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· 临床研究 ·

2001-2010 年我院采用内分泌疗法治疗老年乳腺癌的临床效果分析 *

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摘要 目的:分析内分泌治疗在老年患者乳腺癌中的疗效。**方法:**回顾性分析 2001 年 1 月至 2010 年 12 月我院外科手术切除的≥60 岁的 116 例乳腺癌患者的临床资料,按照内分泌治疗分成三组,不进行内分泌治疗的对照组、三苯氧胺(TAM)组和芳香化酶抑制剂(AI)组,比较不良反应、存活时间及存活率。**结果:**对照组的副作用发生率为 75.86%,副作用主要为关节痛、其他关节症状和子宫内膜增厚;TAM 组的副作用发生率为 63.33%,副作用主要为其他关节症状和子宫内膜增厚;AI 组的副作用发生率为 55.56%,副作用主要为其他关节症状和子宫内膜增厚。三组患者的不良反应如潮红、妇科症状、子宫切除和静脉栓塞等发生率低,总不良反应发生率无显著性差异($P=0.802$)。对照组的中位生存时间为 7.35 年,TAM 组的中位生存时间为 10.46 年,AI 组的中位生存时间为 9.94 年,三组患者的生存时间具有显著性差异($P=0.001$),TAM 组和 AI 组的生存时间显著高于对照组。对照组、TAM 组、AI 组的 5 年生存率为 74%、90%、71%,10 年生存率为 24%、71%、68%,三组患者的生存率具有显著性差异($P=0.007$),TAM 组和 AI 组的生存率均显著高于对照组。**结论:**性激素受体阳性老年乳腺癌患者总体预后较好。TAM、AI 用于性激素受体阳性的老年乳腺癌患者的治疗,具有较好的疗效与安全性。

关键词:老年乳腺癌;性激素受体;随访;存活时间

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Clinical Effects of Endocrinotherapy on the Treatment of Breast Cancer for Elderly Patients from 2001 to 2010*

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ABSTRACT Objective: To analyze the therapeutic effect of endocrinotherapy on the treatment of breast cancer for elderly patients.

Methods: 116 cases with breast cancer who were more than 60 years old and received surgical treatment from January 2001 to December 2010 in our hospital were selected and randomly divided into three groups: the control group, in which the patients didn't accept endocrinotherapy, the TAM group and the AI group on the basis of endocrinotherapy. Then the adverse reactions, the rate and time of survival were compared and analyzed. **Results:** The rate of adverse reactions in the untreated group was 75.86%, which mainly including the arthralgia, symptoms of other joints, and endometrial thickening; The rate of adverse reactions in the TAM group was 63.33%, which mainly including the symptoms of other joints and endometrial thickening; The rate of adverse reactions in the AI group was 55.56%, which mainly including the symptoms of other joints and endometrial thickening. The adverse effect rates of flushing, gynecological symptoms, hysterectomy and venous embolism were lower in three groups with no statistically significant differences ($P=0.802$). The intermediate time of survival was 7.35 years in the untreated group, 10.46 years in TAM group and 9.94 years in AI group with statistically significant differences among three groups ($P=0.001$). The rate of five-year's survival in the untreated group, the TAM group and AI group were 74%, 90% and 71%, respectively. The rate of ten-year's survival in untreated, TAM and AI groups were 24%, 71% and 68%, respectively, there was significant differences($P=0.007$). The survival rate in TAM and AI groups were significantly higher than that of the untreated group. **Conclusion:** The prognosis of estrogen receptor positive elderly breast cancer patients was comparatively good. Applying TAM or AI on estrogen receptor positive elderly breast cancer patient showed satisfying therapeutic effect and safety.

Key words: Breast cancer in elderly patients; Estrogen receptor; Follow-up; Survival time

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前言

乳腺癌是女性最常见的恶性肿瘤之一。据资料统计,其发病率占有所有恶性肿瘤的 7-10 %^[1,2]。是一种影响女性健康的最常见的恶性肿瘤。尽管女性乳腺癌的发病率仍呈逐渐上升趋势,但死亡率已慢慢趋于下降,其中一个重要原因就是化疗和内分泌治疗取得了明显进展。1896 年 Beatson 首先在 Lancet 杂志上报道内分泌方式治疗乳腺癌:乳腺癌患者切除卵巢后可使肿瘤缩小^[3]。内分泌治疗药物开始出现于 20 世纪 30-40 年代,三苯氧胺(TAM)的问世具有里程碑的意义^[4,5]。近些年来,乳腺癌内分泌治疗的新药物不断问世如第三代芳香化酶抑制剂(AI),更使内分泌治疗达到了前所未有的高度^[6]。

首先,在非转移性乳腺癌辅助治疗中内分泌治疗具有等同与化疗的价值,在老年患者的治疗中有时甚至优于化疗。E-BCTCG(Early Breast Cancer Trialists' Collaborative Group)荟萃分析了 55 组共 37000 例随机病例,临床试验结果证实^[7],雌激素受体(ER)阳性的乳腺癌患者,术后辅助应用 TAM 药物 5 年能使肿瘤复发和死亡危险较辅助化疗降低很多。一线解救治疗中根据雌激素受体(ER)及孕激素受体(PR)免疫组化检测结果将患者分类统计,ER(+)(PR)(+)患者的有效率甚至可达 50 %~60 %,ER(+)(PR)(-)或 ER(-)(PR)(+)患者有效率达 20 %~40 %,而在 ER(-)(PR)(-)的病人中同样有 5 %~10 %有效,其中绝经后患者的有效率明显高于绝经前患者^[8]。再者内分泌治疗还是非浸润性乳腺癌最重要的治疗手段之一^[9,10]。内分泌敏感型乳腺癌在乳腺癌中占的比例约为 70%^[11],内分泌治疗的优势在于副作用小、相比化疗有良好的生活质量、交叉耐药少、口服服药方便经济。

2002 年,美国临床肿瘤学会(ASCO)年会公布了一项 1477 例患者随访 8 年的随机临床试验^[12],结果显示,ER(+)乳腺癌病人化疗后加三苯氧胺较同时应用疗效更好,因三苯氧胺抑制了肿瘤的生长,可能会降低肿瘤细胞的化疗敏感性。但近来研究结果显示:在老年患者中,无论在术后的辅助治疗还是复发转移的解救治疗中,三苯氧胺的地位都正受到第三代抗芳香化酶药物强有力的挑战^[13-15]。

据中国医学科学院肿瘤医院近 10 年的统计资料显示,65 岁及以上老年人乳腺癌占 16.4 %^[16]。老年乳腺癌患者因其特殊的生理、心理特征,有别于年轻及中年患者。其乳腺癌的生物学行为较年轻患者要好,大都属于低危复发风险的患者。对我国性激素受体阳性的老年乳腺癌的 5 年随访资料,目前国内报道文献较少。本研究即回顾性分析我院 5 年积累的老年乳腺癌患

者的临床资料,比较分析两种内分泌治疗药物的有效性及安全性,为以后改善老年性乳腺癌的内分泌治疗提供初步参考数据。

1 临床资料及方法

1.1 临床资料

回顾性分析 2001 年 1 月至 2010 年 12 月第二军医大学附属长海医院普通外科手术切除的≥ 60 岁的 116 例乳腺癌患者的临床资料,在我院病案室搜集其病案资料。其中 115 为女性,1 例为男性。年龄 60~91 岁,平均年龄 70.4 岁。116 例患者均经病理切片证实为乳腺癌,性激素受体均为阳性(ER 和 / 或 PR≥ 30 %),均行乳腺癌改良根治术、乳腺肿物切除术或全乳腺切除术,且排除远处转移性乳腺癌。患者术前均未接受任何治疗。排除标准:①未手术的患者;②远处转移(Ⅳ期)的患者;③无联系方式的患者。采用电话随访,并且将病例拍照后,建立 Excel 统计表格,记录基线情况,记录患者联系方式,联系地址等。

1.2 治疗方法

乳腺改良根治术 83 例(71.6 %),乳腺肿块切除术(含区段切除术及部分切除术)22 例(19.0 %),乳腺单纯切除术 11 例(9.5%);17 例(14.7%)进行了化疗,其中 6 例化疗后续贯了 TAM 药物内分泌治疗,5 例化疗后续贯了 AI 药物内分泌治疗,6 例化疗后无内分泌治疗。化疗方案:TC、AT、CAF、X 方案;内分泌治疗情况如下:无内分泌治疗 29 例(25 %),采用 TAM 方案治疗 60 例(51.7%),采用 AI 治疗 27 例(23.2 %),其中 AI 治疗包含:来曲唑片(2.5 mg 瑞士诺华),用法 2.5 mg 口服 1/日;依西美坦片(25 mg 辉瑞制药),用法 25 mg 口服 1/日。

1.3 统计学处理

将所有患者按内分泌治疗药物使用情况分为:没有使用内分泌药物为对照组;使用三苯氧胺为 TAM 组;使用芳香化酶抑制剂为 AI 组。年龄分布,采用均数±标准差($\bar{x} \pm s$),组间比较采用单因素方差分析的方法。计数资料采用卡方检验或 Fisher 精确检验。生存率计算则采用 Kaplan-Meier 法,三组的生存率差异显著性检验应用 Long-rank 法。所有数据采用 SPSS18.0 统计软件处理,双侧检验, $\alpha=0.05$ 为检验水准, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 三组患者年龄比较

由表 1 可见,三组患者年龄差异无统计学意义($P=0.9$),其年龄具有可比性。

表 1 三组患者年龄比较

Table 1 Comparison of age in the three groups($\bar{x} \pm s$)

	Untreated	TAM	AI	F value	P value
Number of cases	29	60	27		
Age	70.97± 7.18	70.28± 7.73	70.11 ± 8.38	0.1	0.9

2.2 三组患者临床特征比较

三组患者的临床资料见表 2,表中各项值均不具有显著差异($P>0.05$)。

2.3 不良反应发生情况

由表 3 可见,对照组的不良反应发生率为 75.86 %,主要包括关节痛、其他关节症状和子宫内膜增厚。TAM 组的不良反应

表 2 三组患者临床特征比较

Table 2 Comparison of clinical features in three groups

Clinical feature	Untreated		TAM		AI		X ² value	P value
	Cases	Percentage	Cases	Percentage	Cases	Percentage		
Gender								
Male	0	0	1	1.67	1	3.70	Fisher	0.474
Female	29	100	59	98.33	26	96.30		
Hypertension								
No	23	79.31	53	88.33	26	96.30	Fisher	0.154
Yes	6	20.69	7	11.67	1	3.70		
Diabetes								
No	26	89.66	56	93.33	26	96.30	Fisher	0.709
Yes	3	10.34	4	6.67	1	3.70		
Axillary lymph node metastases								
No	17	58.62	30	50	13	48.15	Fisher	0.351
Yes	9	31.03	24	40	8	29.63		
Unknown	3	10.34	6	10	5	18.52		
Pathological pattern								
1=invasive ductal carcinoma	22	75.86	46	76.67	19	70.37	Fisher	0.674
2=mucinous breast carcinoma	1	3.45	4	6.67	3	11.11		
3=invasive lobular carcinoma	0	0	3	5.00	2	7.41		
4=Mammary gland papillary carcinoma	4	13.79	5	8.33	1	3.70		
5=other rare types	2	6.90	2	3.33	2	7.41		
ER								
Negative	1	3.45	1	1.67	2	7.41	Fisher	0.735
Positive	28	96.55	59	98.33	27	100.00		
cer-bB-2								
-	11	37.93	24	40.00	10	37.04	Fisher	0.78
+	11	37.93	23	38.33	11	40.74		
++	4	13.79	11	18.33	3	11.11		
+++	3	10.34	2	3.33	3	11.11		
Chemotherapy								
No	26	89.66	47	78.33	26	96.3	Fisher	0.067
Yes	3	10.34	13	21.67	1	3.7		
Surgical procedure								
Breast modified operation	21	72.41	41	68.33	21	77.78	Fisher	0.944
Breast tumors resection	5	17.24	13	21.67	4	14.81		
Simple mastectomy	3	10.35	6	10	2	7.41		
Recurrence								
No	27	93.10	59	98.33	26	96.30	Fisher	0.438
Yes	2	6.90	1	1.67	1	3.70		

发生率为 63.33%, 主要为其他关节症状和子宫内膜增厚。AI 组的不良反应发生率为 55.56%, 主要为子宫内膜增厚和其他关节症状。三组患者的潮红、妇科症状、子宫切除和静脉栓塞发生率较低, 其组间差异无统计学意义 ($P=0.802$)。

2.4 三组患者存活时间比较

由表 4 可见, 对照组的中位生存时间为 7.35 年, TAM 组的中位生存时间为 10.46 年, AI 组的中位生存时间为 9.94 年, 三组患者的生存时间具有显著性差异 ($P=0.001$), TAM 组和 AI 组的生存时间显著高于不治疗组 (图 1)。

2.5 三组患者的生存率比较

由表 5 可知, 对照组的 5 年生存率为 74 %, 10 年生存率为 24 %; TAM 组的 5 年生存率为 90 %, 10 年生存率为 71 %; AI 组的 5 年生存率为 85 %, 10 年生存率为 68 %。三组患者的生存率具有显著性差异 ($P=0.007$), TAM 组和 AI 组的生存率均显著高于对照组。

3 讨论

近些年来, 随着人们防癌意识的加强和乳腺癌普查的推

表 3 三组患者不良反应发生情况比较
Table 3 Comparison of rate of adverse reactions of patients in the three groups

Adverse effect	Untreated		TAM		AI		X ² value	P value
	cases	Percentage	cases	Percentage	cases	Percentage		
None	7	24.14	22	36.67	12	44.44	Fisher	0.802
Flushing	2	6.90	3	5.00	1	3.70		
Gynecological symptoms	2	6.90	3	5.00	1	3.70		
Hysterectomy	1	3.45	3	5.00	1	3.70		
Venous embolism	1	3.45	2	3.33	0	0.00		
Arthralgia	8	27.59	6	10.00	2	7.41		
Symptoms of other joints	4	13.79	12	20.00	4	14.81		
Endometrial thickening	4	13.79	9	15.00	6	22.22		

表 4 三组患者存活时间比较
Table 4 Median survival time of patients in three groups

Time	Untreated	TAM	AI	F value	P value
Median survival time (year)	7.35	10.46	9.94	14.83	0.001

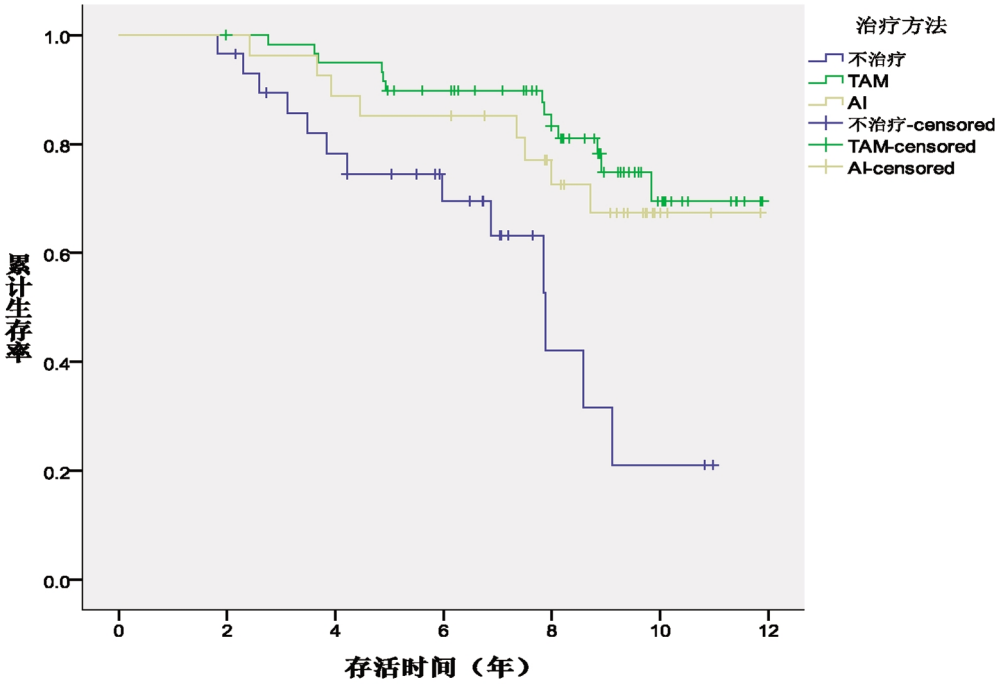


图 1 三组患者累计生存率比较
Fig.1 Accumulative survival rate of patients in three groups at different time point

表 5 三组患者的生存率比较
Table 5 Comparison of survival rate in three groups

Group	3-year (%)	5-year (%)	10-year(%)	X ² value	P value
Untreated	0.89	0.74	0.24	9.991	0.007
TAM*	0.98	0.90	0.71		
AI*	0.96	0.85	0.68		

Note: Compared with the untreated group, *P<0.05.

广, 乳腺的早期诊断率不断提高, 虽然年轻乳腺癌的死亡率有所下降, 但老年乳腺癌的死亡率变化不大, 所以提高老年乳腺癌长期生存率和生活质量越显重要。老年乳腺癌具有一下一些特征: 侵袭性低、疾病发展慢、区域淋巴结转移较晚; 此外, 老年

乳腺癌还具有一些独特的临床特点:①机体多器官功能呈不同程度的老化衰退,常伴不少老年病,如糖尿病、心脏病、慢性支气管炎、肝肾功能不全等;②老年乳腺癌患者肿瘤生长较慢,临床症状轻,老人就诊意识差,发现时病程已较长,多有局部晚期表现;③老年患者正常乳腺组织已退化,如早期就诊易检出组织包块;④老年患者因多脏器功能衰退,耐受手术差,术后愈合慢且并发症多。⑤骨转移发生相对较多^[17]。因此老年乳腺癌除了手术之外,对于性激素受体阳性老年乳腺癌内分泌治疗作为首选。本文通过这些患者的随访发现,ER阳性的老年乳腺癌总体预后较好,乳腺复发也明显比年龄较轻患者少,这与老年乳腺癌本身的特性相关。

研究发现,性激素受体阳性的老年乳腺癌患者,应用TAM予中晚期1.5-9个月的综合治疗,其总有效率可达37%-81%,TAM目前已广泛用于受体阳性的老年乳腺癌患者。AI的临床应用进一步提高了ER(+)和或PR(+)乳腺癌患者的临床疗效。2007年,美国乳腺癌年会公布了阿那曲唑、来曲唑分别对比TAM治疗乳腺癌的两项大规模临床试验研究结果^[18,19]。德国一项27例性激素受体阳性、绝经后、T2-4分期的乳腺癌患者参与的研究发现,予依西美坦治疗4个月,10例部分缓解,17例病情稳定,14例进行了保乳手术^[19]。俄罗斯一项随机对照研究中,151例绝经后乳腺癌患者,随机分为依西美坦组与他莫昔芬组,术前治疗3个月。两组临床触诊客观有效率分别为76.3%和40.0%($P=0.05$),但超声检查有效率、钼靶检查有效率组间无统计学差异。依西美坦组、他莫昔芬组保乳手术率分别为36.8%和20.0%($P=0.05$),不良反应发生率无明显差异^[20]。

新辅助内分泌治疗的优点及老年乳腺癌的临床特点决定了其在老年患者治疗中的重要地位。TAM的疗效无年龄相关性差异,在老年患者中疗效确切,AI药物疗效同样与年龄无关,但其疗效、耐受性方面优于TAM。在不良反应方面,TAM常见血栓栓塞、阴道出血/排液、子宫内膜情况等副作用,而AI多见肌肉关节症状、骨密度降低、心血管情况、脂质代谢异常等^[22,23]。因此TAM、AI在临床选用时尚需考虑老年患者的个体情况,以减少其潜在副作用的不良影响。多项研究显示^[24,25],手术联合TAM治疗与单用TAM相比,可提高患者无病生存率;单用TAM与单用手术相比,局部复发率更高,需更多的后续治疗,影响患者的生活质量。拒绝手术与接受手术的患者相比,前者死于乳腺癌的风险是后者的2.1倍。已有证据显示,单用TAM治疗与手术相比,局部控制率更差。因此,对能够耐受手术的老年患者,还应建议行乳腺切除手术。

总之,本研究对116例老年乳腺癌患者的临床资料进行回顾性及随访研究,将患者分为对照组、ATM组、AI组,三组患者年龄、性别、伴高血压、伴糖尿病、是否有腋窝淋巴结转移、病理类型、ER、cer-bB-2、是否化疗、手术方式以及是否转移均无统计学差异。性激素受体阳性老年乳腺癌患者总体预后较好,10年总生存率达到58.6%。对照组的中位生存时间为7.35年,TAM组的中位生存时间为10.46年,AI组的中位生存时间为9.94年,TAM组和AI组的生存时间显著高于对照组。对照组、ATM组、AI组10年生存率为24%、71%、68%,三组患者的生存率具有显著性差异($P=0.007$),TAM组和AI组的生存率均显著高于对照组。各组之间未见严重不良反应事件。表明TAM、AI用于性激素受体阳性的老年乳腺癌患者的治疗,具有

较好的疗效与安全性,但新辅助内分泌治疗如何结合其它疗法如生物靶向治疗以进一步提高临床疗效,值得深入临床研究。

4 总结

从本研究中,我们看到内分泌治疗明显提高了雌激素受体阳性老年乳腺癌患者的中位生存时间与生存率,在老年乳腺癌患者中,AI组中位生存时间低于TAM组,同时AI组不良反应明显低于TAM组。

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(上接第 4821 页)

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