Downstaging by Combination Therapy with Flutamide and an LHRH Agonist before Radical Prostatectomy

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INTRODUCTION

Although little information is available on the best choice of therapy for early stage prostate cancer (Kolata, 1987), it is well recognized that the only opportunity for a cure of prostate cancer is at an early stage when the cancer is still localized to the prostate (Walsh and Jewett, 1980; Kolata, 1987; Labrie *et al,* 1992). The main objective in prostate cancer should thus be early diagnosis and treatment of organ confined disease since it is known that such patients treated by radical prostatectomy have a life expectancy comparable to that of men who do not have prostate cancer (Jewett *et al,* 1968; Walsh and Jewett, 1980).

Unfortunately, not all men who are thought to have organ confined prostate cancer at diagnosis are found to have organ confined disease at surgery. In fact, in 50–60% of cases, the pathological analysis of the specimen obtained at radical prostatectomy shows that the cancer is more advanced than originally predicted at diagnosis (Boxer *et al,* 1977; Veenema *et al,* 1977; Catalona and Stein, 1982; Elder *et al,* 1982; Lange and Narayan, 1983; Gibbons *et al,* 1989; Brawer and Lange, 1990).

A possible means of improving the proportion of patients with organ confined disease and cancer negative margins at surgery was clearly suggested by

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the observation that patients treated by combination therapy using a pure anti-androgen associated with medical or surgical castration for metastatic disease show a much more rapid and marked regression of their cancer in the prostatic area compared with distant metastatic disease (Labrie *et al,* 1982, 1985, 1993a).

Following an encouraging preliminary trial (Monfette *et al,* 1989), we have conducted a prospective, randomized clinical trial in order to assess precisely the potential advantages of neoadjuvant combination therapy with the pure anti-androgen flutamide and a luteinizing hormone releasing hormone (LHRH) agonist administered for 3 months before radical prostatectomy compared with surgery alone (Labrie *et al,* 1993b). This chapter is an update of this first randomized trial and an analysis of the data on organ confined disease and specimen confined disease and on the comparison of the final stage at histopathology of the surgical specimen with the clinical stage at diagnosis.

METHODS

Patients

A total of 161 men aged between 46 and 72 years with histopathology proven adenocarcinoma of the prostate took part in the study. Six patients were classified at diagnosis as having stage B_0 disease, defined as one localized nodule at digital rectal examination (DRE) and/or a lesion found on transrectal ultrasonography (TRUS) of <1.0 cm (mean TRUS diameter); 82 had stage B_1 disease, defined as one localized nodule at DRE and/or a lesion on TRUS of between 1.0 and 1.5 cm (mean TRUS diameter); 46 had stage B_2 disease, defined as more than one palpable nodule at DRE and/or a lesion >1.5 cm (mean TRUS diameter); 15 had stage C_1 disease, defined as minimal palpable extracapsular extension and/or invasion of the prostatic capsule seen at histopathology of biopsy specimen; and 12 had stage C_2 disease, defined as C_1 but with, in addition, invasion of seminal vesicles and/or neurovascular bundle seen at histopathology of biopsy specimen.

The median and average ages of the patients as well as the distribution of stages at diagnosis showed no significant difference between the two groups. Among patients assigned to have retropubic radical prostatectomy alone, 26 declined randomization; in the group assigned to neoadjuvant combination therapy for 3 months (leuprolide or [$DTRP_6$, des-$GlyNH_2^{10}$] LHRH ethylamide 7.5 mg intramuscularly every 28 days or 250 μg subcutaneously daily + flutamide 250 mg every 8 hours orally) before radical prostatectomy, only four refused. Therefore, a logistic regression analysis of randomized and non-randomized patients, including covariates for treatment and important prognostic factors (age and stage), was done for each group to assess and confirm the validity of the trial, in which all eligible patients were studied (Olschewski *et al,* 1992). All patients had liver function tests on a monthly basis for 3 months, as described previously (Gomez *et al,* 1992).

TABLE 1. Effect of 3 month neoadjuvant combination therapy with the antiandrogen flutamide and an LHRH agonist on positive margins at radical prostatectomy in stages B and C prostate cancer

Group	Negative margins	Positive margins	Total
Control	47 (66.2%)	24 (33.8%)	71
Combination therapy	83 (92.2%)	7 (7.8%)	90
Total			161

χ^2 test: $p<0.001$

RESULTS

As Table 1 shows, the incidence of cancer positive surgical margins was reduced in a highly significant way to only 7.8% (7 of 90) in the group of patients who received an LHRH superagonist and flutamide for 3 months before radical prostatectomy compared with 33.8% (24 of 71) in the group of men who had no endocrine therapy before radical prostatectomy (χ^2 test, $p<0.001$). The decrease in cancer positive surgical margins is of major amplitude at all stages of the disease except at stage B_0, where there were only three patients in each group. In fact, although cancer positive margins were found in the surgical specimen in 25.6% of stage B_1, 58.8% of stage B_2, and 80% of stage C_2 control patients, the incidence of positive margins decreased to 2.6% in stage B_1, 10.8% in stage B_2 and 14.3% in stage C_2 patients who received combination therapy for 3 months before surgery.

It is then of particular interest to examine the final staging at histopathological examination of the specimen obtained at surgery compared with clinical staging at diagnosis and to determine the effect of combination therapy at each stage of the disease. Upstaging is particularly striking at stages B_1 and B_2 in the control untreated group. In fact, of 39 cancers originally classified as B_1, 21 showed a more advanced stage at surgery, including 5 C_1 and 10 C_2 disease (Table 2). Similarly, of 17 cancers originally classified as B_2 disease in the control group, 3 became C_1, 8 became C_2 and 2 became D_1 disease. On the other hand, it can also be seen in Table 2 that downstaging following neoadjuvant combination therapy was frequent at all stages of the disease: in fact, in the patients originally classified as having B_1 disease, 14 of 43 (32.5%) tumours originally classified as having a mean diameter of 1.0–1.5 cm decreased to <1.0 cm, while no cancer was found in 6 patients after thorough examination of additional histological sections. Downstaging was seen in 13 of 29 (44.8%) of patients originally classified as having stage B_2 disease. Although the number of patients is small, the downstaging effect was particularly important in patients originally classified as having C_1 disease at diagnosis, where six of eight (75.0%) had downstaging, and in patients originally classified at diagnosis as stage C_2, where six of seven cancers (85.7%) were downstaged following neoadjuvant combination therapy.

TABLE 2. Effect of 3 month neoadjuvant combination therapy with flutamide and an LHRH agonist on the final histopathological stage at surgery compared with the initial clinical stage at diagnosis

Original stage	Final histopathological stage at surgery							
	No	NC	B_0	B_1	B_2	C_1	C_2	D_1
A. Control–untreated								
B_0	3	0	1	0	1	1	0	0
B_1	39	0	7	11	6	5	10	0
B_2	17	0	0	3	1	3	8	2
C_1	7	0	1	1	2	3	0	0
C_2	5	0	0	0	1	0	1	3
B. 3 month neoadjuvant combination therapy								
B_0	3	0	1	0	0	1	1	0
B_1	43	6	14	11	7	3	2	0
B_2	29	0	2	11	6	5	3	2
C_1	8	0	2	1	3	1	1	0
C_2	7	0	1	2	2	1	0	1

NC = No Cancer

Comparison of the initial clinical stage at diagnosis with the final stage at histopathological examination of the surgical specimen following radical prostatectomy can be more easily seen in Fig. 1. The downstaging effect of combination therapy is thus clearly seen at all stages of the disease except at stage B_0. The net advantages of combination therapy are best illustrated by the final stage at surgery, which was, on average, worsened by 35.9% (14 of 39) in stage B_1 disease, 58.8% (10 of 17) in stage B_2 disease and 40% in stage C_2 disease in patients who had radical prostatectomy alone, whereas the final stage of the disease, on the contrary, was improved following combination therapy by 18.5% (8 of 43) in stage B_1 disease, 10.3% (3 of 29) in stage B_2 disease, 62.5% (5 of 8) in stage C_1 disease and 71.4% (5 of 7) in stage C_2 patients.

After 3 months of combination therapy, average upstaging decreased to 28.9% (26 of 90) in patients who received neoadjuvant combination therapy compared to 54.9% (39 of 71) in the control group. Thus, net upstaging (difference between the number of patients who had upstaging and the number of those who had downstaging) occurred on average in 33.8% of control patients, whereas 21.1% of patients were downstaged at analysis of the surgical specimen in the group of patients who had combination therapy before surgery, for a net difference of 54.9% in favour of neoadjuvant combination therapy (Fig. 2).

The net effect of neoadjuvant therapy on specimen confined margins and organ confined disease can be clearly seen in Fig. 3. Since organ confined disease has such an important prognostic value, it is of major interest to see in Fig. 3A that organ confined disease increased from 49.3% (35 of 71) in the control group to 77.8% (70 of 90) for a 57.8% improvement in the group of

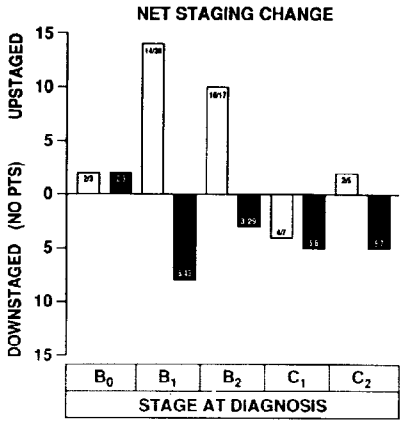

Fig. 1. Effect of 3 month combination therapy with flutamide and an LHRH agonist on the final histopathological stage at surgery v. the clinical staging at diagnosis. Data are expressed as number of patients showing upstaging or downstaging in each group (Labrie *et al*, in press)

men who received neoadjuvant combination therapy. In fact, organ confined disease increased from 61.5% (24 of 39) to 88.4% (38 of 43) in stage B_1 disease, from 23.5% (4 of 17) to 65.5% (19 of 29) in stage B_2 disease, from 57.1% (4 of 7) to 87.5% (7 of 8) in stage C_1 disease and from 20% (1 of 5) to 71.4% (5 of 7) in stage C_2 disease. On the other hand, specimen confined disease or cancer negative margins increased from 66.2% (47 of 71) in men who had radical prostatectomy alone to 92.2% (83 of 90) ($p<0.001$) in those who received neoadjuvant combination therapy before radical prostatectomy (Fig. 3B).

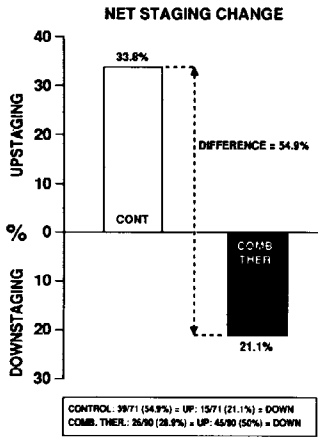

Fig. 2. Net change of stage between initial staging at diagnosis and final staging at radical prostatectomy in patients who had radical prostatectomy alone and those who received combination therapy for 3 months before radical prostatectomy. Data are expressed as percentage of patients in each group (Labrie *et al*, in press)

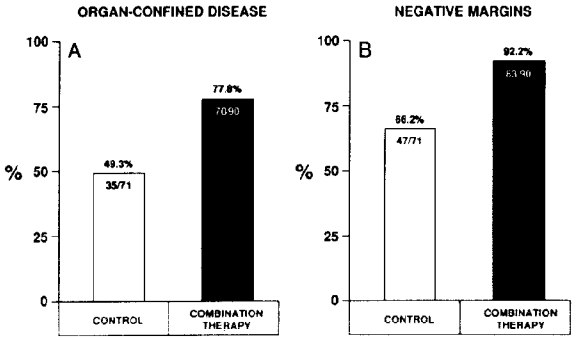

Fig. 3. Effect of 3 month neoadjuvant combination therapy with flutamide and an LHRH agonist on organ confined disease (A) and specimen confined disease (B) in stages B and C prostate cancer (Labrie *et al*, in press)

Thus, there is a 57.8% increase in the incidence of organ confined disease after 3 months of neoadjuvant combination endocrine therapy compared to control untreated men (Fig. 3A) while the incidence of cancer positive margins is 4.3-fold higher in the group of control untreated men (33.8% v. 7.8%) (Fig. 3B).

DISCUSSION

The essential objective of treatment of early stage prostate cancer is complete removal or elimination of cancer tissue. Although the long term effects of androgen deprivation achieved by neoadjuvant combination therapy on survival remain to be assessed by long term follow-up of the patients, the present data show that prostate cancer cell death or apoptosis occurs at a relatively high rate in the prostate area, under the influence of combination therapy: such cancer cell death leads to a relatively rapid downstaging of the disease. In fact, after only 3 months of neoadjuvant combination therapy with flutamide and an LHRH agonist, cancer positive surgical margins decreased from 33.8% to only 7.8% while organ confined disease increased from 49.3% to 77.8%.

The present data show that neoadjuvant combination therapy eliminates the previous serious limitation that 50% of men had a disease more advanced than expected at diagnosis when the final and true staging was obtained by histopathological examination of the surgical specimen. After 3 months of combination endocrine therapy, on average, the stage of the disease was decreased by 23% compared to the initial staging at diagnosis. Such histopathological findings, which remain to be supported by long term follow-up of the patients, offer the hope of a major improvement in the morbidity and mortality from prostate cancer.

SUMMARY

A total of 161 patients diagnosed as having stage B (134 patients) or C (27 patients) prostate cancer were randomly assigned to radical prostatectomy alone or to 3 months of neoadjuvant combination therapy with the antiandrogen flutamide and an LHRH agonist before radical prostatectomy. Neoadjuvant combination therapy before radical prostatectomy decreased cancer positive surgical margins from 33.8% in the control group to only 7.8%, thus leaving 92.2% of patients with negative margins at surgery for a 39.2% increase in specimen confined disease. Although on average the final stage determined at histopathological examination of the surgical specimen was more advanced than predicted at initial diagnosis in 33.8% of control patients, an opposite observation was made in the group of men who received the 3 month neoadjuvant combination therapy where the final stage, instead of being more advanced, was less advanced than at diagnosis in an average of 21.1% of men for a net 54.9% improvement of staging in favour of combination therapy. On the other hand, organ confined disease increased from 49.3% to 77.8% of patients after 3 months of combination therapy, for a 57.9% increase in the incidence of organ confined disease. Although long term follow up of these patients is required to determine the impact on survival, the marked influence of neoadjuvant combination therapy on the stage of the disease suggests the possibility of a major improvement in the morbidity and mortality from prostate cancer.

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