpenter *et al.* 1996). The progression of the atherosclerotic process may be due to a long history of cervical irradiation (>6 years) and to the total dose of radiation administered. This may be true of cancer of the head and neck, but we do not know whether it also applies to lymphoma or not, on which there are contrasting opinions and only indirect reports. The arterial calcification visible by computed tomography scans has an important role, but it does not measure the extent and size of plaques, and it cannot predict an alteration of the endothelial wall and an increase of IMT, which are markers of early atherosclerosis (Telmelkova-Kurktscjiev *et al.* 2001). A greater IMT in lymphoma patients by comparison with healthy subjects provides no conclusive evidence, because it also depend on the timing and dosage of the RT and also on the chemotherapy administered (Corrretti *et al.* 2002; Bilora *et al.* 2006). Hence, our attempt to establish whether lymphoma patients showed an increase in IMT or plaques over a 3-year period receiving RT. We found that IMT increased soon after RT but then tended to become thinner again. This is probably due to oedema caused by the radiation treatment. We consequently concluded that lymphoma and its therapy do not accelerate the atherosclerotic process. We also studied FMD in the second year (FMD was not used in 2003 because we were still learning to use this method), and the results suggest that although the IMT improves, the early endothelial damage persists, which means that atherosclerotic process may have been triggered. Perhaps adopting prophylactic measures, such as antioxidant therapy, can prevent the evolution of this alteration towards full-blown atherosclerosis (Jalal *et al.* 1990; Jalal & Grundy 1993; Tam *et al.* 2005; Baragetti *et al.* 2006).

In conclusion, lymphoma therapy may not only induce reversible changes in the endothelial wall but also be responsible for an endothelial imbalance. Prophylactic antioxidant therapy may help to prevent any progression to atherosclerosis proper.

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